FDA Briefing Document

Joint Meeting of the Antimicrobial Drugs Advisory Committee and the

Drug Safety and Risk Management Advisory Committee

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The Benefits and Risks of Systemic Fluoroquinolone Antibacterial Drugs for the Treatment of Acute Bacterial Sinusitis (ABS), Acute Bacterial Exacerbation of Chronic Bronchitis in Patients Who Have Chronic Obstructive Pulmonary Disease (ABECB-COPD), and Uncomplicated Urinary Tract Infections (uUTI).

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Divisions or Offices. We have brought safety and efficacy information for the systemic fluoroquinolone antibacterial drugs in the context of three indications: acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease, and uncomplicated urinary tract infections. The purpose of the joint meeting is to gain the Committees' insights and opinions and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion at this joint meeting of the advisory committees. The FDA will not issue any final determinations on the issues at hand until input from the advisory committees processes have been considered and all reviews have been finalized. The final determinations may be affected by issues not discussed at the advisory committee meeting.

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I. INTRODUCTION

The control of infectious diseases is one of the top ten public health achievements of the twentieth century (CDC, 1999). The reduction in mortality associated with antibacterial drugs to treat serious and life-threatening infectious diseases such as bacterial pneumonia was a remarkable public health success (Dowling, 1972; Finland, 1943), and the introduction of the systemic fluoroquinolone antibacterial drugs contributed to this public health achievement. The benefits and risks of fluoroquinolone antibacterial drugs are favorable in the treatment of certain serious and life-threatening infectious diseases. However, while many infectious diseases are serious and life-threatening, a few infectious diseases have more recently been shown to be potentially self-limited in a large proportion of patients.

A pre-approval clinical trial safety database may not demonstrate adverse reactions that occur infrequently. During the life-cycle of any approved drug, adverse reactions that occur infrequently become evident as larger numbers of patients are exposed to the drug. During the life-cycle of the fluoroquinolone antibacterial drugs, adverse reactions such as tendinitis and tendon rupture, prolongation of the QT interval, and peripheral neuropathy only became evident post-approval.

We are asking the advisory committees to discuss the benefits and risks of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease (ABECB-COPD), and uncomplicated urinary tract infections (uUTI).[1] The fluoroquinolone antibacterial drugs currently available with one or more of these three indications are ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin. This document provides a summary of the treatment effects of antibacterial drugs for these three clinical conditions. In addition to a summary review of safety-related labeling changes for all fluoroquinolone drugs, we reviewed the safety findings of the fluoroquinolone antibacterial drugs in several contexts. An epidemiological review of publications characterized the incidence and relative risks of selected adverse reactions associated with fluoroquinolone antibacterial drugs. A search of the FDA Adverse Event Reporting System (FAERS) with a focus on adverse reactions associated with disability was reviewed. Finally, we evaluated the drug utilization of oral fluoroquinolone antibacterial drugs in the United States. This document will provide an assessment of efficacy, safety, and current drug use of fluoroquinolones for treatment of ABS, ABECB-COPD, and uUTI.

[1] The use of fluoroquinolone antibacterial drugs in this document refers to the systemic administration of fluoroquinolone antibacterial drugs.

II. TREATMENT EFFECTS OF ANTIBACTERIAL DRUGS FOR TREATMENT OF ABS, ABECB-COPD, AND uUTI

a. Regulatory Overview of Antibacterial Drug Development

Beginning in the 1980s, there was a change in the types of study designs that FDA was recommending for the efficacy evaluations of new antibacterial drugs. This change was driven by advances in our understanding of the pathophysiology of certain infections and implications for clinical trial design. In addition, new regulations were promulgated in 1985 that describe the characteristics of adequate and well-controlled studies (§21 CFR 314.126). During the 1990s and subsequently, FDA recommended clinical trials that were designed to enroll patients with infections involving a particular body site, rather than patients with any of a variety of different types of infections.[2] Clinical trials used to support the approval of antibacterial drugs from this point forward were generally designed as "equivalence" trials that were the predecessor for noninferiority (NI) trials. The equivalence trial is similar to the NI trial, except that equivalence trials were generally underpowered and had less confidence that a test drug was not inferior to a control drug. The NI trial focuses on the lower bound of the two-sided 95% confidence interval of the difference to establish a degree of confidence that a test drug is not inferior to a control drug.

Antibacterial drugs approved before the 1980s were in general used as the control antibacterial drugs in NI trials. Because placebo-controlled trials were not used as a basis for the approval of those drugs, a treatment effect of the control antibacterial drugs over placebo had not been clearly established for ABS, ABECB-COPD, or uUTI. Thus, these active-controlled studies may not provide a reliable means to evaluate efficacy of antibacterial drugs for these indications.

b. Anti-Infective Drugs Advisory Committee Discussions

On several occasions since 2000, FDA Advisory Committees have addressed issues regarding clinical development of antibacterial drugs that are seeking the indication for treatment of ABS or ABECB-COPD and are based on the demonstration of NI to an approved antibacterial drug. The treatment effect of antibacterial drugs for uUTI was not previously discussed at an FDA Advisory Committee.

In 2002, the Anti-Infective Drugs Advisory Committee (AIDAC) discussed clinical trials of antibacterial drugs for treatment of ABECB-COPD; the committee recommended placebo-controlled trials for subjects who are not severely ill in order to demonstrate efficacy. In 2003, AIDAC discussed the trial designs to demonstrate efficacy of an antibacterial drug for the

[2] These recommendations are described in documents that provide advice on designing clinical trials to evaluate antibacterial drugs for each of a variety of different infectious diseases. These documents include the Infectious Diseases Society of America (IDSA) and the FDA Guidelines for the Evaluation of Anti-Infective Drug Products (Beam, Gilbert, et al., 1992) and the FDA Points to Consider Document, *Clinical Development and Labeling of Anti-infective Drug Products*.

treatment of ABS. The committee recommended that trials be designed to show superiority of the test antibacterial drug, for example, through placebo-controlled clinical studies.

In September 2006, the AIDAC discussed an antibacterial drug for consideration of approval based on an active-controlled NI trial for the indication of ABS. The committee of 14 voting members was asked whether efficacy had been demonstrated based on a finding of NI from the NI trial design. Ten out of 14 committee members voted that efficacy for treatment of ABS had not been demonstrated. In December 2006, a joint meeting of the AIDAC and the Drug Safety and Risk Management Advisory Committee discussed safety data in the context of the FDA-approved indications for Ketek® (telithromycin), which were approved on the basis of active-controlled NI trials. The committee recommended removal of the ABS and ABECB-COPD indications from labeling because the risk of hepatotoxicity outweighed benefit, in part because it was not possible to reliably show the effect of the active drug for these two indications on the basis of the NI trial design. The Ketek® (telithromycin) product label was subsequently amended to remove the indications for ABS and ABECB-COPD.[3]

Following these advisory committee discussions, placebo-controlled trials were recommended to support the indications for ABS and ABECB-COPD. Final guidance documents from FDA on developing antibacterial drugs for treatment of ABS and mild ABECB-COPD recommend superiority trials with a placebo control. In the subsequent sections, we describe an assessment of the treatment effect of antibacterial drugs for these three clinical conditions. Any antibacterial drug, including fluoroquinolones, used in a placebo-controlled or non-antibacterial controlled trial was considered for this efficacy evaluation.

c. Acute Bacterial Sinusitis – Antibacterial Efficacy

We reviewed 20 placebo-controlled trials published in the medical literature (see bibliography in Appendix A). Fourteen studies did not show a statistically significant difference over placebo. Among the six studies that demonstrated a statistically significant difference in clinical outcomes, each study's primary efficacy outcome assessment was different and the timing of the outcome assessment was different. In addition to overlapping symptoms with common viral infections and the presence of several confounding treatments and host risk factors, when clinical trials have shown some clinical benefit, the benefit is observed only in patients who have prolonged and more severe symptoms and the statistically significant difference from placebo is not robust.

Several publications have reviewed the literature regarding placebo-controlled trials for treatment of ABS. The Cochrane Collaboration conducted a review of antibacterial drugs for treatment of clinically diagnosed acute rhinosinusitis in adults and provided this statement in their conclusion: "Taking into account antibiotic resistance and the very low incidence of serious complications, we conclude that there is no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis" (Lemiengre, van Driel, et al, 2012). Another

[3] See the February 12, 2007 approval letter and review documents at Drugs@FDA found at: http://www.accessdata fda.gov/drugsatfda_docs/nda/2007/021144Orig1s012Approv.pdf

review by The Cochrane Collaboration of antibacterial drugs for treatment of acute maxillary sinusitis in adults provided the following statements in their conclusion: "There is moderate evidence that antibiotics provide a small benefit for clinical outcomes in immunocompetent primary care patients with uncomplicated acute sinusitis. However, about 80% of participants treated without antibiotics improved within two weeks" (Ahovuo-Saloranta A, UM Rautakorpi, 2014).

A practice guideline from the Infectious Diseases Society of America emphasized the inability to differentiate a viral cause from a bacterial cause of acute sinusitis, but noted that viral causes account for 90% or more in patients with symptoms of acute sinusitis. The guideline recommends antibacterial drug therapy for patients who present with more severe symptoms of acute sinusitis likely to be ABS and discourages the use of respiratory fluoroquinolone antibacterial drugs in favor of beta-lactam antibacterial drugs. The guideline also states a secondary goal to reduce excessive or inappropriate use of antibacterial drugs (Chow, Benninger, et al, 2012).

A meta-analysis of 9 randomized trials enrolling 2,547 patients assessed whether a particular group of signs and symptoms can be used to identify patients who benefit from antibacterial drugs. A subgroup of patients for whom antibacterial drug treatment is clearly justified based on a pattern of signs or symptoms could not be identified. From their analyses, the authors suggest that antibacterial drug treatment might offer no benefit at all or have harmful effects (Young, De Sutter, et al, 2008).

The ability to clearly identify a group of patients who have a bacterial etiology for their symptoms of acute sinusitis is difficult. Even when a bacterial pathogen was documented or the trial was enriched for patients who are more likely to have ABS, the antibacterial drug treatment effect appeared to be small with a large proportion of placebo-treated patients having favorable clinical responses. Current reviews by authoritative scientific bodies and meta-analyses published in the literature question the benefit of antibacterial drugs for treatment of ABS. The treatment effect of antibacterial drugs for ABS appears to be only very modest, at best.

d. Acute Exacerbations of Chronic Bronchitis – Antibacterial Efficacy

We reviewed 15 placebo-controlled studies of ABECB-COPD (see bibliography in Appendix A). Nine studies did not show a difference in clinical outcomes between patients who received placebo and patients who received an antibacterial drug. Six studies showed a statistically significant difference in favor of an antibacterial drug, although the studies enrolled patients with varying disease severity and used different outcome assessments. One study enrolled patients hospitalized with severe ABECB-COPD and found an absolute risk reduction in mortality of 17.5 (95% CI 4.3, 30.7) associated with antibacterial drug therapy (Nouria, Marghi, et al, 2001). Four out of eight studies enrolling only outpatients showed a statistically significant difference from placebo using an outcome assessment incorporating patient symptoms and their improvement. Thus, while outcome assessments based on subjective assessments by clinical investigators or pulmonary function testing did not demonstrate a treatment effect in the other

four studies, there appears to be a treatment effect in mild ABECB-COPD based on symptom improvement from the perspective of the patient.

A review by The Cochrane Collaboration on antibacterial drugs for the treatment of acute exacerbations of chronic obstructive pulmonary disease demonstrated effectiveness, as stated in their conclusions: "…this review supports antibiotics for patients with COPD exacerbations with increased cough and sputum purulence who are moderately or severely ill" (Ram, Rodriguez-Roisin, et al, 2006). A review of bacterial infections in patients with COPD also recommends antibacterial drug treatment for patients with moderate or severe symptoms of ABECB-COPD (Sethi, Murhpy, 2008). In addition, treatment guidelines from the American Thoracic Society and the European Respiratory Society on the management of COPD describe only the consideration of antibacterial drug therapy for outpatients with ABECB-COPD based on certain symptoms of greater severity (Celli, MacNee, et al, 2004). Clinical practice guidelines for treatment of ABECB-COPD published by the American College of Physicians stated, "Among patients with mild attacks, there were no significant differences between those who received antibiotics and those who received placebo" (Bach, Brown, et al, 2001). These publications have a common thread that patients with mild symptoms of ABECB-COPD are not recommended to receive antibacterial drug treatment.

Successful outcomes in the placebo arm have consistently been reported in half or more of the patients enrolling in clinical studies of ABECB-COPD. Adverse reactions were generally mild overall but occurred with greater frequency in the antibacterial drug-treated groups. However, one randomized, prospective, double-blind, placebo controlled trial enrolling outpatients with ABECB-COPD showed a rate of hospitalization due to worsening pulmonary status in the placebo group of 4% versus 2% in the antibacterial drug group (Echols, Tosiello, 2008).

The treatment effect of antibacterial drug therapy for patients who are hospitalized and have moderate or severe ABECB-COPD is clearly evident (e.g., reduction in mortality) and antibacterial therapy is warranted in such patients. However, patients enrolled in ABECB-COPD trials in new drug applications have, in general, included patients with outpatient, milder, or less well-characterized disease.

In outpatients with mild symptoms from ABECB-COPD, current practice guidelines and reviews by authoritative scientific bodies do not uniformly recommend antibacterial drug therapy for such patients. The treatment effect of antibacterial drug therapy from the perspective of the patient is only modest for outpatients with mild ABECB-COPD.

e. Uncomplicated Urinary Tract Infection – Antibacterial Efficacy

We reviewed published trials using a placebo or a non-antibacterial control. Details of our search criteria and the review of each trial are found in Appendix B. We identified five trials that met our criteria (Asbach, 1991; Christiaens, De Meyere, et al, 2002; Bleidorn, Gágyor, 2010; Ferry, Holm, et al, 2007; Dubi, Chappuis, et al, 1982). Four were placebo-controlled trials and one used ibuprofen as a control drug. In general, these trials enrolled mostly young adult women with symptoms such as dysuria and evaluated both resolution of symptoms and eradication of the

bacterial pathogen from urine (e.g., from a baseline urine culture of $\geq 10^5$ CFU/ml demonstrating a single bacterial uropathogen to $\leq 10^2$ CFU/ml or no growth on follow up urine culture).

Figures 1-5 show the results of fixed- and random-effects meta-analyses for these five trials. We considered ibuprofen to be a placebo in these analyses. Figures 1 and 2 show the separate outcome assessments as described in the three respective trials, and Figure 3 shows the responder outcome that was described in those two trials.

Figure 1: Microbiological Eradication Outcome Assessment (study name = first author)

Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Treatment	Events / Total Control
	Christiaens	0.253	0.129	0.017	0.000	0.505	1.963	0.050	17 / 29	9 / 27
	Bleidom	0.253	0.115	0.013	0.027	0.478	2.193	0.028	23 / 33	16 / 36
	Ferry	0.565	0.033	0.001	0.499	0.630	16.884	0.000	594 / 657	77 / 227
Fixed		0.524	0.031	0.001	0.463	0.585	16.801	0.000		
Random		0.378	0.127	0.016	0.130	0.626	2.986	0.003		

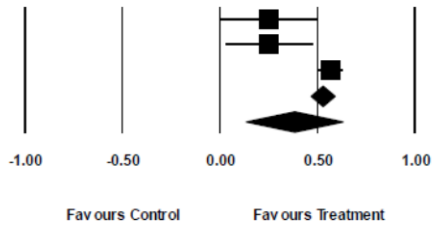


Figure 2: Clinical Resolution Outcome Assessment (study name = first author)

Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Treatment	Events / Total Control
	Christiaens	0.303	0.106	0.011	0.095	0.510	2.860	0.004	30 / 40	17 / 38
	Bleidom	-0.100	0.111	0.012	-0.318	0.118	-0.900	0.368	17 / 40	21 / 40
	Ferry	0.352	0.035	0.001	0.284	0.419	10.181	0.000	396 / 657	57 / 227
Fixed		0.311	0.031	0.001	0.249	0.373	9.878	0.000		
Random		0.198	0.131	0.017	-0.059	0.455	1.510	0.131		

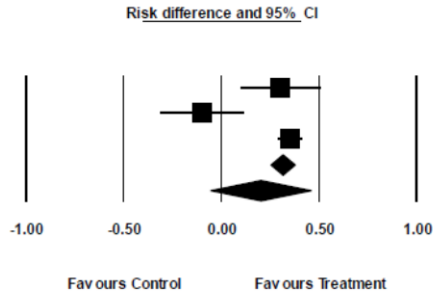
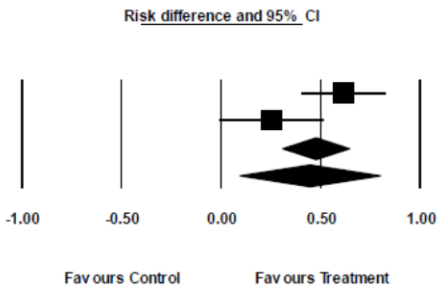


Figure 3: Clinical + Micro Responder Outcome Assessment (study name = first author)

Model	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Treatment	Events / Total Control
	Asbach	0.614	0.110	0.012	0.398	0.830	5.583	0.000	50 / 57	5 / 19
	Dubi	0.253	0.136	0.019	-0.014	0.521	1.856	0.064	30 / 43	8 / 18
Fixed		0.472	0.086	0.007	0.304	0.640	5.512	0.000		
Random		0.443	0.180	0.032	0.090	0.796	2.457	0.014		



The lower limit of the two-sided 95% confidence interval for a treatment effect based on microbiological eradication was 13% based on a random-effects meta-analysis of the three trials. The lower limit of the two-sided 95% confidence interval crossed zero for clinical resolution outcome assessment because the analysis included ibuprofen as a placebo (Bleidorn, Gágyor, 2010). The other two trials describing the responder outcome assessment did not describe the endpoints separately and we did not have access to patient level data, but the analysis showed a lower limit of the two-sided 95% confidence interval for a treatment effect of 9% based on the random-effects meta-analysis.

The analyses in Figures 4 and 5 were performed by imputing the results of the responder outcome in all trials for each outcome assessment: microbiological eradication and clinical resolution. This assumption may represent a conservative approach because patients who were failures based on one component of the responder endpoint (e.g., failure on clinical resolution and success on microbiological eradication) would still be considered failures on each outcome assessment (e.g., imputed as a failure on microbiological eradication instead of success). However, this assumption may result in the introduction of bias towards a treatment effect if one outcome assessment alone is driving the results of the responder outcome. As shown in Figures 4 and 5, the lower limit of the two-sided 95% confidence interval of a treatment effect is 24% and 10% for the outcome assessments of microbiological eradication and clinical resolution, respectively, based on random-effects meta-analyses.

Figure 4: Microbiological Eradication Outcome Assessment (study name = first author)

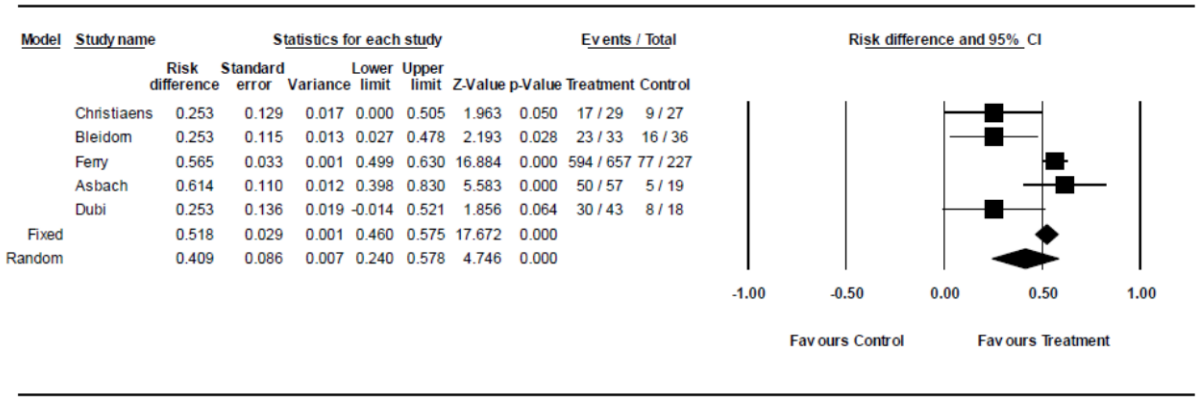
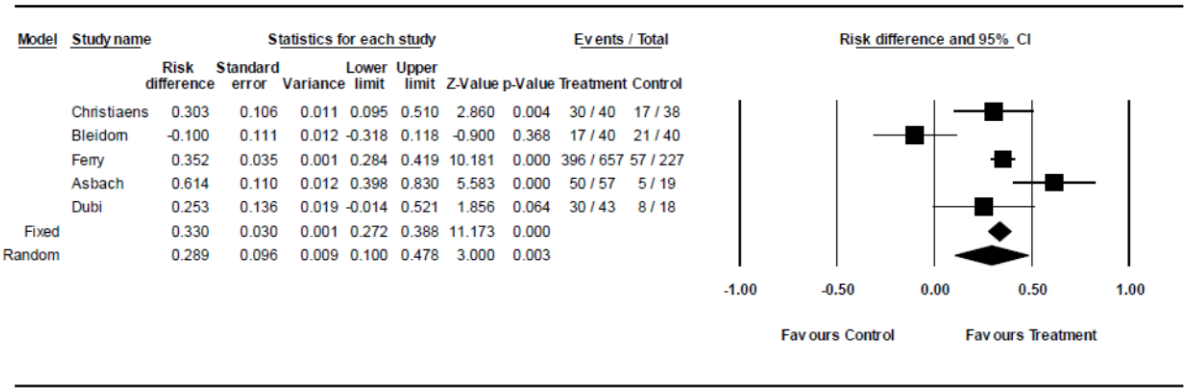


Figure 5: Clinical Resolution Outcome Assessment (study name = first author)



All of these placebo control and non-antibacterial control trials were conducted in Europe; however, the pre-study hypotheses—that the symptomatic improvement and natural course of untreated uUTI is not significantly worse than with the use of antibacterial treatments—suggest ongoing equipoise regarding the role of antibacterial treatment with bacteriological eradication on disease progression/recurrence and the symptomatic aspects of treatment. This includes an ongoing trial with the goal of enrolling approximately 300 patients to evaluate ibuprofen versus mecillinam in the treatment of uncomplicated cystitis in healthy, adult, non-pregnant women (Vik, Bollestad, et al, 2014). Many of these trials are smaller pilot trials, with largely descriptive statistical analysis of various outcomes, but there appeared to be evidence of antibacterial treatment effect over placebo on symptom resolution, with an even larger treatment effect on microbiologic eradication. We did not have access to patient-level data to evaluate a responder outcome assessment of symptom resolution plus microbiological eradication for all trials.

In our literature search we were not able to find a study that clearly defines the course of untreated uUTI and potential infectious complications in a large population. While the fact that placebo-controlled trials found that most patients with uUTI had uneventful short-term courses without antibacterial drug therapy, the incidence of progression to complicated urinary tract infection or pyelonephritis has not been clearly elucidated. In contrast, the incidence of pyelonephritis in untreated pregnant women with asymptomatic bacteriuria has been elucidated; the relative risk of pyelonephritis without screening and antibacterial drug treatment was 3.37 (95% CI 1.68, 6.78) in one study (Gratacós E, Torres P, et al, 1994). Among the five controlled studies there was one patient randomized to receive placebo who was treated for pyelonephritis.

The primary objective of the Cochrane Collaboration review of uUTI was to compare the effectiveness of different antibacterial drug therapies for treatment of acute uUTI; treatment effect against placebo was not under evaluation (Zalmanovici Trestioreanu, Green, et al, 2010). Guidelines prepared by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases (IDSA/ESMID) do not discuss an option of non-antibacterial therapy (Gupta, Hooton, et al, 2011).

These updated IDSA/ESMID guidelines state that three-day regimens of fluoroquinolones have a propensity for the emergence of antimicrobial resistance among uropathogens and should therefore be considered secondary options for treatment.

There is a clear and consistent treatment effect of antibacterial drug therapy for treatment of uUTI on the outcome assessment of microbiologic eradication. In studies that used a placebo control, there is a similar treatment effect using an outcome assessment based on symptom resolution. In a study that used ibuprofen as a control, there was no treatment difference on symptom resolution in comparison to an antibacterial drug. The risk of infectious complications has not been clearly elucidated for otherwise healthy nonpregnant adults who convert from symptomatic to asymptomatic bacteriuria with the use of a nonsteroidal anti-inflammatory drug such as ibuprofen.

f. Summary of Treatment Effects for ABS, ABECB-COPD and uUTI

The treatment effects of antibacterial drug therapy for ABS and mild ABECB-COPD are very modest, at best. The FDA's guidance documents for these two indications are included as attachments in Appendix C and recommend placebo-controlled trial to demonstrate efficacy. The treatment effect of antibacterial therapy for moderate-to-severe ABECB-COPD is robust, and antibacterial therapy is warranted in such patients who are often hospitalized for their illness. In placebo-controlled trials, the treatment effect of antibacterial therapy for uUTI is evident for microbiological eradication of bacteria and resolution of symptoms. In an ibuprofen-controlled trial, there was a treatment effect of antibacterial drug therapy on microbiological eradication outcome assessment, but both treatment groups in this trial showed similar proportions with symptom resolution. See Appendix D for a summary of the labeled indications of ABS, ABECB-COPD, and uUTI for each of the currently available systemic fluoroquinolone antibacterial drugs.

III. FLUOROQUINOLONE SAFETY ISSUES

a. History of Safety-Related Labeling Changes

Since the 1986 approval of norfloxacin, the labeling and accompanying patient information or Medication Guides for the fluoroquinolones have been updated based on analyses of clinical trials, spontaneous safety reports, and information published in the literature. The changes have included revisions to the Warnings and Precautions and Adverse Reactions sections to include the description of the musculoskeletal, cardiac, dermatologic, neurologic, and neuro-psychiatric risks associated with the use of fluoroquinolones. The labeling for all fluoroquinolone antibacterial drugs is in the Physician Labeling Rule (PLR) format. We briefly describe the rationale for selected safety-related labeling changes to the Boxed Warning and Warnings and Precautions section, and specific examples are provided in Appendix E.

Tendinitis and Tendon Rupture Boxed Warning

While original product labeling for norfloxacin (1986) and ciprofloxacin (1987) included nonclinical information on joint pathology in the Warnings and Precautions sections, clinical evidence for tendon/joint toxicity associated with fluoroquinolone use became apparent post-marketing and the labels for all marketed fluoroquinolones were updated to include a warning of tendon rupture in 1996. At the time of approval, the warning of tendon rupture was included in the labels for levofloxacin, moxifloxacin, and gatifloxacin, reflecting the recognition of the class effect of fluoroquinolones on tendon toxicity, even though this adverse reaction was not observed in clinical trials for these products. In 2004, the warning was expanded to include information on the at-risk populations: those on steroid medications and the elderly. Subsequently, language regarding serious tendon effects requiring surgical intervention and guidance on management were added. A Boxed Warning for tendinitis and tendon rupture was added in 2008.[4] This labeling change also provided information regarding the risk of these effects in transplant recipients, in the presence of strenuous physical activity, and renal failure, as well as updated the list of the specific tendon sites prone to rupture. In addition, FDA issued a Medication Guide to patients about serious adverse reactions, including tendinitis, associated with fluoroquinolone use. The Medication Guides continue to be part of the approved labeling for all fluoroquinolones.

Central Nervous System (CNS) Effects Warning

Ciprofloxacin was first in the fluoroquinolone class to include effects on CNS (seizures, tremors, and alterations of mental state) in the Warnings and Precautions sections of the label at the time of approval. The accumulation of postmarketing clinical evidence along with elucidation of the mechanism for fluoroquinolone-mediated CNS toxicity (inhibition of GABA-A receptors in addition to activation of excitatory NMDA receptors) led to updated labeling for all fluoroquinolones. CNS/psychiatric adverse reactions associated with fluoroquinolones, including increased intracranial pressure and psychosis was in the ofloxacin label in 1990 and subsequently was included in Warning and Precautions Section in all fluoroquinolones. In 2011, pseudotumor cerebri was added to the CNS toxicity warning.

Peripheral Neuropathy Warning

After review of the accumulated postmarketing safety data for the approved fluoroquinolones, in 2004 the FDA requested the sponsors for all fluoroquinolone antibacterial drugs to include a warning regarding peripheral neuropathy. A 2013 FDA review identified permanently disabling cases of peripheral neuropathy associated with fluoroquinolone use. No relationship between the duration of therapy and symptom onset and reversibility was noted. Additional safety labeling

[4] See the FDA News Release, "FDA Requests Boxed Warnings on Fluoroquinolone Antimicrobial Drugs", found at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116919.htm

changes were required and FDA issued a Drug Safety Communication regarding possibly permanent nerve damage on August 15, 2013.[5]

Myasthenia Gravis Exacerbation Warning

Cases of exacerbation of myasthenia gravis were observed in some premarketing clinical trials of fluoroquinolones, as well as postmarketing adverse reactions. An FDA review in 2010 identified serious adverse event cases of myasthenia gravis exacerbation associated with use of all fluoroquinolones, some resulting in a fatal outcome. Biological plausibility for such an effect was supported by in vitro data where fluoroquinolones were able to effectively block neurotransmission across synaptic endplate at clinically achievable concentrations, chemical similarity between the fluoroquinolones and other drugs associated with myasthenia exacerbations (quinine), and their calcium-chelating properties. A Boxed Warning was added to describe potential life-threatening consequences of exacerbation in patients with myasthenia gravis and to advise healthcare providers to avoid use of fluoroquinolones in such patients. The Warnings and Precautions section of the package insert and Medication Guide were also updated accordingly.

QT Prolongation and Torsades de Pointes (TdP) Warning

Drug-associated QT prolongation and TdP has been a topic of interest and research for the past 20-25 years. The propensity of fluoroquinolones to induce QT prolongation became apparent in 1990s, when several of the approved products included warning statements of their pro-arrhythmic potential in the label (sparfloxacin 1996, trovafloxacin and grepafloxacin 1997). In 1999, grepafloxacin became the first antibacterial drug removed from the market because of an increased risk of QT prolongation resulting in TdP. Cautionary statements in the Warnings Section were included in most fluoroquinolone labels. Based on an FDA review, precautionary statements for use in geriatric population were added to the labeling of all marketed fluoroquinolones in 2007. Additional review of the spontaneous reports in 2010-2011 prompted revisions of QT prolongation language to include risk factors for QT prolongation for all fluoroquinolones.

Phototoxicity Warning

The differences in the phototoxic potential among the fluoroquinolones appeared to be related to the differences in C8 substituent in the quinolone ring structure. Despite differences in photosensitizing potential among fluoroquinolones, review of FAERS found that phototoxicity reactions were reported in association with all fluoroquinolones. In 2007, phototoxicity was included in the Warnings and Precautions section.

[5] See the FDA Drug Safety Communication: "FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection", found at http://www.fda.gov/Drugs/DrugSafety/ucm365050 htm

Hypersensitivity Warning

The labels include a list of serious and sometimes fatal hypersensitivity reactions associated with use of fluoroquinolones. The fatal hypersensitivity reactions included in labeling continue to be updated based on review of postmarketing safety information.

b. Epidemiological Review of Specific Adverse Reactions

The Division of Epidemiology II in OSE conducted a literature review of observational epidemiologic studies that assess the absolute or relative risk of adverse reactions associated with fluoroquinolones. There were a large number of studies published in the literature, and we focused only on higher-quality assessments of three serious adverse reactions of interest: tendinitis/tendon rupture, cardiac arrhythmia, and peripheral neuropathy. More detailed information about the approaches to the epidemiological reviews can be found in Appendix E.

Tendinitis/Tendon Rupture

We limited our in-depth review for this briefing document to four studies that included clearly confirmed cases of tendinitis/tendon rupture. All four studies found a positive association between fluoroquinolones and tendinitis/tendon rupture, as shown in Table 1.

Table 1: Association between fluoroquinolones and tendinitis/tendon rupture across four selected studies

Study	Adjusted RR/ OR of tendinitis/tendon rupture	95% confidence interval
Seeger, West, et al, 2006	1.2	0.9-1.7
Wilton, Pearce, et al, 1996 [α]	2.7	0.8-9.5
van der Linden, van de Lie, et al, 1999	2.1	0.8-5.1
van der Linden, Sturkenboom, et al, 2003[α]	11.0	5.8-20.8

OR, odds ratio; RR, rate ratio

[α] Crude relative risk estimates and 95% confidence intervals calculated by the FDA reviewer.

One study (Seeger, West, et al, 2006) found an association of fluoroquinolones with tendinitis/tendon rupture in elderly subjects using corticosteroids, but this was a subgroup analysis of a smaller population and thus led to a wide confidence interval (adjusted odds ratio = 5.8; 95% confidence interval [CI] 0.9-38.6). Another study (van der Linden, Sturkenboom, 2003) restricted the study population to elderly subjects and found a high risk associated with fluoroquinolone use relative to fluoroquinolone-associated risk observed in the other studies, suggesting an increased risk among elderly patients.

One of the most concerning outcomes assessed in the four studies was Achilles tendon rupture, a disabling, serious adverse event sometimes requiring surgery and found in the FAERS data. Because the incidence of Achilles tendon rupture is low, a moderately increased relative risk

among fluoroquinolone users would only result in a small increased absolute risk. That is, among the general population or among users of non-fluoroquinolone antibacterial drugs, the incidence density ranged from 0.5 to 1.0 per 10,000 person-years. In contrast, among fluoroquinolone-exposed persons, the incidence density appears to be increased and ranged from 1.3 to 5.6 per 10K person-years among the four studies.

Cardiac Arrhythmias

We included two studies in the in-depth review (Chou, Wang, et al, 2015; and Rao, Mann, et al, 2014) because they captured both fatal and non-fatal cardiac arrhythmias within the drug-exposure period. It is important to note that this epidemiological review focused on the clinical outcome of cardiac arrhythmia and did not focus on QT interval prolongation itself. The studies did not provide sufficient clinical granularity for us to adequately adjust for confounding due to the indication. The insufficient adjustment for confounding by indication was an important limitation for the cardiac arrhythmia outcome since respiratory tract infections can increase risk of the outcome. Table 2 summarizes the main findings from these two studies.

Table 2: Summary of the main findings on the relative risk of adverse cardiac events associated with fluoroquinolone use

Study	Outcomes	Antibacterial Groups	Incidence rate[β]	Crude OR/HR	Adj. OR/HR
Rao, Mann, et al, 2014	5-day all-cause mortality	Amoxicillin Levofloxacin	15 38	1.00 2.92[α] (2.00-4.26)	1.00 2.49[α] (1.70-3.64)
	5-day serious arrhythmia events	Amoxicillin Levofloxacin	9 28	1.00 2.43[α] (1.56-3.79)	1.00 3.13[α] (2.03-4.84)
Chou, Wang, et al, 2015	7-day serious arrhythmia	Amoxicillin-clavulanate Fluoroquinolones Moxifloxacin Ciprofloxacin Levofloxacin	12 23 57 15 26	1.00 1.97[α] (1.49-2.60) 4.92 [α] (3.13-7.74) 1.27 (0.85-1.89) 2.22[α] (1.49-3.30)	1.00 2.07[α] (1.56-2.76) 3.30[α] (2.07-5.25) 1.07 (0.69-1.66) 1.41 (0.91-2.18)
	7-day cardiovascular death	Amoxicillin-clavulanate Fluoroquinolones Moxifloxacin Ciprofloxacin Levofloxacin	13 24 46 12 39	1.00 1.89[α] (1.45-2.49) 3.60[α] (2.20-5.88) 0.91 (0.59-1.40) 3.04[α] (2.18-4.25)	1.00 1.97[α] (1.49-2.59) 2.31[α] (1.39-3.84) 0.70 (0.44-1.12) 1.77[α] (1.22-2.59)

OR: odds ratio; HR: hazard ratio

[α] $p<0.05$

[β]Unit of Incidence rate was per 100,000 prescriptions in Rao, Mann, et al., 2014 study, and per 100,000 patients in Chou, Wang, et al., 2015 study.

Both studies found an increased risk of serious cardiac arrhythmias associated with fluoroquinolone use. The Rao, Mann, et al., 2014 study found a statistically significant three-fold risk of serious arrhythmias and a 2.5 fold risk of all-cause mortality over five days of levofloxacin use. The Chou, Wang, et al., 2015 study found a statistically significant two-fold

risk of serious cardiac arrhythmias or cardiovascular mortality over seven days of fluoroquinolone use (together including moxifloxacin, levofloxacin, and ciprofloxacin). Although these two studies showed a statistically significant increased risk, the absolute risks of serious cardiac arrhythmias associated with fluoroquinolone use show that these adverse reactions are infrequent and ranged from15 to 57 per 100,000 users of fluoroquinolones. However, this should be compared to absolute risk of 9-12 per 100,000 users of amoxicillin or amoxicillin-clavulanate. Fluoroquinolone users with underlying cardiovascular disease appeared to have a higher baseline risk for serious cardiac arrhythmias than those without cardiovascular disease. The absolute risk of serious cardiac arrhythmias ranged from 46-85 per 100,000 users with cardiovascular diseases versus 5-44 per 100,000 users without cardiovascular diseases.

Of note, the Rao and Chou studies were previously reviewed by DEPI in an earlier examination of arrhythmia and mortality with use of azithromycin. The reviewer, Dr. Mosholder, recommended moving the existing warning for QT prolongation to the boxed warning section in the fluoroquinolone labels. However, Dr. Mosholder's recommendation arose as an incidental finding, and he had not conducted a systematic review of the fluoroquinolone literature. Dr. Staffa, The Director of DEPI-II, determined that a complete review of the fluoroquinolone literature was warranted prior to recommending a boxed warning for the fluoroquinolone products, and wrote a memo recommending further study of the issue and discussion of Dr. Chen's review at this advisory committee meeting. We provide both Dr. Mosholder's review and Dr. Staffa's memo in Appendix F.

Peripheral Neuropathy

An observational analytic epidemiologic study of fluoroquinolones and peripheral neuropathy was found to contain sufficient information for the in-depth review (Etminan, Brophy, et al, 2014). The authors report a statistically significant two-fold risk (absolute RR = 2.07; 95% CI 1.56-2.74) of peripheral neuropathy with current new use (within the past 14 days) compared to no use of fluoroquinolones in a nested case-control study of older males. The results from this study are limited because of insufficient adjustment for confounders, lack of outcome validation, narrow patient population of older males, and lack of sample size justification.

Summary of Epidemiological Review

A review of higher-quality epidemiological studies published in the literature showed an increased relative risk for the adverse reactions of tendinitis/tendon rupture, cardiac arrhythmias, and peripheral neuropathy among users of fluoroquinolones. We found that the incidence of tendinitis/tendon rupture among fluoroquinolone-exposed persons ranged from 1.3 to 5.6 per 10,000 person-years and the incidence of cardiac arrhythmias ranged between 15-57 per 100,000 patients exposed to fluoroquinolones. Both adverse events are infrequent but appeared to be higher in comparison to unexposed persons or persons exposed to a different antibacterial drug. There appears to be a two-fold increase in the incidence of peripheral neuropathy, but the incidence rate is also likely to be similarly infrequent.

c. FDA Adverse Event Reporting System Review

A review of the FDA Adverse Event Reporting System (FAERS) was performed to characterize a constellation of symptoms leading to disability that had been observed during FDA monitoring of fluoroquinolone safety reports. This constellation of symptoms will be referred to in this review as "fluoroquinolone-associated disability" (FQAD). While most of the individual AEs that exist within FQAD are currently described in fluoroquinolone labeling, the particular constellation of symptoms across organ systems is not. Individuals with FQAD were defined as U.S. patients who were reported to be previously healthy and prescribed an oral fluoroquinolone antibacterial drug for the treatment of uncomplicated sinusitis, bronchitis, or urinary tract infection (UTI). To qualify, individuals had to have AEs reported in two or more of the following body systems: peripheral nervous system, neuropsychiatric, musculoskeletal, senses, cardiovascular, and skin. These body systems were chosen as they had been observed to be frequently involved with the fluoroquinolone reports describing disability. In addition, the AEs had to have been reported to last 30 days or longer after stopping the fluoroquinolone, and had to have a reported outcome of disability.

The regulatory definition of disability was used for this review, i.e., "a substantial disruption of a person's ability to conduct normal life functions," (21 CFR 314.80: Postmarketing reporting of adverse drug experiences). Whether a case report met a legal definition of disability was not a consideration for this review, and FQAD should not be construed to represent a legal definition of disability. A "healthy patient" was defined as a person able to perform all of the usual activities of daily living without significant restrictions prior to taking the fluoroquinolone. Patients were included if they had controlled disease states, such as hypertension, hypothyroidism, or hyperlipidemia.

The FAERS database was searched with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Date of search	May 30, 2015
Time period of search	November 1, 1997† – May 30, 2015
Product Terms	Avelox (moxifloxacin), Cipro, Cipro XR, Proquin XR (ciprofloxacin), Factive (gemifloxacin), Levaquin (levofloxacin), Floxin (ofloxacin)
Indication	Sinusitis acute, Sinusitis bacterial, Sinusitis Bronchitis acute, Bronchitis, Bronchitis bacterial Cystitis, Acute cystitis, Cystitis bacterial Urinary tract infection, UTI-urinary tract infection, Urinary tract infection bacterial
MedDRA Search Terms	All PT terms searched
Other Criteria	US cases only Outcome: Disability only Oral dosage forms
* See Appendix G for a description of the FAERS database. † Date that AERS database went online.	

FAERS reports were excluded if they met any of the following criteria:

1. Events reported to have resolved within 30 days of stopping the fluoroquinolone.

2. Adverse events reported from only one or none of the following body systems: Peripheral Nervous System; Musculoskeletal; Neuropsychiatric; Senses (vision, hearing, etc.); Cardiovascular; or Dermatology.

3. Reported to be diagnosed with an indication other than uncomplicated acute bacterial sinusitis, bronchitis, or UTI.

4. Patient with a reported pre-existing medical history or taking medications that could confound the case. Examples include disease states such as fibromyalgia, rheumatoid arthritis, lupus, history of long-term steroid use, diabetes with complications, Lyme disease, multiple sclerosis, renal or hepatic impairment, cancer chemotherapy, HIV, joint replacement, or organ transplant.

5. Duplicate reports.

6. If more than one fluoroquinolone was described in the report, the case was selected for the fluoroquinolone most recently taken or being taken when the disability occurred (i.e., cases were not included twice).

7. Not enough information to properly evaluate the report.

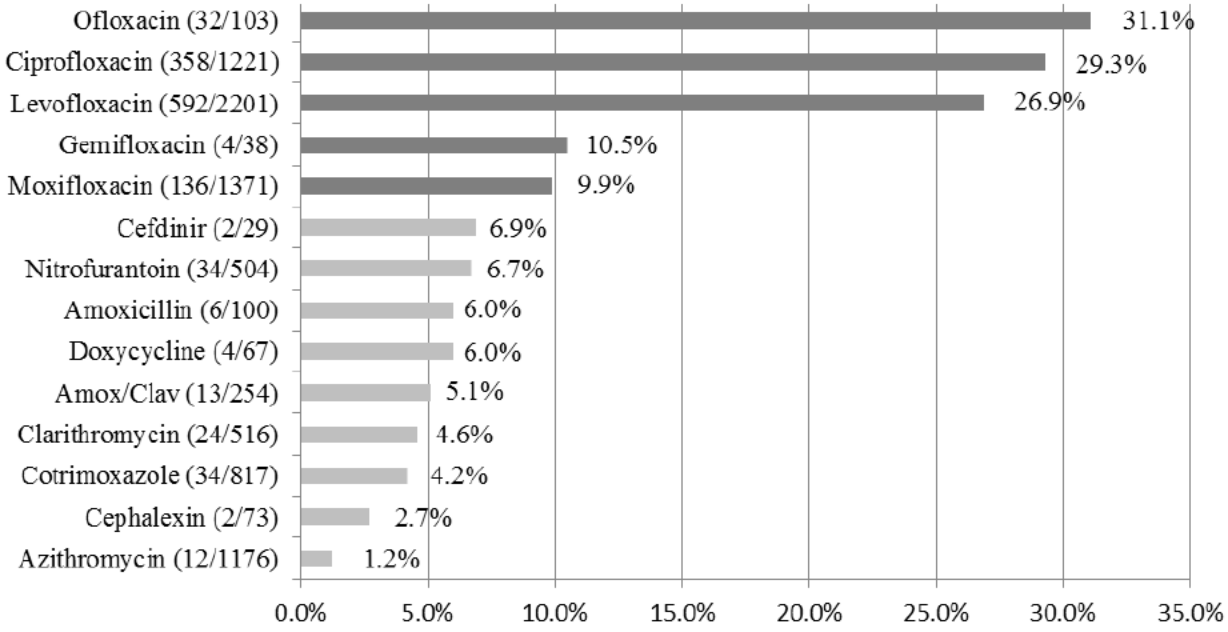
The FAERS search retrieved a total of 1,122 reports. Table 4 shows the number of disability reports for each fluoroquinolone in US patients who were being treated for the indications of uncomplicated sinusitis, bronchitis, or UTI.

Table 4: Number of Disability Reports in FAERS in US Patients Orally Treated for the Indication of Uncomplicated Cases of Sinusitis, Bronchitis, and/or UTI	
Fluoroquinolone	**Number of Reports***
Levofloxacin	592
Ciprofloxacin	358
Moxifloxacin	136
Ofloxacin	32
Gemifloxacin	4
TOTAL	1,122

* The numbers of reports listed are crude counts that may include duplicate reports.

The numbers of reports listed are crude counts that may include duplicate reports, and are presented without regard to causality assessment. The percentage of disability reports among all serious reports for each fluoroquinolone was also calculated (Figure 6). This was then compared to 9 other antibacterial drugs that have been, or are being used, for the treatment of these three uncomplicated infections. The search criteria for the other 9 antibacterial drugs were the same as for the fluoroquinolones.

Figure 6: Percentage of Disability Reports* Among all Serious Reports During Use for Uncomplicated Sinusitis, Bronchitis, and UTI (Oral and US only)

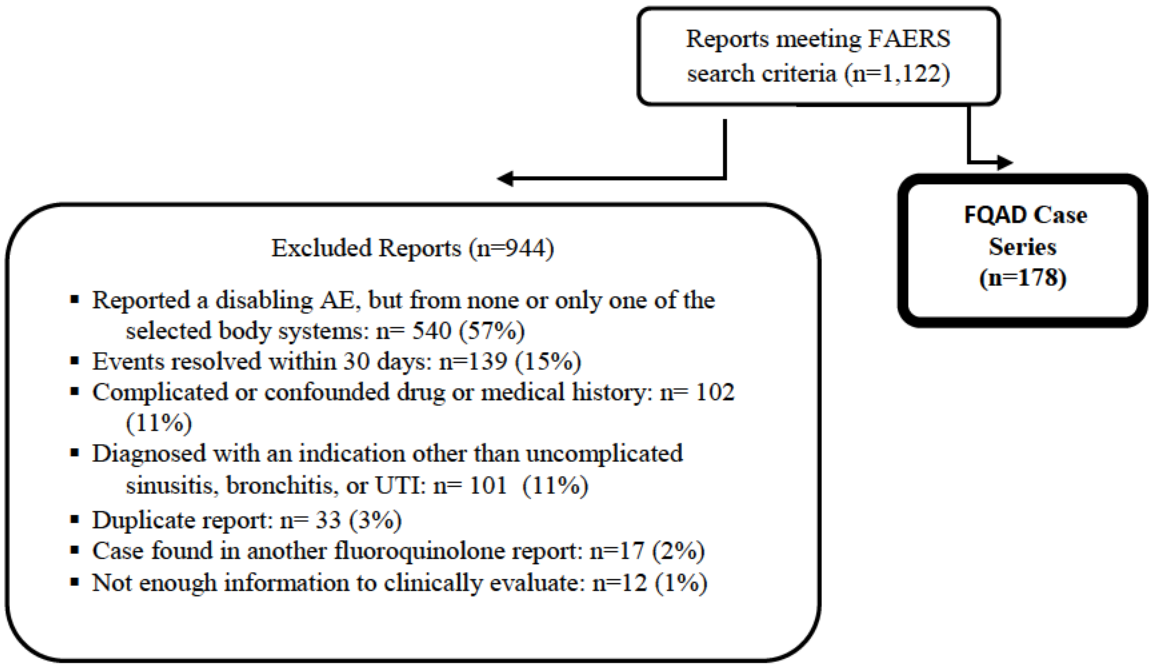


*Number of reports reporting disability divided by the total number of serious adverse event reports for oral dosage forms, from November 1, 1997 to May 30, 2015

Compared with the other 9 antibacterial drugs, all 5 fluoroquinolones had the highest percentages of disability reports for these uncomplicated infections, ranging from 9.9% to 31.1%.

After reviewing each of the 1,222 individual reports and applying the exclusion criteria described above, 178 cases were included in this case series of FQAD (Figure 7). See Appendix J for the FAERS case report information.

Figure 7: FAERS Case Selection



A majority of the reports that were excluded (57%) were patients who did not report an AE from two or more of the selected body systems. These reports, a total of 540, still described a disabling outcome, such as peripheral neuropathy or tendon rupture.

The percentage of FQAD cases identified among the total disability reports for each fluoroquinolone was similar (Table 5).

Table 5: US Disability Reports associated with Oral Fluoroquinolones and FQAD Cases			
	Total Disability Reports	**Total FQAD Cases**	**Percentage of Reports**
Levofloxacin	592	91	15%
Ciprofloxacin	358	65	18%
Moxifloxacin	136	19	15%
Ofloxacin	32	2	--*
Gemifloxacin	4	1	--*
TOTAL	1,122 reports	178 cases	

*Ofloxacin and gemifloxacin had too few cases for evaluation so a percentage is not calculated.

Although comparing reports to cases is not equivalent because reports in Table 5 were not de-duplicated, these data still provide a general idea of the percentages of FQAD among all disability reports.

Table 6 summarizes descriptive characteristics of the 178 FAERS cases of FQAD reported with all 5 currently marketed oral fluoroquinolones in the U.S.

Table 6: Descriptive Characteristics of FQAD Cases Reported to FDA from November 1, 1997-May 30, 2015 (n=178)		
Age (n=173)	Mean: 48.1 years Median: 48 years Range: 13-84 years	0-29 years: n=15 (9%) 30-59 years: n= 128 (74%) ≥ 60 years: n=30 (17%)
Report type	Direct: 152 (85%) Expedited: 18 (10%) Non-expedited: 8 (5%)	
Sex	All cases (n=178) Female: 138 (78%) Male: 40 (22%)	Non-UTI cases (n=93): Female: 74% Male: 26%
Reported Indication for FLUOROQUINOLONE Therapy	Cystitis/UTI—84 (47%) Sinusitis—59 (33%) Bronchitis—26 (15%) Sinusitis/bronchitis—7 (4%) Bronchitis/UTI—1 (<1%) Sinusitis/bronchitis/UTI—1 (<1%)	
Onset of AEs from start of FLUOROQUINOLONE therapy (n=102)	Mean: 5.4 days Median: 3 days Range: 1 hour-3 months Onset 1-2 days of starting FLUOROQUINOLONE: n=49 (48%) Onset 3-4 days of starting FLUOROQUINOLONE: n=20 (20%) Onset 5-10 days of starting FLUOROQUINOLONE: n=21 (20%) Onset >10 days of starting FLUOROQUINOLONE: n=12 (12%)	
Duration of AEs *at the time the report was sent to the FDA* (n=166)	Mean: 61.2 weeks (14 months) Median: 30 weeks (7 months) Range: 30 days—9 years ≥ 1 year: n=39 (23%)	

The mean and median age for the patients in this case series were 48.1 and 48 years, respectively. Although there was a wide range in age, from 13 to 84 years, nearly three-quarters of the cases (74%) occurred in patients 30-59 years of age.

There were also two characteristics of this case series that stood out. The first was that 85% of the cases were direct reports to FDA from the public, which is an unusually high number. Over the past 10 years, the percentage of direct reports overall in FAERS has ranged from 2.4 to 6.3%.

The other characteristic was that 78% of the patients were female. Even when all UTI cases were removed (approximately 80% of the UTI cases were in women), 74% of the cases still occurred in women. Of note, 59% of FAERS reports for ciprofloxacin, levofloxacin, and moxifloxacin for all indications were for female patients. Assuming that a clinical entity such as FQAD exists, it is unclear whether women may be at increased risk, if they are more likely to submit a report, or if there may be another unidentified reason. The drug use data sheds some light on this imbalance

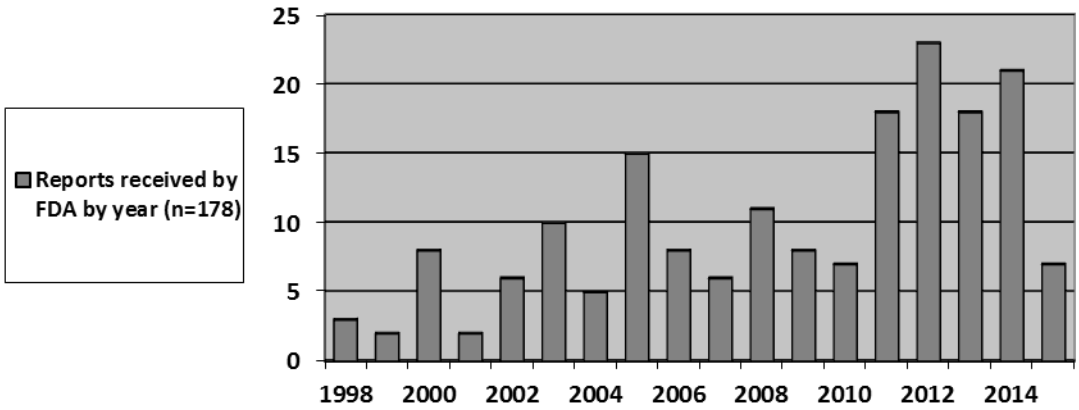
because women were more likely to be offered a prescription for a fluoroquinolone (see section IV on drug utilization patterns).

The mean and median time to onset of adverse events was 5.4 days and 3 days, respectively. However, the range was very wide, from 1 hour after taking the first dose to 90 days after the drug was discontinued. In almost half of the cases (48%), the onset was rapid, occurring after one or two doses of the drug. In 12% of the cases, the onset occurred more than 10 days after starting the fluoroquinolone, which in most cases would have been after fluoroquinolone therapy had ended.

The duration of the disabling adverse events was defined as the ongoing duration at the time the report was sent to FDA. The mean was 61.2 weeks (14 months), and the longest duration reported was 9 years after the events started. The actual duration cannot be determined without regular follow-up over a period of years, and it is possible that some symptoms may become permanent.

Figure 8 shows the years that FDA received the FQAD cases. Most notable is the increase in reporting over the last 5 years. Drug use data does not show an overall increase in fluoroquinolone prescribing over the same time period. This increase may be related to a general increase in reporting to FAERS or a focused effort by patients to report these AEs to the FDA. In addition, there was no U.S. geographic clustering of the cases.

Figure 8: FQAD Cases Received by Year from Nov 1, 1997 to May 30, 2015



For inclusion in this case series, each of the 178 cases had to have an AE in two or more of six body systems. Musculoskeletal events, which included tendon, joint, and/or muscle, were reported in 97% of the cases. This was followed by neuropsychiatric events in 68%, and

peripheral nervous system events in 63% (Table 8). These 3 body system events were reported much more frequently than the other 3 included body systems (senses, skin, and cardiovascular). The most commonly reported symptom across almost all cases was pain. Of note, if patients reported that their ongoing pain was causing insomnia, depression, or some other secondary AE, those secondary AEs were not included.

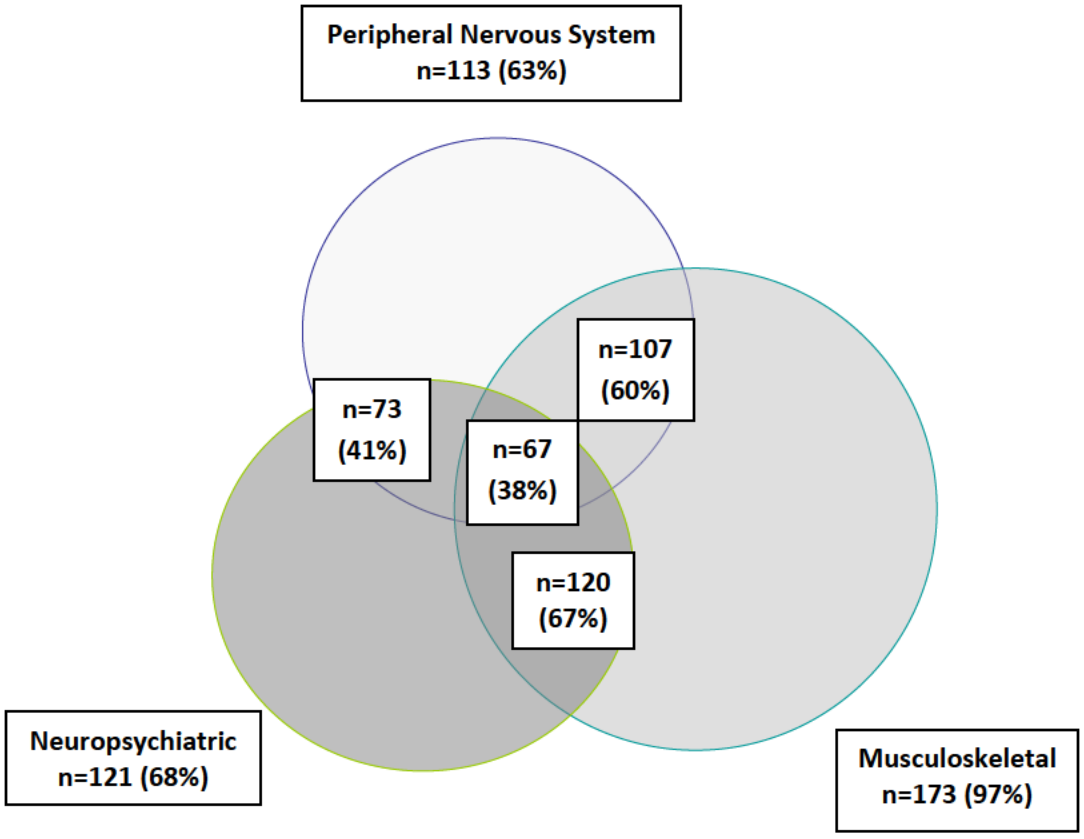
Table 8: Body Systems in FQAD Cases

Organ System	**Percentage of Cases Involved** (n = 178)
• Musculoskeletal (tendon/joint/muscle):	97%
• Neuropsychiatric:	68%
• Peripheral Nervous System:	63%
• Senses (vision, hearing, etc.):	32%
• Skin:	15%
• Cardiovascular:	12%

Most of the specific AE terms found in the FAERS database are already included in the labels for all fluoroquinolones.

Figure 10 is a Venn diagram showing the number of cases in the three body systems that had the highest number of reports (musculoskeletal, peripheral nervous system, and neuropsychiatric), as well as the overlap among these body systems.

Figure 10: Venn Diagram of FQAD Cases that Reported an Adverse Event from One of the Top 3 Body Systems (n=178)



There was considerable overlap among these three groups. Forty-one percent of patients who had a neuropsychiatric AE also experienced an AE from the peripheral nervous system; 60% of patients had AEs from both the musculoskeletal and peripheral nervous system; and 67% had both neuropsychiatric and musculoskeletal AEs. In addition, 38% of patients had AEs from all 3 body systems.

In Table 9, the percentage of AE cases that occurred with each individual fluoroquinolone was calculated by body system.

Table 9: Percentage of Adverse Events Cases for Each Fluoroquinolone by Body System

	Musculo-skeletal	Peripheral Nervous System	Neuropsychiatric	Senses	Cardio-vascular	Skin
Levofloxacin (n=91)	98%	52%	74%	30%	10%	10%
Ciprofloxacin (n=65)	94%	78%	66%	31%	12%	15%
Moxifloxacin (n=19)	95%	79%	65%	30%	10%	15%
Ofloxacin* (n=2)	--	--	--	--	--	--
Gemifloxacin* (n=1)	--	--	--	--	--	--

*Ofloxacin and gemifloxacin had too few cases for evaluation so a percentage is not calculated.

Overall, the musculoskeletal system was most commonly involved, followed by the peripheral nervous system and neuropsychiatric system.

The following direct report was illustrative of the case series:

Case #5699626, Direct report, 2004

This patient received a 10-day supply of levofloxacin 500 mg to treat a sinus infection. The onset of adverse reactions occurred 2 days after starting the drug.

"Prior to taking this drug, I was a healthy 49-year old, an advanced downhill skier, with NO medical problems. I could barely walk, had to crawl up my staircase. I had severe muscle weakness, muscle burning and joint pain in all my limbs…I ached and burned in what seemed every tendon and muscle in my body…I continue to suffer 22 months later with the following disabling conditions: Severe tendon/muscle pain and tightness, tendinitis, tingling, numbness, prickling, pins and needles sensations in my extremities. Electrical sensations. Feeling of worms crawling under my skin. Severe arm and leg weakness. Muscle twitching, spasms and contractions. Severe muscle tenderness. To poke my muscles feels like a bee sting! Inability to sleep due to pain 24 hours per day, 7 days per week. Inability to work due to pain and weakness. Difficulty thinking clearly, confusion. Chronic fatigue."

This FAERS review identified 178 previously healthy patients who took an oral fluoroquinolone for the treatment of uncomplicated sinusitis, bronchitis, or UTI, and developed FQAD. Although a wide age range was reported, the majority of cases (74%) were in patients 30 to 59 years of age. Quite a few reporters described how seriously the disability impacted their lives, including losing jobs, the resulting lack of health insurance, large medical bills, financial problems, and family tension or dissolution. In addition, the Boxed Warning states that fluoroquinolones "…are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age." In this case series, which included cases of tendon rupture, only 17% of patients were found to be 60 years of age or older.

The mean duration of the disabling adverse events at the time of the reports was 14 months, and the longest duration reported was 9 years. Several cases reported that selected adverse events either resolved or improved, but these cases also reported events that got worse or continued unchanged. It is possible that the symptoms may be permanent in patients who continue to have symptoms years after stopping the drug.

Long-term pain (of any kind) was the most commonly reported symptom across almost all cases, which is not surprising with 97% of all cases reporting one or more musculoskeletal (tendon/joint/muscle) symptoms. The impact of the neuropsychiatric events in these cases was also compelling. The ongoing AEs were reported to be quite distressing and affected employment and quality of life.

A potential limitation of this review is that the patient population in this case series was narrow in scope. These were patients who reported being previously healthy and were being treated for uncomplicated infections that developed FQAD. Other reports with patients who were being treated for more serious infections, had a pre-existing confounding medical history, or who were taking concomitant medications that could cause additive or synergistic AEs, were excluded from the definition of FQAD. Another limitation is that we are currently unaware of a plausible biological mechanism that could explain the pattern of involvement of multiple organ systems that were observed during this review. A final limitation is that all cases described as UTI were included in this case series. The focus on oral antibacterial drug use likely restricted cases to uUTI, but we acknowledge that oral fluoroquinolones may be used for the treatment of complicated UTI.

In conclusion, we find an association between oral fluoroquinolone use in previously healthy U.S. patients being treated for uncomplicated cases of sinusitis, bronchitis, or UTI, and the development of FQAD. While the individual components are included in fluoroquinolone labels, a description of the constellation of disabling adverse events is not currently described in the fluoroquinolone labels.

IV. DRUG UTILIZATION PATTERNS FOR ORAL FLUOROQUINOLONES

Proprietary drug utilization databases available to the Agency were used to conduct drug utilization analyses of the selected systemic oral fluoroquinolones (see Appendix H for full database descriptions and limitations).

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for the oral forms of ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin. Sales data for 2014 indicated that approximately 82% of oral ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin bottles were distributed to outpatient retail pharmacy settings, followed by 17% to non-retail pharmacy settings, and 1% to mail-order/specialty pharmacies.[6] As a result of these distribution patterns and the nature of the questions being addressed, only U.S. outpatient retail pharmacy utilization data were analyzed. Data from mail-order/specialty and non-retail settings, including inpatient hospitals, were not included in this analysis.

The IMS, National Prescription Audit™ (NPA) database was used to provide the nationally estimated number of prescriptions for oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin) dispensed from outpatient retail pharmacy settings in the U.S., from 2010 through 2014. The database was also used to obtain prescriber specialty data for the selected oral fluoroquinolones for 2014.

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide the nationally estimated number patients receiving dispensed prescriptions for oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin) from outpatient retail pharmacies in the U.S., from 2010 through 2014, stratified by patient age and sex.

The Encuity Treatment Answers™ with Pain Panel was used to provide the most common diagnoses mentioned during visits to office-based physicians, associated with the use of ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gemifloxacin for 2010 and 2014. This U.S. office-based physician survey database was also used to provide the most common drugs mentioned to be associated with selected ICD9 codes for possible acute sinusitis, ABECB, and uUTI, stratified by molecule, for 2010 and 2014. Acute sinusitis was broadly captured using ICD9 461.x. Possible ABECB was broadly defined using ICD9 codes for COPD with exacerbation [ICD9: 49121.2]; obstructive chronic bronchitis with exacerbation [ICD9: 49121.0]; and obstructive chronic bronchitis with acute bronchitis [ICD9: 49122.0]; and possible uUTI were broadly defined using the ICD9 codes for acute cystitis [ICD9: 59500.0]; cystitis NEC [ICD9: 59589.0]; cystitis NOS [ICD9: 59590.0]; and urinary tract infection NOS [ICD9: 59900.0]).

Drug Utilization Results

The results of the IMS NPA database showed that during each year approximately 32 million to 33 million total prescriptions for oral fluoroquinolone products were dispensed from outpatient

[6] IMS Health National Sales Perspective (NSP), Y2014, Extracted AUG2015, Source File: NSP_2015-896 FQ AC 2014

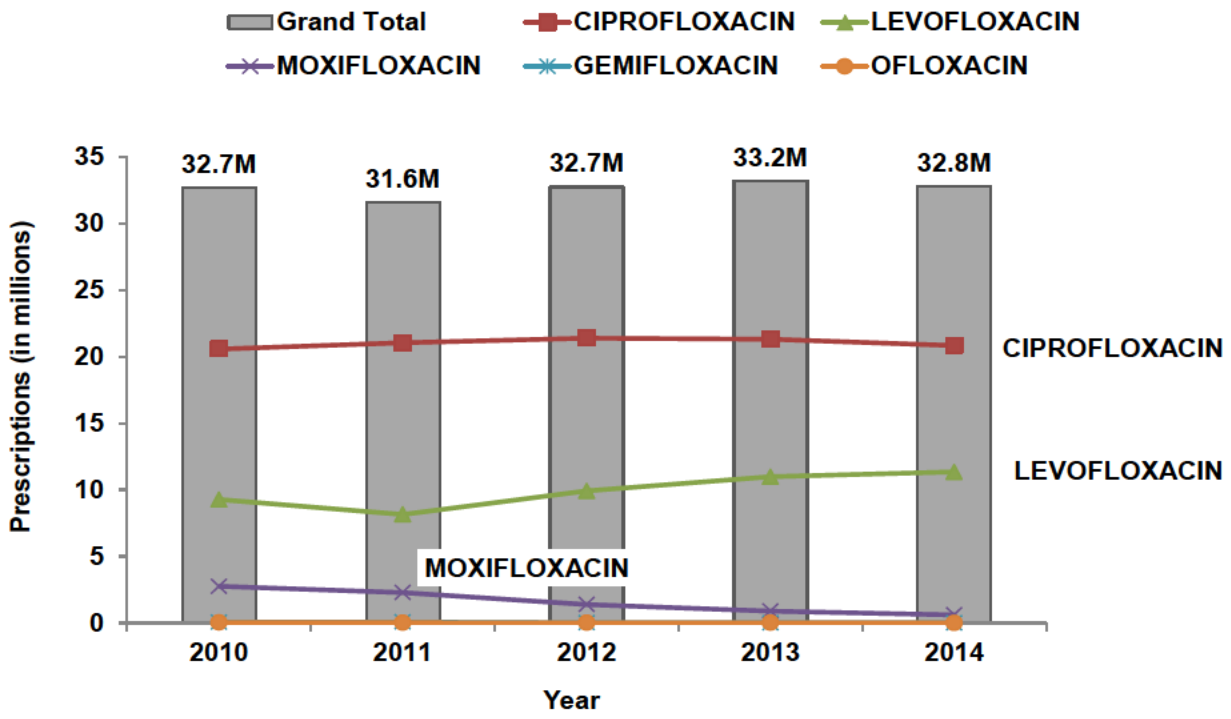
retail pharmacies in the U.S. Ciprofloxacin accounted for the majority of dispensed prescriptions each year with 63% to 66% of the total (approximately 21 million prescriptions) dispensed each year. Levofloxacin prescriptions dispensed increased from 9.3 million in 2010 to 11.3 million in 2014. The number of moxifloxacin prescriptions dispensed decreased by 78% from 2.7 million prescriptions in 2010 to 609,000 prescriptions in 2014. Gemifloxacin prescriptions dispensed decreased by 90% from 64,000 prescriptions in 2010 to 6,700 prescriptions in 2014. Ofloxacin prescriptions dispensed decreased by 74% from 37,000 prescriptions in 2010 to 9,500 prescriptions in 2014. Table 10 and Figure 11 show the number of dispensed oral fluoroquinolones from the years 2010 through 2014.

Table 10: Nationally estimated number of prescriptions for oral forms of selected fluoroquinolones dispensed from outpatient retail pharmacies in the U.S., stratified by molecule, from 2010 through 2014

	2010		2011		2012		2013		2014	
	TRx (N)	*Share%*	TRx (N)	*Share%*	TRx (N)	*Share%*	TRx (N)	*Share%*	TRx (N)	*Share%*
Total Prescriptions	32,666,213	*100%*	31,567,306	*100%*	32,712,846	*100%*	33,177,263	*100%*	32,768,680	*100%*
CIPROFLOXACIN	20,555,284	*62.9%*	21,033,382	*66.6%*	21,380,631	*65.4%*	21,286,243	*64.2%*	20,812,217	*63.5%*
LEVOFLOXACIN	9,263,006	*28.4%*	8,149,894	*25.8%*	9,903,630	*30.3%*	10,970,182	*33.1%*	11,331,292	*34.6%*
MOXIFLOXACIN	2,746,720	*8.4%*	2,282,053	*7.2%*	1,386,744	*4.2%*	893,422	*2.7%*	608,903	*1.9%*
GEMIFLOXACIN	64,307	*0.2%*	73,696	*0.2%*	22,869	*0.1%*	12,300	*0.0%*	6,733	*0.0%*
OFLOXACIN	36,896	*0.1%*	28,281	*0.1%*	18,972	*0.1%*	15,116	*0.1%*	9,535	*0.0%*

Source: IMS Health, National Prescription Audit (NPA), Y2010-2014, Extracted AUG2014

Figure 11: Nationally estimated number of prescriptions for oral forms of selected fluoroquinolones dispensed from U.S. outpatient retail pharmacies, stratified by drug, from 2010 through 2014



Source: IMS Health, National Prescription Audit (NPA), Y2010-2014, Extracted AUG2014

Of the estimated 33 million oral fluoroquinolone prescriptions dispensed in 2014, family practice was the top prescriber specialty with 20% (6.7 million prescriptions) of the total, followed by internal medicine with 19% (6.3 million prescriptions) and nurse practitioner with 10% (3.2 million prescriptions). Table 11 outlines the prescriber specialties from these data.

Table 11: Nationally estimated number of prescriptions dispensed for the oral forms of selected fluoroquinolones, stratified by prescriber specialties, from outpatient retail pharmacies in the U.S. in 2014

	TRx (N)	*Share %*
Grand Total	**32,768,680**	***100.0%***
Family Practice	6,706,881	*20.5%*
Internal Medicine	6,287,868	*19.2%*
Nurse Practitioner	3,209,545	*9.8%*
Osteopathic Medicine	3,172,033	*9.7%*
Physician Assistant	2,676,992	*8.2%*
Urology	2,186,872	*6.7%*
Emergency Medicine	1,685,179	*5.1%*
Specialty Unspecified	770,250	*2.4%*
Obstetrics/Gynecology	768,209	*2.3%*
General Surgery	487,293	*1.5%*
All Other Specialties	4,817,558	*14.7%*

Source: IMS Health National Prescription Audit (NPA), 2014, Extracted AUG 2014, Source File: NPA 2015-896 FQ AC 2014 by prescriber.xls

Next we describe the nationally estimated number of patients who received prescriptions for selected oral fluoroquinolones from U.S. outpatient retail pharmacies, stratified by the oral fluoroquinolone, from 2010 through 2014. The total number of patients who received a prescription for an oral fluoroquinolone remained stable with approximately 23 million patients in 2010 and 22 million patients in 2014. Unique patients who received ciprofloxacin dispensed prescription accounted for 64% (15 million patients) of the total patients in 2010, increasing slightly to 68% (15 million patients) of total patients in 2014. Unique patients who received levofloxacin dispensed prescription accounted for 33% of the total in 2010 (7.7 million patients) and increased slightly to 36% (8 million patients) of the total in 2014. Conversely, the number of unique patients who received a dispensed prescription for moxifloxacin, gemifloxacin, and ofloxacin declined overall from 2010 through 2014. Approximately 2.3 million unique patients received a dispensed prescription for moxifloxacin in 2010, decreasing to 479,000 patients in 2014. Unique patients who received a dispensed prescription for gemifloxacin increased slightly from 53,000 patients in 2010 to 62,000 patients in 2011, followed by a sharp decline to 4,900 patients in 2014. Unique patients who received dispensed prescription for ofloxacin declined steadily from 26,000 patients in 2010 to 6,000 patients in 2014.

In 2014, of the approximately 22 million unique patients who received a dispensed prescription for a selected oral fluoroquinolone, adult patients aged 18 years and older accounted for 98% of the total, while pediatric patients aged 0-17 years accounted for approximately 2% of the total patients. Female patients accounted for 65% of the total patients who received a dispensed prescription for oral fluoroquinolone in 2014. This is described in Table 12.

Table 12: Nationally estimated number of patients who received a dispensed prescription for a selected oral fluoroquinolone* from outpatient retail pharmacy in the U.S., stratified by patient age and sex, for year 2014

	Year 2014										
	Total Patients (N)	*Share %*	Male Patients (N)	*Vert Share %*	*Horiz Share %*	Female Patients (N)	*Vert Share %*	*Horiz Share %*	Unspecified Sex	*Vert Share %*	*Horiz Share %*
Total Patients	22,235,393	*100%*	7,739,277	*100%*	*34.8%*	14,469,902	*100%*	*65.1%*	26,501	*100%*	*0.1%*
0-17 years	379,773	*1 7%*	143,050	*1 8%*	*37.7%*	233,936	*1.6%*	*61.6%*	2,386	*9.0%*	*0.6%*
18+ years	21,801,950	*98.1%*	7,576,728	*97.9%*	*34.8%*	14,201,554	*98.1%*	*65.1%*	24,014	*90.6%*	*0.1%*
Unknown Age	82,949	*0.4%*	28,236	*0.4%*	*34.0%*	54,671	*0.4%*	*65.9%*	55	*0 2%*	*0.1%*

Unique patient counts may not be added across patient age subtotals due to patients aging during the study. Patients may be counted more than once in the individual age categories. Therefore, summing across patient age bands is not advisable and may result in overestimates of patient counts.
Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients 0-17 years of age include patients 17 years and 11 months
Source: IMS Health, Vector One® : Total Patient Tracker (TPT), Y2014, Extracted AUG2015, Source File: TPT 2015-896 FQ AC age sex 2014 AUG2015

We also evaluated the top diagnoses associated with the selected oral fluoroquinolones based on U.S. office-based physician surveys, stratified by molecule and ICD9 code (DX4), for 2010 and 2014. For 2010 and 2014, ciprofloxacin was the most commonly mentioned fluoroquinolone, followed by levofloxacin, moxifloxacin, gemifloxacin, and ofloxacin.

Urinary tract infection, not otherwise specified (ICD9 code 599.0) was the most common diagnosis associated with ciprofloxacin for each year, with 43% of drug use mentions[7] in 2014. Pneumonia, organism not otherwise specified (ICD9 code 486.0) was the top diagnosis associated with levofloxacin for each year with 17% of drug use mentions in 2010 and 22% in 2014. Chronic sinusitis, not otherwise specified (ICD9 473.9) was the top diagnosis associated with moxifloxacin with 21% of drug use mentions in 2010, whereas bronchitis, not otherwise specified (ICD9 code 499.0) was the top diagnosis in 2014, accounting for 22% of drug use mentions. Bronchitis, not otherwise specified (ICD9 490.0) was the top diagnosis associated with gemifloxacin with 49% of drug use mentions in 2010, whereas acute bronchitis (ICD9 466.0) was the top diagnosis in 2014, accounting for 90% of drug use mentions. Urinary tract infection, not otherwise specified (ICD9 code 599.0) was the most common diagnosis associated with ofloxacin for each year; however, the number of drug use mentions was too low to provide reliable national estimates. See Appendix I for data table.

The following Tables 13 through 18 show the drug use mentions with the respective ICD9 codes for ABS, AEBCB-COPD and uUTI.

[7] The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Tables 13 & 14: ABS: Top systemic antibiotics (oral forms only) by number of drug use mentions associated with acute sinusitis code ICD9 461.x, stratified by drug, as reported by U.S. office-based physician surveys for years 2010 and 2014

Table 13

2010	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	**5,199**	***100.0%***	**4,859 - 5,539**
amoxicillin/clav	1,223	*23.5%*	1,058 - 1,388
amoxicillin	1,015	*19.5%*	864 - 1,165
azithromycin	914	*17.6%*	771 - 1,057
cefdinir	569	*10.9%*	456 - 681
levofloxacin	393	*7.6%*	299 - 486
moxifloxacin	255	*4.9%*	179 - 330
cefuroxime	251	*4.8%*	176 - 326
sulfamethoxazole/tmp	129	*2.5%*	76 - 183
doxycycline	113	*2.2%*	63 - 163
clarithromycin	107	*2.1%*	58 - 155
cephalexin	72	*1.4%*	32 - 112
cefprozil	68	*1.3%*	29 - 107
gemifloxacin	30	*0.6%*	4 - 55
erythromycin	20	*0.4%*	< 0.5 - 41
cefuroxime	20	*0.4%*	< 0.5 - 41
All Others	21	*0.4%*	< 0.5 - 43

Table 14

2014	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	**8,884**	***100.0%***	**8,412 - 9,356**
amoxicillin/clav	2,515	*28.3%*	2,264 - 2,766
amoxicillin	2,274	*25.6%*	2,035 - 2,512
azithromycin	1,784	*20.1%*	1,573 - 1,996
levofloxacin	551	*6.2%*	434 - 669
cefdinir	545	*6.1%*	428 - 662
sulfamethoxazole/tmp	314	*3.5%*	225 - 402
moxifloxacin	244	*2.7%*	166 - 322
cephalexin	163	*1.8%*	99 - 226
cefuroxime	117	*1.3%*	63 - 171
clarithromycin	116	*1.3%*	62 - 170
cefixime	99	*1.1%*	49 - 149
cefprozil	52	*0.6%*	16 - 88
doxycycline	47	*0.5%*	13 - 82
cefuroxime	47	*0.5%*	13 - 81
penicillin	16	*0.2%*	0 - 36

Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015

Tables 15 & 16: ABECB-COPD: Top systemic antibiotics (oral forms only) by number of drug use mentions associated with broadly defined acute bacterial exacerbation of chronic bronchitis (ABECB)* as reported by U.S. office-based physician surveys, stratified by drug, for years 2010 and 2014

Table 15

2010	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	**510**	***100%***	**403 - 617**
levofloxacin	158	*30.9%*	98 - 217
moxifloxacin	136	*26.7%*	81 - 191
doxycycline	94	*18.5%*	48 - 140
azithromycin	71	*14.0%*	31 - 111
clarithromycin	12	*2.5%*	< 0.5 - 29
tetracycline	12	*2.3%*	< 0.5 - 28
ciprofloxacin	9	*1.8%*	< 0.5 - 23
amoxicillin	6	*1.2%*	< 0.5 - 18
amoxicillin/clav	6	*1.2%*	< 0.5 - 18
cefuroxime	5	*1.0%*	< 0.5 - 16

Table 16

2014	Uses (000)	*Share %*	95% C.I. (000)
Systemic Antibiotics	**594**	***100%***	**472 - 716**
azithromycin	162	*27.3%*	98 - 226
levofloxacin	138	*23.3%*	79 - 197
doxycycline	98	*16.6%*	49 - 148
amoxicillin/clav	43	*7.2%*	10 - 75
ciprofloxacin	39	*6.6%*	8 - 70
moxifloxacin	39	*6.6%*	8 - 70
cefuroxime	35	*5.9%*	5 - 64
amoxicillin	20	*3.4%*	< 0.5 - 42
clarithromycin	13	*2.1%*	< 0.5 - 30
amoxicillin	7	*1.2%*	< 0.5 - 20

**ABECB definition was expanded to include COPD with exacerbation (ICD9: 49121.2), obstructive chronic bronchitis with exacerbation*
(ICD9: 49121.0), and obstructive chronic bronchitis with acute bronchitis (ICD9: 49122.0)
Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015

Tables 17 & 18: uUTI: Top drug molecules (oral forms only) by number of drug use mentions associated with broadly defined uncomplicated urinary tract infection* (uUTI) as reported by U.S. office-based physician surveys, stratified by drug, for years 2010 and 2014

Table 17

2010	Uses (000)	*Share %*	95% C.I. (000)
Total Market	**22,338**	***100.0%***	**21,632 - 23,043**
ciprofloxacin	7,773	*34.8%*	7,357 - 8,189
sulfamethoxazole/tmp	5,550	*24.8%*	5,198 - 5,901
nitrofurantoin	4,534	*20.3%*	4,217 - 4,852
phenazopyridine	1,524	*6.8%*	1,340 - 1,709
levofloxacin	1,155	*5.2%*	994 - 1,315
cephalexin	502	*2.3%*	396 - 608
doxycycline	128	*0.6%*	74 - 181
cefdinir	96	*0.4%*	49 - 142
meth/me bl/salicy/na phos/hyos	93	*0.4%*	48 - 139
ampicillin	89	*0.4%*	44 - 133
All Others	894	*4.0%*	753 - 1,035

Table 18

2014	Uses (000)	*Share %*	95% C.I. (000)
Total Market	**25,177**	***100%***	**24,383 - 25,971**
ciprofloxacin	8,100	*32.2%*	7,649 - 8,550
nitrofurantoin	5,822	*23.1%*	5,440 - 6,204
sulfamethoxazole/tmp	5,610	*22.3%*	5,235 - 5,985
phenazopyridine	1,980	*7.9%*	1,758 - 2,203
levofloxacin	1,223	*4.9%*	1,048 - 1,399
cephalexin	968	*3.8%*	812 - 1,124
amoxicillin	226	*0.9%*	151 - 301
amoxicillin/clav	165	*0.7%*	100 - 229
cefdinir	113	*0.5%*	60 - 166
cefuroxime	80	*0.3%*	35 - 124
All Others	890	*3.5%*	741 - 1,040

Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015

**uUTI definition was expanded to include acute cystitis (ICD9: 59500.0), cystitis NEC (ICD9: 59589.0), cystitis NOS (ICD9: 59590.0), and urinary tract infection NOS (ICD9 59900.0)*

In summary, the results of the drug utilization analyses show that oral fluoroquinolones are widely used in the U.S. outpatient retail pharmacy settings with approximately 33 million prescriptions dispensed to approximately 22 million patients in year 2014. Ciprofloxacin was the most commonly used fluoroquinolone during the study period, followed by levofloxacin. The vast majority of use was observed in adult patients aged 18 years and older. Females accounted for approximately two-thirds of the total patients who received a dispensed prescription for an oral fluoroquinolone in 2014.

According to office-based physician survey database in 2014, the most common diagnosis associated with ciprofloxacin was urinary tract infection NOS. Pneumonia organism NOS was the most commonly mentioned diagnosis for levofloxacin. For the diagnoses of interest (e.g. ABS, ABECB-COPD, and uUTI) we were unable to search on specific ICD9 codes for ABECB-COPD and uUTI in our search criteria because the terms “ABECB” and “uUTI” may be considered colloquial; therefore, we broadened the definitions of ABECB and uUTI to include ICD9 diagnosis codes likely to encompass ABECB and uUTI. As a result of our broadening the definitions of ABECB and uUTI using ICD-9 codes, we increased the potential for misclassification by possibly including more severe diagnoses. The degree of misclassification, if any, is not known.

We utilized the Encuity database’s predefined market categories for the drugs most commonly associated with one of the three diagnoses of interest. Specifically, “systemic antibiotics” mentioned to be associated with selected ICD9 codes for ABS and ABECB-COPD were assessed and any drug mentioned to be associated with the ICD9 codes for uUTI were assessed.

This step was conducted to capture use of other drugs possible used to treat uUTIs such as nitrofurantoin and fosfomycin products which are approved for treating uUTI but were not included in this database's definition of "systemic antibiotics" category. As a result, we found that other non-antibiotic treatments, such as phenazopyridine, were commonly associated with uUTI. Also, we analyzed other drugs mentioned for acute sinusitis and ABECB and found that "systemic antibiotics" was the most common drug category or "class" associated with acute sinusitis in 2010 and 2014; whereas for ABECB, "systemic antibiotics" was the most common category mentioned in 2010, but "corticosteroids plain oral" was the top category reported for 2014. And, although the data from the "total market" category for acute sinusitis and ABECB are not shown, these results were included to show that other non-antibiotic treatments were commonly associated with acute sinusitis and ABECB.[8]

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of some of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

From our analyses we observed that oral fluoroquinolones are a widely used class of antibacterial drugs, with ciprofloxacin and levofloxacin accounting for the majority of use. Adult female patients accounted for the largest proportion of patients for oral fluoroquinolones, nearly double the number of male patients. According to an office-based physician survey database, fluoroquinolones were among the most common antibacterial drugs associated with possible acute sinusitis, uUTI (broadly defined), and ABECB-COPD (broadly defined). However, due the limitations in the use of ICD9 codes to characterize drug use for these diseases and other limitations discussed, these results should be interpreted with caution.

V. OVERALL SUMMARY

An evaluation of placebo-controlled trials in ABS or mild ABECB-COPD show that a large proportion of patients randomized to receive placebo recovered and thus these illnesses appear to be self-limited for many patients. Indeed some of these trials showed no differences in outcome measures when comparing the antibacterial drug to placebo. There appears to be strong evidence for the benefit of antibacterial drug therapy for patients hospitalized for moderate or severe ABECB-COPD. The evaluation of trials in uUTI using a placebo or a non-antibacterial control showed a treatment benefit of antibacterial drug therapy on the outcome measure of microbiologic eradication on follow-up urine culture. On the outcome measure of symptom resolution, the placebo-controlled trials showed a treatment benefit but the ibuprofen-controlled trial showed similar outcome findings between treatment groups. A random effects meta-

[8] Source: Encuity Treatment Answers with Pain, Y2014, Extracted AUG2015

analysis of all five trials including the ibuprofen controlled trial showed an overall treatment benefit on both outcome measures.

When considering the potentially modest treatment benefits of antibacterial drugs for these three indications, the risks of the fluoroquinolone antibacterial drugs should be taken into consideration. Over the life-cycle of these drugs, several adverse reactions have been reported, and most of them were not evident in the pre-approval safety databases. While the actual incidence of each adverse reaction is difficult to ascertain, the seriousness of certain uncommon adverse reactions deserves attention, such as tendinitis/tendon rupture, peripheral neuropathy, or cardiac arrhythmias. The identification of constellations of adverse reactions that appear to be long-term or permanently disabling is also a particular concern.

The use of fluoroquinolone antibacterial drugs has not shown an overall change in the past several years. This is particularly notable in light of the introduction of Boxed Warnings for tendinitis and tendon rupture in 2008 and the enhancement of Warnings and Precautions for the potential irreversibility of peripheral neuropathy in 2013.

VI. ISSUES FOR DISCUSSION

1. Consider the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the indication for the treatment of acute bacterial sinusitis (ABS), in the context of available safety information on fluoroquinolone antibacterial drugs and the treatment effects of antibacterial drugs for ABS. Discuss any specific recommendations concerning labeling, if any, including the safety information regarding the constellation of adverse reactions that were characterized as FQAD.

2. Consider the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the indication for the treatment of acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease (ABECB-COPD), in the context of available safety information on fluoroquinolone antibacterial drugs and the treatment effects of antibacterial drugs for ABECB-COPD. Discuss any specific recommendations concerning labeling, if any, including the safety information regarding the constellation of adverse reactions that were characterized as FQAD.

3. Consider the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the indication for the treatment of uncomplicated urinary tract infection (uUTI), in the context of available safety information on fluoroquinolone antibacterial drugs and the treatment effects of antibacterial drugs for uUTI. Discuss any specific recommendations concerning labeling, if any, including the safety information regarding the constellation of adverse reactions that were characterized as FQAD.

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APPENDIX A: BIBLIOGRAPHY OF PLACEBO-CONTROLLED TRIALS IN ABS AND ABECB-COPD

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APPENDIX B: REVIEW OF TRIALS IN UNCOMPLICATED URINARY TRACT INFECTION

APPENDIX B: REVIEW OF TRIALS IN UNCOMPLICATED URINARY TRACT INFECTION

We considered uUTI to be an indication distinct from complicated urinary tract infections (cUTI) and limited the search to studies with non-pregnant women and no known urological abnormalities or comorbidities, such as diabetes.

Our review of published literature met the following criteria:

- Identified by PubMed search, including articles published in the early 20th century
- Search terms included "randomized" and "placebo" and "urinary tract infection"
- Trials for prevention/prophylaxis, asymptomatic bacteriuria, recurrent UTIs, UTIs in pregnant women or cUTIs were excluded
- Active-controlled trials were also excluded, but we considered trials that used a non-antibacterial control, such as a non-steroidal anti-inflammatory drug
- Patient population must have presented with a clinical history of dysuria, frequency or urgency, pyuria (leukocytes detected on urinalysis) and no signs of systemic illness indicative of cUTI
- For confirmatory baseline cultures, significant bacteriuria was defined as $\geq 10^5$ CFU/mL (cultures with more than two isolates were considered contaminated and therefore excluded)

Seven articles (6 in English, 1 in French) were found and represented randomized, placebo-controlled trials in uUTI meeting the criteria above. Two articles were not included in this assessment of the treatment effect for uUTI. One trial is currently ongoing (Vik, Bollestad, 2014). Another trial used a non-standard microbiologic method, which brought into doubt the reliability of the diagnosis of uUTI for patients enrolled in the trial (Brooks, Garrett, 1972). In general, the studies used a definition of uUTI as relevant symptoms such as dysuria plus a finding of $\geq 10^5$ CFU/mL of bacteria on baseline urine culture.

For the five trials that we identified, response to treatment was defined as microbiologic eradication of bacteriuria (micro-ITT population) and symptom resolution (ITT population), but two trials described subsequently used a responder endpoint requiring both resolution of symptoms and eradication of bacteriuria after the end of treatment to be considered a success. Additionally, results were also reviewed for incidence of the development of resistance, as well as incidence of adverse events and complications such as pyelonephritis. The findings of the five trials that we considered as reliable are summarized below.

One trial was prospective, randomized, double-blind, and placebo-controlled (Asbach, 1991). Eighty (80) female subjects (ages 15 – 35 years) with acute lower urinary tract infections were enrolled. Subjects were assigned to receive single-dose treatments of cefixime, co-trimoxazole, ofloxacin or placebo. Response was defined as microbiologic eradication plus complete symptom resolution, and microbiological eradication alone was described. Table 1 provides a summary of outcome assessments. Approximately 25% of patients in the placebo group still had persistent symptoms at trial completion.

Table 1: Summary Outcome Assessments for uUTI (Asbach 1991)

Treatment groups		**Microbiological Eradication:** Day 14-17 (micro-ITT)	**Clinical + Micro Responder:** Complete symptom resolution Day 14-17 (micro-ITT)
Cefixime 400 mg x1	N=20	17/19 (89%)	17/19 (89%)
Co-trimoxazole (160 mg/800 mg) x1	N=20	17/19 (89%)	17/19 (89%)
Ofloxacin 200 mg x1	N=20	16/19 (84%)	16/19 (84%)
Placebo x1	N=20	5/19 (26%)	5/19 (26%)

A prospective, randomized, double-blind, placebo-controlled trial recruited 166 patients with uUTI (Christiaens, De Meyere, et al, 2002). A total of 78 female subjects (ages 15 – 54 years) were enrolled and 56 had a bacteriologically documented uUTI. Subjects were assigned to receive nitrofurantoin 100 mg or placebo four times daily for three days. Clinical response was defined as either symptomatic cure or improvement, and a microbiological cure was a negative culture result. Seven patients in placebo group and one patient in nitrofurantoin group each met early failure criteria and were given off-study antibacterial treatment. One patient in the placebo group developed pyelonephritis. Table 2 provides the summary of outcome assessments.

Table 2: Summary Outcome Assessments for uUTI (Christiaens, De Meyere, et al, 2002)

Treatment groups		**Microbiologic response:** Culture negative Day 7 (micro-ITT)	**Clinical Responders:** Improved/complete Day 7 (ITT)
Nitrofurantoin 100mg QID x 3 d	N=40	17/29 (59%)	30/40 (75%)
Placebo QID x 3 d	N=38	9/27 (33%)	17/38 (45%)

Eighty female subjects (ages 18 to 85 years) were enrolled in this double-blind, randomized controlled pilot trial (Bleidorn, Gágyor, 2010). Patients were assigned to receive either ibuprofen 3 × 400 mg or ciprofloxacin 2 × 250 mg for 3 days. Fifty-five subjects had a bacteriologically documented uUTI. The primary endpoint was symptom resolution on Day 4. Urine cultures were also obtained on Day 7. Twelve patients in the ibuprofen group and six patients in the ciprofloxacin group met early failure criteria and required off-study antibacterial drug treatment. Table 3 provides the summary of outcome assessments.

Table 3: Summary Outcome Assessments for uUTI (Bleidorn, Gágyor, 2010)

Treatment groups		**Micro results:** Culture negative Day 7 (per protocol)	**Clinical Responders:** Improved/complete Day 4 (ITT)
Ciprofloxacin 500 mg x 3 d	N=40	23/33 (72%)	17/40 (43%)
Ibuprofen 1200 mg x 3 d	N=40	16/36 (49%)	21/40 (53%)

A fourth trial was prospective, randomized, double-blind and placebo-controlled (Ferry, Holm, et al, 2007). A total of 1162 female subjects aged 18 and above were enrolled. Patients were randomized to three different regimens of pivmecillinam: 200 mg × 3 × 7 days, 200 mg × 2 × 7 days or 400 mg × 2 × 3 days or placebo (i.e. all patients were given 2 + 1 + 2 identical tablets each day for 7 days). At baseline, 278 subjects (23%) did not have significant bacteriuria on baseline culture. Clinical cure was defined as no persisting symptoms during and post-therapy. Bacteriological cure was defined as eradication of initial bacteriuria at the follow-up visits. Outcome assessments are summarized in Table 4. The percentages of subjects with both clinical and microbiological cures at both post-therapy visits were 56-58% for the pivmecillinam groups and 21% for placebo.

Table 4: Summary Outcome Assessments for uUTI (Ferry, Holm, et al 2007)

Treatment groups		**Micro results:** Culture negative (mITT)	**Clinical Responders:** complete symptom resolution (ITT)
Pivmecillinam 600 mg x 7 d	N=217	202/217 (93%)	134/217 (62%)
Pivmecillinam 400 mg x 7 d	N=220	207/220 (94%)	141/220 (64%)
Pivmecillinam 800 mg x 3 d	N=220	185/220 (84%)	121/220 (55%)
Placebo	N=227	77/227 (34%)	57/227 (25%)

An article published in French described a prospective, randomized, double-blind and placebo-controlled trial (Dubi, Chappuis, et al, 1982). Sixty-one female subjects (aged 18-84 years) were enrolled. Each patient was randomized to one of three possible treatments, either a single dose of co-trimoxazole (trimethoprim/sulfamethoxazole 480/2400 mg, three capsules), a single dose of amoxicillin (amoxicillin 3 g, as four 750 mg capsules) or symptomatic treatment of sodium bicarbocarbonate (two capsules of 1 g every 4 hours during the first day). Outcome assessments are summarized in Table 5. Among symptomatic subjects with non-recurrent UTIs, all 8 subjects treated with co-trimoxazole were cured, compared to 3 of 7 treated with amoxicillin and 3 of 6 treated with sodium bicarbonate; resistance rates were 2.9% to co-trimoxazole and 18.5% to amoxicillin.

Table 5: Summary Outcome Assessments for UUTI (Dubi, Chappuis, et al, 1982)

Treatment groups		**Micro results:** Culture negative (mITT)	**Clinical + Micro Responder:** Culture negative and complete symptom resolution (ITT)
Co-trimoxazole 480/2400mg (3 caps) x1	N=21	20/21 (95%)	20/21 (95%)
Amoxicillin 3g (4 caps of 750mg) x1	N=22	10/22 (45%)	10/22 (45%)
Sodium-bicarb (2 caps of 1g) q4h x1day	N=18	8/18 (44%)	8/18 (44%)

APPENDIX C: Guidance for Industry Documents for ABS and ABECB-COPD

Guidance for Industry

Acute Bacterial Sinusitis: Developing Drugs for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2012
Clinical Antimicrobial

Guidance for Industry

Acute Bacterial Sinusitis: Developing Drugs for Treatment

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Contains Nonbinding Recommendations

Guidance for Industry[1] Acute Bacterial Sinusitis: Developing Drugs for Treatment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs[2] for the treatment of acute bacterial sinusitis (ABS). This guidance defines ABS as "inflammation of the paranasal sinuses as a result of *the presence of a bacterial pathogen within the sinus space* when the duration of illness is less than 4 weeks."

Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of ABS. This guidance does not address the development of drugs for other purposes such as prevention of ABS or treatment of chronic sinusitis, or developing drugs for the nonantimicrobial treatment of sinusitis.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[3]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

There have been a number of public discussions regarding the design of clinical trials to study ABS.[4] These discussions have focused primarily on trial designs for ABS and other important issues such as the following:

- Inclusion criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of concomitant medications
- Role of microbiological outcomes
- Noninferiority and superiority trial designs

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Nonclinical Development Considerations

New drugs being studied for ABS should have nonclinical data documenting activity against the most commonly implicated pathogens associated with ABS (i.e., *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*). Animal models of ABS have been developed, particularly for *S. pneumoniae* infection, and pathological and histological responses to antibacterial treatment have been shown in animals. Although these models may contribute to the scientific understanding of ABS and its treatment, the results should be carefully interpreted when being used to help design subsequent human trials. Because clinical trials can be conducted in patients with ABS, animal studies cannot substitute for the clinical trials that must be conducted to evaluate drug safety and efficacy.[5]

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[4] In October 2003, the Anti-Infective Drugs Advisory Committee (AIDAC) discussed ABS clinical trials with a focus on the use of noninferiority designs (see http://www fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective). In September 2006, the AIDAC addressed appropriate use of noninferiority trials for ABS in the context of a specific drug (see http://www fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective). In a December 2006 joint meeting of the AIDAC and the Drug Safety and Risk Management Advisory Committee, the issue of noninferiority trial design was discussed in the context of evaluating the risk-benefit profile of a drug. In this case, three indications were under discussion: ABS, acute bacterial exacerbation of chronic bronchitis, and community-acquired bacterial pneumonia (see http://www fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective).

[5] 21 CFR 314.600 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.600)

2. Drug Development Population

As previously noted, this guidance defines ABS as "inflammation of the paranasal sinuses as a result of *the presence of a bacterial pathogen within the sinus space* when the duration of illness is less than 4 weeks." This guidance also considers ABS to be restricted to maxillary disease with or without involvement of other sinuses, which is the most common presentation of ABS. Although isolated disease of the frontal or sphenoid sinus exist as clinical entities, they are rare and have a different pathophysiology, microbiology, and clinical course from maxillary sinusitis. Sponsors should discuss with the FDA if patients with maxillary ABS and concurrent nonmaxillary ABS are being considered for clinical trial enrollment.

In addition, although the medical literature commonly refers to disease of the sinuses in conjunction with nasal symptoms as *acute rhinosinusitis*, we consider rhinitis and sinusitis to be distinct disease entities. The administration of antimicrobial drugs is appropriate only for study of bacterial infection of the sinuses. Rhinitis symptoms without sinus disease are most commonly caused by viral infection, allergic rhinitis, and/or vasomotor instability. Because we have approved nonantimicrobial drugs specifically for rhinitis symptoms alone, it is important to separate the effect of antimicrobial therapy on ABS from treatment of nasal symptoms caused by nonbacterial sources.

3. Efficacy Considerations

We have not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABS with antimicrobial drugs from reviewing previous ABS trials. Such an estimate would be a precondition for a noninferiority trial. Accordingly, we recommend only superiority trials for ABS.

The goal of ABS clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of ABS caused by *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*. If sponsors wish to add additional organisms to this indication, they should provide data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in ABS. For example, some trials have implicated *Staphylococcus aureus* as a pathogen in ABS in a setting where this has been the sole pathogen isolated. Sponsors should discuss with the FDA during drug development the methods to provide data on relevant bacterial pathogens that cause ABS. For example, microbiological data can be obtained by one or more of the following approaches: (1) baseline sinus puncture and aspiration (or endoscopy) performed on all patients enrolled in the phase 3 trial (see section III.B.5.b., Baseline sinus aspiration and endoscopy); (2) a subset of patients who have baseline sinus puncture and aspiration (or endoscopy) performed in the phase 3 trial; (3) baseline sinus puncture and aspiration (or endoscopy) performed on patients enrolled in a phase 2 trial; or (4) microbiological data obtained during clinical development of the investigational drug for treatment of another infectious disease in which the bacterial pathogens are identical or similar to bacterial pathogens known to cause ABS.

The number of trials needed for approval of an ABS indication depends on the overall development plan for the drug under consideration. If the development plan for a drug has ABS

as the sole marketed indication, we recommend that two adequate and well-controlled trials establishing safety and efficacy be conducted for this indication.

A single trial for an ABS indication may be appropriate if: (1) there are data from other clinical trials demonstrating effectiveness in other respiratory tract diseases; and (2) there is additional supportive information such as pharmacokinetic and pharmacodynamic studies demonstrating concentration of the antibacterial drug in the sinuses at a level expected to be active against the common pathogens causing ABS. For example, evidence of efficacy from community-acquired bacterial pneumonia (CABP) trials may be supportive of a single superiority trial of ABS because of the similar microbiology and greater seriousness of CABP relative to ABS.

The disease course and treatment for ABS is of a short-term duration. Direct assessment of ABS symptoms to support a conclusion of treatment benefit in response to antibacterial drug therapies is readily measured. As such, there are no surrogate markers accepted by the FDA. Sponsors who wish to propose a surrogate marker for clinical outcome or the initial diagnosis of ABS should discuss this with the FDA early in the drug development process.

4. Safety Considerations

Antimicrobial drugs with clinically significant toxicity should not be considered appropriate for study of this indication unless treatment of a more seriously ill patient population is being considered.

A sufficient number of patients should be studied at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety. This information can be derived from trials of the new drug for infections other than ABS if exposure is similar to or greater than the exposure for ABS. However, if ABS is the sole indication being studied, it is likely that additional patients may need to be studied for safety beyond the number of patients needed to show clinical efficacy for ABS. This can be accomplished either by enhancing clinical trial enrollment to arrive at a sufficient sample size for safety evaluations or by enrolling an appropriate number of patients in another trial designed to evaluate safety. The total number of patients needed for a drug development program that includes an ABS indication should be discussed with the FDA early in the drug development process.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Design

Currently, we recommend only superiority trials for ABS. Sponsors who are considering a noninferiority trial for ABS should justify a proposed noninferiority margin to the FDA as early as possible during protocol development and before trial initiation. This situation is discussed further in section III.B.12., Statistical Considerations.

Superiority trials in the treatment of ABS can consist of the following general forms:

- **Placebo-controlled trial with a background of best available nonantimicrobial therapy** — This design tests the safety and efficacy of an investigational antimicrobial drug as an addition to a standardized regimen of the best available analgesic and decongestant medications compared to the same standardized regimen plus placebo.

- **Dose-response** — Patients in each arm receive different antimicrobial drug doses (or dosing regimens) for which there is equipoise together with a standardized regimen of the best available nonantimicrobial therapy. To demonstrate efficacy, the arm receiving a higher dose (or more intensive therapy) should be superior to the lower dose (or less intensive) regimen.

- **Superiority of the investigational antimicrobial to another antimicrobial** — Patients in one arm receiving the investigational drug (with standardized regimen of the best available background nonantimicrobial therapy) are compared with patients in a control arm receiving another antimicrobial drug (with standardized regimen of the best available background nonantimicrobial therapy). To demonstrate efficacy, the arm receiving the investigational antimicrobial drug should demonstrate superiority to the arm receiving the control antimicrobial drug.

A three-arm trial with the investigational treatment arm, an active-controlled arm (e.g., an antibacterial drug approved for ABS), and a placebo-controlled arm permits the demonstration of superiority and also can provide risk-benefit information relative to an approved comparator.

ABS trials should be parallel group designs, because crossover designs may be subject to carry-over and period effects. Other trial designs to demonstrate superiority can be discussed with the FDA.

2. Trial Population

ABS trials should include patients of both sexes and all races. ABS should be diagnosed by a combination of signs and symptoms with radiographic imaging included with the initial assessment to increase diagnostic specificity for bacterial disease. If it is feasible to perform sinus puncture and aspiration, documenting the presence of bacteria in the sinus cavity can be an important means of enriching the trial population for analysis, and can also serve to confirm that enrollment procedures have succeeded in enrolling an adequate percentage of patients with bacterial disease.

To improve specificity for ABS (i.e., to better select for bacterial rather than viral sinusitis), patients should have a history of symptoms for a minimum of 7 to 10 days before enrollment, without improvement over the 3 days immediately before enrollment.

An alternative trial design can be used where patients are enrolled at days 4 to 7 and a 3-day run-in period is used before randomization. Randomization of patients with symptoms that have not

improved over the 3-day run-in period may enrich the trial population for patients with a bacterial etiology of sinusitis.

We do not recognize different forms of ABS based on disease severity at presentation. However, we recognize that investigators in a placebo-controlled trial may be less likely to enroll patients presenting with *severe* disease than patients with milder symptoms, and that enrollment of hospitalized patients may be incompatible with a placebo-controlled trial. Current practice guidelines state the following conclusions and research needs: "More placebo-controlled RCTs [randomized clinical trials] that incorporate both pre- and posttherapy [sic] sinus cultures and a clinical severity scoring system are urgently needed to provide critical information regarding the natural history of ABRS [acute bacterial rhinosinusitis] as well as the timeliness and efficacy of antimicrobial therapy."[6] If sponsors wish to study patients with severe disease (or hospitalized patients), we strongly encourage discussion with the FDA regarding protocol design and adherence to current practice guidelines.

3. Inclusion Criteria

a. Symptoms

At least two of the following symptoms should be present in patients with ABS:

- Maxillary tooth pain (unilateral findings can be more specific)
- Facial pain (unilateral findings can be more specific)
- Frontal headache
- Purulent nasal discharge (unilateral findings can be more specific)
- New onset fetor oris (bad breath)
- Morning cough
- Nasal obstruction

b. Signs

At least one of the following signs should be present in patients with ABS:

- Purulent secretions from sinus ostia on examination
- Abnormal sinus transillumination
- Pain on palpation over sinuses
- Facial swelling

c. Generalized signs and symptoms

Additional generalized signs and symptoms that are consistent with a diagnosis of ABS but are otherwise nonspecific include:

[6] Chow, AW, MS Benninger, I Brook et al., 2012, IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults, Clinical Infectious Diseases, doi: 10.1093/cid/cir1043, published March 20 2012, ahead of print.

- Fever (e.g., temperature greater than or equal to 38 degrees Centigrade)
- Malaise

Although review of the medical literature has not identified a combination of patient characteristics with high specificity for bacterial sinusitis relative to other causes of acute sinusitis, the presence of a greater number of symptoms is associated with a higher likelihood of bacteria being isolated by sinus aspiration. A duration of illness greater than 7 to 10 days at the time of presentation and a history of previous episodes of acute sinusitis also improve specificity for bacterial disease.

Radiographic findings consistent with acute sinusitis also should be documented to be present at baseline (see section III.B.5.a., Radiography). If baseline sinus puncture and aspiration is performed in the trial, the radiographic findings may help to guide the sinus puncture and aspiration procedure (see section III.B.5.b., Baseline sinus aspiration and endoscopy), which enhances the ability to identify a bacterial pathogen on culture.

4. Exclusion Criteria

The following patients should be excluded from ABS trials:

- Patients with symptoms attributed to sinus disease for longer than 4 weeks
- Patients with disease history consistent with allergic and other types of rhinitis
- Patients with isolated frontal and sphenoidal disease given the different pathophysiology and etiologic pathogens[7]
- Patients with cystic fibrosis
- Immunocompromised patients or patients with other medical conditions that may affect interpretation of the effect of trial drugs
- Patients who are allergic to any of the trial drugs
- Patients with nasal polyposis

Sponsors can exclude patients who have received antimicrobial therapy for the current episode of ABS. If patients who have received prior antimicrobial therapy are included, they should be stratified before enrollment to ensure balance across the treatment arms.

[7] If sponsors plan to include patients with maxillary sinusitis and evidence of concurrent frontal, sphenoidal, or ethmoidal sinusitis, they should discuss with the FDA the enrollment criteria and efficacy evaluation before trial initiation.

5. Additional Clinical Trial Entry Procedures

a. Radiography

Previous evaluations have attempted to identify radiographic abnormalities associated with bacterial causes of sinusitis versus other etiologies. In general, these modalities, including plain sinus radiography, computed tomography, magnetic resonance imaging, and ultrasound, have been nonspecific for the presence of bacteria by sinus puncture. However, radiography may have a strong negative predictive value for bacterial sinusitis (i.e., the absence of radiographic abnormalities identifies patients with a lower likelihood of a bacterial sinus infection). Because of this, we strongly recommend radiological assessment as a means to enrich the trial population. In clinical trials, the number of patients who are screened for enrollment but then have negative radiography should be recorded and included in the trial report. The clinical characteristics of patients screened but not enrolled also should be recorded.

b. Baseline sinus aspiration and endoscopy

A microbiological diagnosis of ABS can be confirmed by isolating a bacterial pathogen from a specimen obtained by maxillary sinus puncture at baseline. If sinus puncture and aspiration is performed in the trial, Gram stain of the aspirate material with examination for white blood cells (WBCs) should be performed, as well as in vitro antimicrobial susceptibility testing of bacterial isolates.

Sponsors considering endoscopic cultures at baseline should discuss this with the FDA in advance of trial initiation.

Other techniques, such as the placement of a small-bore indwelling catheter during treatment, if feasible to perform, can be useful for examining the microbiological response to treatment across treatment arms over time in phase 2 trials.

If baseline sinus puncture or endoscopy is performed, the trial should be conducted at sites with expertise in the procedure. The protocol should describe the specific methods to be used for obtaining, transporting, and processing specimens and should describe specific culture techniques to be used on specimens.

6. Randomization, Stratification, and Blinding

Patients should be randomized for treatment assignment at enrollment. All trials should be double-blinded for therapy and assessment of outcome.

When microbiological sampling is performed, investigators should be blinded to the microbiological data obtained at entry. If patients fail therapy and require rescue therapy, the results of baseline and any subsequent microbiological data should be made available promptly to the treating clinician.

7. Special Populations

Sponsors will likely be required to conduct trials to support labeling for use in the pediatric population.[8] Pediatric patients 1 year old and older can be included along with adults in ABS trials if a dose, regimen, and formulation for these patients has been identified that yields drug exposure similar to that in adults; pediatric patients over 12 years of age often receive the same dose and formulation as adults and usually can be enrolled in these trials. Sinus puncture may not be appropriate for pediatric patients in certain situations. Sponsors should discuss with the FDA when sinus puncture in pediatric patients is planned, before trial initiation, to ensure compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations. Other considerations for compliance with subpart D include whether there are sufficient safety data to allow study of pediatric patients, and the acceptability of both the trial design and diagnostic procedures in pediatric patients. Sponsors pursuing an indication for ABS are strongly encouraged to discuss the requirements for pediatric studies in their overall drug development program with the FDA early in development, including the potential for extrapolation of adult efficacy data, appropriate pharmacokinetic studies in pediatric patients to support the selection of the dose, and preapproval of a safety database in children.

Drug development programs should include a sufficient number of geriatric patients to characterize safety and efficacy in this population. Patients with renal or hepatic impairment can be enrolled provided pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined.

8. Dose Selection

Selection of an appropriate dose and duration of therapy for phase 3 clinical trials should use information gathered in earlier clinical development; for example, data from pharmacokinetic and pharmacodynamic studies (including information regarding sinus penetration of the drug) and data from phase 2 dose-ranging trials.

9. Concomitant Medications

ABS clinical trials should determine the additional contribution of the antimicrobial drug to clinical outcome beyond nonantimicrobial therapies. Lack of standardization of concomitant medications can introduce an important source of confounding in clinical trials if there are imbalances in receipt of nonantimicrobial therapies between trial groups. Such confounding may occur even if the number of patients receiving concomitant medications is similar between treatment groups but the reasons for administering concomitant medications differ. Confounding also may occur when the patients in one group who receive concomitant medications differ in baseline characteristics from those patients who do not receive concomitant medications.

[8] The Pediatric Research Equity Act (Public Law 108-155) requires the conduct of pediatric studies for certain drug and biological products (see section 505B(b) of the Federal Food, Drug, and Cosmetic Act). See the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Therefore, sponsors should make every attempt to control for potential confounders such as concomitant medications.

Treatment groups should be well-balanced with the use of nonantimicrobial therapies to ensure that the treatment effect on an outcome measure would be attributed to the investigational antibacterial drug. This can be accomplished through a protocol-specified nonantimicrobial background regimen with the dose and frequency of use similar for all patients in the trial; however, the use of standardized, nonantimicrobial therapy in the protocol should be based on experimental evidence that the treatment is effective. At a minimum, the protocol should specify appropriate options for nonantimicrobial therapies during the trial.

Concomitant medication use should be captured in all patients using a daily medication log. Use of concomitant medications alone should not be an efficacy endpoint but should be analyzed in combination with a symptom assessment using a patient-reported outcome (PRO) or caregiver-reported instrument. For example, the endpoint can be defined to evaluate whether symptoms persist after concomitant medication administration.

10. Efficacy Endpoints

The primary emphasis of the trial should be the effect of the antimicrobial drug on outcomes that are clinically important to patients. A well-defined and reliable PRO measure designed to capture the important symptoms of ABS can be considered a direct measure of treatment benefit and can be used in a trial to support labeling claims for efficacy. Patient outcome should be based on symptom response per patient rather than per sinus (i.e., outcome is measured identically regardless of whether unilateral or bilateral disease is present). The primary outcome assessment can be characterized as a *success* or *failure* as follows:

- *Clinical success.* Clinical success can be documented when a patient reports improvement or resolution of clinically meaningful symptoms present at enrollment and the absence of new symptoms or complications attributable to sinusitis.

- *Clinical failure.* Clinical failure can be documented as follows:

  - Protocol-defined worsening of symptoms or failure to improve at certain time points (e.g., failure to have symptomatic improvement 72 hours after treatment onset)

  - Development of a new symptom of ABS during treatment

  - Development of complications of ABS such as meningitis and/or brain abscess, subdural empyema, cortical or sinus vein thrombosis, or extension of disease to the orbit of the eye

  - Treatment with nontrial antibacterial drugs for another related infectious disease (e.g., for treatment of CABP)

A PRO instrument can measure responses based on a scale score, and then the score should be used as the outcome variable. For patients who cannot report for themselves (e.g., young children), a caregiver assessment can be developed that reports on behaviors and signs that are probably related to the patient's symptoms. Development of a new PRO or caregiver-reported instrument should begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol.[9] For example, after content validity is established, sponsors can evaluate construct validity, reliability, and responsiveness of the instrument during phase 2 trials. Evaluation of the patient responses using the instrument in phase 2 could be used to inform sample size calculations for phase 3 trials.

We recommend that the primary efficacy endpoint should be the time to clinical success, defined as the period from the start of trial drug therapy to clinically meaningful symptomatic improvement or resolution. Sponsors who choose to use response at a fixed time point as the primary outcome (i.e., as the *test-of-cure* assessment) should provide evidence to support the selection of that specific time point.

Patients who experience improvement of symptoms but then worsen during clinical trial participation should be considered clinical failures on the primary efficacy analysis. Sinus puncture in patients who experience additional symptoms may be valuable for secondary analyses, because the results would allow a differentiation between patients who may still harbor the initial pathogen (relapse) compared with those patients who have acquired a new pathogen or have a noninfectious etiology for symptoms (recurrence). Bacterial isolates obtained from clinical relapse or recurrences should be subjected to an appropriate in vitro method (e.g., pulse field electrophoresis gel) to determine if the original isolate and the subsequent isolate are indistinguishable (relapse) or different (recurrence). The susceptibility profile should be performed for any pathogens isolated.

Patients who discontinue therapy because of an adverse event should be evaluated at the time of discontinuation of the trial drug therapy. These patients should not be considered *withdrawn from the trial* in terms of overall evaluation; investigators should continue to follow all such patients at trial visits as scheduled and continue to record information on both safety and efficacy outcomes. If at the time the trial drug therapy is discontinued the patient is alive, without complications, and does not receive additional antimicrobial therapy, then the patient should be evaluated following the protocol criteria; discontinuation of therapy because of an adverse event should not automatically be considered a clinical failure.

Sponsors can present secondary analyses on variables such as:

- Clinical response based on the number of sinuses involved (e.g., isolated maxillary disease compared to maxillary disease with other sinuses involved)
- Clinical response in unilateral versus bilateral disease
- Investigator assessment of the patient's clinical signs

[9] For more information regarding the development of PRO measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

- Subgroup analyses based on patient demographics

Analyses of secondary and additional endpoints usually should be considered exploratory because a trial usually is not designed to address the questions raised by these analyses, either because of multiple comparisons and/or concerns with subgroup analyses (see section III.B.12., Statistical Considerations). However, the conclusions of such analyses can be strengthened if hypotheses related to these endpoints are prespecified in the protocol, if adjustments for multiple comparisons (maintenance of type I error) are outlined in the protocol, and if the trial is appropriately powered to determine differences between groups related to these variables. Analyses of secondary and additional endpoints can be most helpful for identifying areas for study in future trials.

11. Trial Visits and Timing of Assessments

a. Entry visit

At entry, the investigator should evaluate the patient by performing an appropriate history and physical examination. Information recorded on the case report form during the entry examination should include the following:

- **History and demographic characteristics**

  - Date of visit
  - Age and sex
  - Underlying medical conditions, if any
  - History of previous episodes of acute sinusitis and history of allergic rhinitis
  - History of tobacco use
  - History of smoking
  - Previous or current use of antibacterial drugs, and the indication or reason for use
  - Recent and/or current use of nonantibacterial concomitant medications

- **Symptoms**

  The presence of each symptom, as discussed in section III.B.2., Trial Population, and section III.B.3., Inclusion Criteria, should be documented directly as reported by the patient (or caregiver). Baseline symptoms also can be recorded by patients or caregivers in a PRO or caregiver-reported instrument that is well-defined and reliable in the population to be studied.

- **Signs**

  - Vital signs including body temperature measurement
  - Presence of unilateral or bilateral disease
  - Findings on transillumination of sinuses

- Findings on nasal speculum examination
- Presence of purulent secretions
- Radiographic testing by plain radiographs, computed tomography, or ultrasound
- Other laboratory tests (e.g., peripheral WBC count)

- **Sample collection**

  At clinical trial sites where sinus puncture and aspiration will be performed, baseline sinus puncture with aspirate should be sent for culture and identification and in vitro susceptibility testing of bacterial isolates. All isolates considered to be possible pathogens should be saved in the event that additional testing of the isolate is needed. For microbiological assessment, the investigator should collect the following information:[10]

  - Identification of the affected sinuses sampled (right and/or left).

  - A description of how the sample was obtained, processed, and transported to the laboratory.

  - Identification of the bacterial isolate (this information should remain blinded while the patient is receiving trial drug therapy).

  - In vitro susceptibility (preferably minimum inhibitory concentration) testing of the isolates to both the trial and control drugs. This information should remain blinded while the patient is receiving trial drug therapy. In vitro susceptibility testing should be performed by using standardized methods, such as the Clinical and Laboratory Standards Institute methods, unless otherwise justified.

  Quantification of the bacterial load at baseline may be helpful for analysis but is not required. If bacterial quantification will be used, the protocol for quantification should be provided to the FDA for review before initiating clinical trials.

b. On-therapy visits

Each patient should have daily on-therapy assessments of symptoms using a well-defined and reliable PRO or caregiver-reported instrument that ensures that any potential biases in the method of questioning do not affect trial outcome. The ability to detect differences between therapies for a time-to-resolution endpoint may be increased if assessments are done more often (e.g., twice daily). Therapy should be continued as described in the protocol regardless of whether symptoms have resolved; however, patients with resolution of symptoms can be considered as having achieved clinical success if this is a trial-defined outcome (i.e., patients with continuing symptoms should be classified as not having achieved clinical success at the measured time point). Investigators should attempt to allow a minimum of 72 hours on trial drug therapy before classifying a patient as a clinical failure.

[10] Similar procedures should be followed if endoscopy is performed as part of the protocol.

Assigning clinical failure and permitting use of rescue antibacterial therapy should be reserved for patients who are worsening on their assigned treatment arm; specific criteria to identify these patients should be included in the protocol. It is important that investigators distinguish patients who are worsening (i.e., where rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy and thereby achieve clinical success at a later time point.[11] Sinus puncture can be performed in patients whose therapy has failed and the sample sent for culture and identification and in vitro susceptibility testing of isolates. In the case of clinical failure, therapy should then be changed to an appropriate alternative antimicrobial treatment for ABS, with other therapeutic modifications as necessary; results from baseline cultures (if available) can be released to the investigator at this time to guide treatment, although blinding to original treatment arm should still be maintained.

Consideration should be given to obtaining blood sample for the measurement of drug concentration (e.g., a sparse sampling strategy). An assessment of drug exposure in phase 3 could help explain trial outcomes related to efficacy and/or safety. It could also be used to assess the relationship between the pharmacokinetic/pharmacodynamic indices and observed clinical outcomes. The protocol should provide a description of the sampling strategy and the proposed analysis plan.

c. Early follow-up visit

The early follow-up visit should occur after completion of all trial drug therapy at a time when the investigational drug is expected to clear from the infection site. For example, if the investigational drug with a short half-life is administered for 10 days, this visit can occur on day 11 to 14 after therapy initiation. At this visit the investigator should perform a directed medical history and physical examination, as well as appropriate laboratory measurements. The investigator also should inquire about adverse events. If clinical relapse or recurrence is suspected, a specimen should be obtained for bacterial culture by sinus puncture and aspiration.

d. Late follow-up assessment

The late follow-up assessment should occur 10 to 14 days after the completion of all therapy (e.g., if trial drug therapy is administered for 10 days, this assessment can occur on days 20 to 24 after therapy initiation). For patients who have no adverse events noted at the early follow-up assessment and who are clinical successes (i.e., previous resolution of all symptoms), this assessment can be performed by a telephone contact or other interactive technology. For patients with adverse events occurring at or after the early follow-up assessment, investigators should perform an assessment that includes a medical history, a physical examination, appropriate laboratory evaluations, identification of any new adverse events, and follow-up on unresolved adverse events. The follow-up assessment should include questions regarding any symptoms of

[11] In a time-to-resolution analysis, a patient should be classified as a success at the time of complete resolution of symptoms. Although the patients that remain are failures at each time point, failure is not carried forward unless a patient has reached a specific failure endpoint (e.g., the development of a bacterial complication of ABS and the need to administer rescue therapy). Criteria for failure or the need for rescue therapy should be explicitly outlined in the clinical protocol.

ABS to ascertain if clinical relapse or recurrence has occurred; if clinical relapse or recurrence is suspected, a specimen should be obtained for bacterial culture.

e. Safety evaluations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations also may be needed because of the nonclinical and clinical profile of the specific drug under study. Longer term assessment of adverse events after discontinuation or completion of the antimicrobial also can be considered depending on the specific drug being studied.

All patients should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the test drug has been discontinued. Although serious and unexpected adverse events and follow-up information about these events are required to be reported (21 CFR 312.32 (c)(1)(i)(A) and 21 CFR 312.32(d)(1) and (2)), we recommend that in general all adverse events should be followed until resolution, even if time on trial would otherwise have been completed.

12. Statistical Considerations

Sponsors should designate the hypotheses to be tested before trial initiation. These hypotheses should be stated in the statistical analysis plan and the trial should be powered to detect differences between trial arms. If sponsors choose to test multiple hypotheses, they should address issues related to the potential increase in obtaining false positive results (type I error) because of multiple comparisons, either by adjusting the type I error or using a stepwise, closed testing strategy for hypothesis testing. If sponsors use a closed testing hypothesis strategy, they should justify the order of hypothesis testing before trial initiation. These issues should be discussed with the FDA in advance of trial enrollment.

a. Analysis populations

The following definitions apply to various populations for analyses in ABS clinical trials:

- **Safety population —** All patients who receive at least one dose of assigned therapy during the trial.

- **Intent-to-treat (ITT) population** — All patients who are randomized.

- **Microbiological intent-to-treat (micro-ITT) population —** When sinus aspiration or endoscopy is performed as defined in the protocol, patients who are randomized and who have a pathogen known to cause ABS isolated at baseline. Patients should not be excluded from this population based upon events that are measured after randomization (e.g., loss to follow-up).

- **Per-protocol populations (also referred to as the *clinically evaluable* or *microbiologically evaluable* populations) —** The population of patients who meet the definition for the primary analysis population (ITT or micro-ITT population) and who follow important components of the protocol as specified (e.g., administration of a specified minimum amount of trial drug therapy). Traditionally, adequacy of therapy for a per-protocol analysis population has been defined as patients who have received greater than 80 percent (or within 80 to 120 percent) of the prescribed dose amount and/or dosing regimen. Sponsors should document compliance with dosing (e.g., daily assessment, patient or caregiver diary, urine testing, or MEMS caps).

In general, the ITT population should be considered the primary analysis population. Trials that enroll patients with baseline sinus aspiration can chose to evaluate the micro-ITT population as the primary analysis population. The micro-ITT population is the population most likely to show the largest treatment effect of antibacterial treatment.[12] Other analysis populations in the trial should be evaluated as well to ensure consistency of results. It is important to note that the per-protocol population analyses are subgroup analyses because they exclude patients based upon events that occur after randomization. Patients in such subgroup analyses may differ by important factors (both measured and unmeasured) other than the drug received.

b. Noninferiority margins

FDA review of previous ABS trials has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABS by antimicrobial drugs. Therefore, we do not recommend the use of noninferiority trials to establish evidence of effectiveness for regulatory approval of a new indication for ABS. See also the draft guidance for industry *Non-Inferiority Clinical Trials*[13] and the guidance for industry *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval*.

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate, and the amount by which the investigational drug is expected to be superior to the control (effect size). Sample size should be based upon the number of patients needed to draw conclusions based on the analysis population. For example, the effect size for an antibacterial drug is likely to be larger among patients in a micro-ITT analysis population with confirmed bacterial pathogens. There may be circumstances where a sample size estimate for an efficacy analysis in ABS trials may not include a sufficient number of patients for an adequate evaluation of safety,

[12] The culture results (i.e., the specific bacterial organisms) that define whether a patient should be included in the micro-ITT population should be stated in the protocol. For example, a trial design with all isolates obtained by endoscopy may wish to include only patients with *S. pneumonia* or *H. influenzae* isolates in the micro-ITT analysis to improve specificity.

[13] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

in which case there are several choices to enhance the number of patients in an overall preapproval safety database (see section III.A.4., Safety Considerations).

d. Missing data

There is no single optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. Analyses that exclude patients are subgroup analyses, and patients who do not complete the trial may differ substantially from those patients who remain in the trial in both measured and unmeasured ways. Therefore, sponsors should prespecify in the protocol the method of how missing data will be included in the analysis of trial results. Sponsors also should present sensitivity analyses in the final report such as including all missing patients as failures, including all missing patients as successes, and including all missing data as successes or failures in each treatment group respectively.

Different rates of missing data or differences in the reasons for missing data across treatment arms can be a cause for concern in the interpretation of a clinical trial. If this situation occurs, it should be addressed in the report.

e. Statistical analysis plan

The sponsor should submit to the FDA before trial initiation the statistical analysis plan for any phase 3 ABS trial.

13. Ethical Considerations

Review of previous placebo-controlled trials of the treatment of ABS has shown variable results, with several placebo-controlled trials showing no effect of antimicrobial treatment for ABS. Accordingly, trials have not shown a risk to placebo-treated patients that make future placebo-controlled trials unethical; the risk from placebo treatment may be similar to that associated with antibacterial therapy because low-frequency severe events (e.g., pseudomembranous colitis or serious allergic reactions) have been observed with almost all antibacterial drugs. The occurrence of common but less-severe adverse events (e.g., diarrhea) from antibacterial drugs also can be relevant in assessing the risk-benefit to patients in a placebo-controlled trial where the expected treatment effect may be small. Rescue antibacterial therapy can be incorporated into the trial design so that individual patients are treated at the time a failure outcome is assigned; this may serve to mitigate concerns regarding inclusion of a placebo group in an ABS trial. All trial designs should provide appropriate provisions for patient safety.

14. Labeling Considerations

The following is an example of a labeled indication for the treatment of ABS.

> "Drug X is indicated in the treatment of acute bacterial sinusitis due to susceptible isolates of (Genus and species of the relevant bacterial pathogens)."

Guidance for Industry

Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2012
Clinical/Antimicrobial

Guidance for Industry

Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment

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Contains Nonbinding Recommendations

Guidance for Industry[1]
Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of antimicrobial drugs[2] for the treatment of acute bacterial exacerbations of chronic bronchitis in patients with chronic obstructive pulmonary disease (ABECB-COPD), a disease that previously has been referred to as acute bacterial exacerbations of chronic bronchitis (ABECB). (The term ABECB-COPD is further defined in section III.A.2., Definition of ABECB-COPD.)

Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for antimicrobial drugs to support an indication for treatment of ABECB-COPD.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[3] This guidance focuses on specific drug development and trial design issues that are unique to the study of treatment of ABECB-COPD. It does not address issues related to the development of drugs for COPD or COPD exacerbations caused by factors other than bacterial

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

infection, and does not address issues related to the development of drugs for the prevention of ABECB-COPD. Information regarding developing drugs for the treatment of COPD is available in the draft guidance for industry *Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment*.[4]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Since the FDA published its first draft guidance on the development of antimicrobial drugs for the treatment of ABECB in 1998, there have been several public discussions regarding the design of clinical trials to study indications for infections involving the respiratory tract, including the indication of ABECB-COPD.[5] These discussions have focused on trial design issues for ABECB-COPD such as the following:

- Superiority versus noninferiority trial designs
- Use of a placebo control
- Inclusion criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of efficacy outcome measures
- Timing of outcome assessments
- Use of concomitant medications
- Role of microbiological outcomes

Since these public discussions were held, publications of reviews and treatment guidelines of ABECB-COPD have suggested a stratified approach in which antibacterial drugs are recommended for patients with ABECB-COPD characterized as *moderate* or *severe*, but not for patients with ABECB-COPD characterized as *mild*. This guidance discusses the trial design issues listed above as well as a different stratification for ABECB-COPD based on *inpatient* versus *outpatient* treatment (see Appendix A).

[4] When final, this guidance will represent the FDA's current thinking on this topic.

[5] The design of ABECB clinical trials was discussed at a meeting of the Anti-Infective Drugs Advisory Committee on February 19, 2002, and an Infectious Diseases Society of America/Pharmaceutical Research and Manufacturers of America/FDA workshop on November 19-20, 2002. Transcripts of these meetings are available at http://www fda.gov/ohrms/dockets/ac/02/transcripts/3837t1 htm and http://www regulations.gov/#!documentDetail;D=FDA-2002-N-0319-0003, respectively.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

New drugs being studied for ABECB-COPD should have nonclinical data documenting activity against the pathogens most commonly associated with ABECB-COPD (i.e., *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*).

2. Definition of ABECB-COPD

The term ABECB-COPD is used in this guidance to more accurately identify the disease that has previously been referred to as acute bacterial exacerbations of chronic bronchitis. ABECB-COPD refers to a clinical diagnosis of presumptive bacterial infection superimposed on a chronic pulmonary condition. This situation is best described pathologically as bronchial inflammation associated with the isolation of pathogenic bacteria from sputum or bronchial lavage specimens. However, it is important to note that there is some uncertainty as to the role of bacteria in causing ABECB-COPD because chronic bacterial colonization may be present in the airways of patients with COPD.

The acute component of ABECB-COPD is usually manifested as a worsening of the same symptoms patients experience when they are not experiencing an acute infection.[6] Accordingly, to enroll patients in ABECB-COPD trials, clinical trials should be designed to:

- Define and document the underlying pulmonary condition in enrolled patients
- Accurately measure the symptoms of the acute episode at trial entry
- Define the criteria for occurrence of an episode of ABECB-COPD (i.e., the change in symptoms that define an acute episode against the background of chronic pulmonary disease)

3. Efficacy Considerations

FDA review of previous ABECB-COPD trials has not been able to establish a reliable estimate of the magnitude of benefit for antibacterial drug treatment of ABECB-COPD, which is a precondition for a noninferiority trial.[7] Accordingly, only superiority trials are currently recommended for ABECB-COPD.[8]

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[6] See References, section D., Publications that provide definitions for COPD and ABECB-COPD.

[7] See ICH E10 and the draft guidance for industry *Non-Inferiority Clinical Trials* (when final, this guidance will represent the FDA's current thinking on this topic).

[8] We recognize that treatment guidelines suggest a stratification of patients in which those with more severe ABECB-COPD should receive treatment with an antibacterial drug. A reliable and well-defined magnitude of the treatment effect for patients with more severe ABECB-COPD has not been established.

The goal of ABECB-COPD clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of ABECB-COPD associated with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*. If sponsors wish to add additional organisms to this indication based on current epidemiological data or other organisms encountered in the clinical development, they should provide data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in ABECB-COPD. Bacteria that may be colonizers following recent antimicrobial therapy are unlikely to be pathogens in this setting.

The number of trials that should be conducted in support of an ABECB-COPD indication depends on the overall development plan for the drug under consideration. If the development plan for a drug has ABECB-COPD as the sole marketed indication, then two adequate and well-controlled trials establishing safety and efficacy should be conducted.

A single randomized, double-blind trial supporting the indication may be appropriate if data demonstrate effectiveness in other lower respiratory tract diseases. For example, robust findings of efficacy from well-designed community-acquired bacterial pneumonia development programs with similar dosing regimens may be supportive of a single superiority trial of ABECB-COPD.

The disease course and treatment for ABECB-COPD is of a short-term duration and the clinical outcome is readily measured. Currently, there are no surrogate markers accepted by the FDA as substituting for clinical outcomes in ABECB-COPD trials. Sponsors who wish to propose use of a surrogate marker should discuss this with the FDA early in the drug development process.

4. Safety Considerations

A sufficient number of patients should be studied at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety. This includes the ability to evaluate the potential for relatively uncommon serious adverse events as well as commonly expected adverse events. The information should be derived primarily from adequate and well-controlled trials of ABECB-COPD, but also can be derived from trials of the new drug for infections other than ABECB-COPD if exposure is similar to or greater than the exposure for ABECB-COPD. The total number of patients needed for a drug development program that includes an ABECB-COPD indication should be discussed with the FDA early in the drug development process.

Antimicrobials with clinically significant toxicity may not be appropriate for study of ABECB-COPD unless the treatment goal is directed at a more seriously ill patient portion of the ABECB-COPD population.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Design

As previously mentioned, we recommend only superiority trials for ABECB-COPD trials (see section III.B.11.b., Noninferiority margins).

Superiority trials in the treatment of ABECB-COPD can consist of the following forms:

- **Placebo-controlled trial with a background of best available nonantimicrobial therapy —** All patients receive the best available nonantimicrobial therapy and are randomized to receive, in addition, an investigational antibacterial drug or matching placebo. To demonstrate efficacy, the group receiving the investigational antibacterial drug should demonstrate superiority to the control group receiving matching placebo. A three-arm trial with the experimental treatment group, an active comparator group, and a placebo-controlled group permits the demonstration of superiority to placebo and also can provide risk-benefit information relative to an approved comparator.

- **Dose-response —** Patients in each treatment group receive different doses (or dosing regimens) of an investigational antibacterial drug together with the best available nonantimicrobial therapy. To demonstrate efficacy, the group receiving a higher dose (or more intensive therapy) should be superior to the lower dose (or less intensive) regimen.

- **Superiority of the trial antimicrobial to another antimicrobial —** Patients in one group receiving the investigational drug (with best available background nonantimicrobial therapy) are compared with patients in a control group receiving another antibacterial drug (with best available background nonantimicrobial therapy). To demonstrate efficacy, the group receiving the investigational antibacterial drug should demonstrate superiority to the group receiving the control antibacterial drug.

ABECB-COPD trials should be parallel group designs because crossover designs may be subject to carryover and period effects. Other trial designs to demonstrate superiority can be discussed with the FDA.

2. Trial Population

ABECB-COPD clinical trials should enroll males and females 35 years old and older because COPD occurs primarily in older individuals; a diagnosis in younger individuals may reflect misclassification. We anticipate that most patients in ABECB-COPD clinical trials will be older than 50 years of age. ABECB-COPD does not occur in a pediatric population.

We recognize that it is not appropriate for patients with ABECB-COPD of greater severity (e.g., patients who are mechanically ventilated) to be enrolled in placebo-controlled trials of a new antibacterial for ABECB-COPD. We strongly encourage discussion with the review division if study of patients with greater severity is being considered. It is essential that in any proposed trials, adequate provisions are in place so that human subjects are not exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42).

3. Entry Criteria

The diagnosis of ABECB-COPD can be challenging. Both a diagnosis of COPD and an acute change superimposed against the background of chronic symptoms should be used for trial enrollment.

Traditionally, COPD has been defined as containing aspects of chronic bronchitis and emphysema. A diagnosis of chronic bronchitis is made clinically based on the presence of symptoms of cough and sputum production on most days of 3 consecutive months in at least 2 consecutive years. Although useful for clinical practice, this definition lacks specificity for clinical trials because there is no standardized definition of the number of days that constitutes *most* days of 3 months out of the year or quantification of degree of sputum and cough.

Because of the overlap of symptoms in patients with chronic bronchitis and/or emphysema and the limitations of the definition of chronic bronchitis, it is more appropriate to use the term COPD to describe the underlying disease in this patient population. The definition and severity of underlying obstructive pulmonary disease is based on the results from spirometry testing compared to predicted normative values as follows:

- Mild COPD = FEV1/FVC < 70% and FEV1 ≥ 80% predicted
- Moderate COPD = FEV1/FVC < 70% and 50% ≤ FEV1 < 80%
- Severe COPD = FEV1/FVC < 70% and 30% ≤ FEV1 < 50%
- Very severe COPD = FEV1/FVC < 70%, or FEV1 < 30% predicted or FEV1 < 50% plus chronic respiratory failure

Spirometry may be difficult to perform at the time of ABECB because these tests are effort dependent. Spirometry data used for enrollment should be obtained from recent medical records; patients without spirometry-documented COPD should not be enrolled in ABECB-COPD trials. Spirometry data obtained at the time an episode of ABECB-COPD is diagnosed have not been demonstrated to be predictive of severity or outcome.

The diagnosis of an acute exacerbation presents additional concerns. A diagnosis of ABECB-COPD reflects a change in patient symptoms from their usual baseline; for a trial to demonstrate efficacy of antimicrobial therapy to be effective, patients who have a true change in symptoms should be selected. Because symptoms and signs as reported by the patient are critical to the diagnosis and clinical management of COPD and ABECB-COPD, a well-defined and reliable patient-reported outcome (PRO) instrument should be used in clinical trials for the treatment of ABECB-COPD.[9]

The specificity of sputum cultures for selecting patients with bacterial disease is unknown in ABECB-COPD because sputum is not normally sterile between exacerbations in these patients, and the etiologic role of bacteria in ABECB-COPD is uncertain. However, if there is a pathogenic role for bacteria in this disease, a negative sputum culture may reduce the chance of demonstrating a significant benefit from an antibacterial drug. Sponsors may wish to restrict

[9] Sponsors should define the description of ABECB-COPD to be used in the inclusion criteria. We are also aware of ongoing evaluations of a PRO instrument in ABECB-COPD.

enrollment in trials to patients with a positive sputum culture at baseline for any one of the three most common bacteria implicated as a cause of ABECB-COPD (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*).[10]

a. Inclusion criteria

The following are recommended inclusion criteria for patient enrollment in trials conducted for the treatment of ABECB-COPD.

- **Patient history and characteristics.** The following patient demographic characteristics should be used for a better chance of selecting patients more likely to have ABECB-COPD:

  - Male and female patients 35 years old and older
  - History of at least mild COPD previously defined by the spirometry criteria above
  - History of more than two previous episodes of acute exacerbations in the previous year
  - History of tobacco use consistent with a diagnosis of COPD

- **Signs and symptoms.** Signs and symptoms that can be present in patients over the previous 7 days with ABECB-COPD include the following:

  - Increased dyspnea or breathlessness
  - New or increased cough
  - New or worsening chest tightness or discomfort
  - Sleep disturbances (i.e., insomnia or sleepiness)
  - Decrease in exercise tolerance or limitation of usual activities
  - Increase in sputum volume and/or sputum purulence
  - New or increase in wheezing
  - New or worsening crackles on auscultation of lung fields

  Generalized signs and symptoms occurring over the previous 7 days that are consistent with a diagnosis of ABECB-COPD (but are otherwise nonspecific) include:

  - Fever (e.g., temperature greater than 38.0 degrees Centigrade)
  - Malaise or fatigue
  - Confusion or change in mental status

[10] This situation can be addressed by use of a run-in period, if feasible, when patients with a negative culture at baseline are excluded before beginning trial therapy or during analysis by analyzing patients with a positive culture at baseline separately. This is discussed further in sections III.B.10., Clinical Trial Visits and Timing of Assessments, and III.B.11., Statistical Considerations.

All signs and symptoms that may be present in patients with ABECB-COPD should be captured on the case report form (symptoms and patient-reported signs should be captured by a PRO instrument), as should current tobacco use.

b. Exclusion criteria

The following patients should be excluded from trials for the treatment of ABECB-COPD:

- Patients with ABECB-COPD characterized as severe (e.g., requiring hospitalization).
- Patients with pneumonia documented by chest X-ray at the time of initial screening. All patients should receive a screening chest X-ray before or at enrollment.
- Patients with asthma and no evidence of other chronic lung disease.
- Patients with any concomitant illness that may confound the interpretation of the effect of trial drugs (e.g., pulmonary malignancy, congestive heart failure, bronchiectasis, pneumothorax).
- Immunocompromised patients; however, patients receiving systemic corticosteroids at baseline for treatment of COPD can be enrolled.
- Patients who are allergic to any of the trial drugs.

Depending on the trial design, sponsors also may wish to exclude patients who have received antimicrobial therapy for the current episode of ABECB-COPD, or alternatively, permit enrollment of patients with symptoms that are not improving or worsening on prior antimicrobial therapy.

4. Randomization, Stratification, and Blinding

Patients should be randomized for receipt of trial drugs at enrollment. If trials allow enrollment of patients who have received prior antimicrobial therapy, prior antibacterial drug therapy should be included as a stratification factor. All trials should be double-blinded.

5. Special Populations

Drug development programs should include a sufficient number of geriatric patients, including patients older than 75, to characterize safety and efficacy in this population.[11] Pharmacokinetics of the drug in patients with hepatic impairment or in patients with renal impairment may be evaluated before initiation of phase 3 trials to determine whether dose adjustments are necessary; this evaluation may help avoid the exclusion of such patients from phase 3 clinical trials.

[11] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

6. Dose Selection

Data from phase 1 and phase 2 studies and dose-ranging pharmacokinetic/pharmacodynamic studies (including information regarding bronchial/lung penetration of the drug) can be integral to selecting an appropriate dose and duration of therapy for phase 3 clinical trials.

7. Choice of Comparators

The control group for these superiority trials can be placebo or another antibacterial drug.

8. Concomitant Medications

Patients can receive appropriate nonantimicrobial therapies at the time of enrollment based on their condition, which may include bronchodilator and/or systemic corticosteroid therapies. Lack of standardization of concomitant medications can introduce an important source of confounding in clinical trials if there are imbalances in receipt of nonantimicrobial therapy between trial groups. Such confounding may occur even if the number of patients receiving concomitant medications is similar between treatment groups but the reasons for administering concomitant medications differ. Confounding also may occur when the patients in one group who receive concomitant medications differ in baseline characteristics from those patients who do not receive concomitant medications.

Because nonantimicrobial therapies might influence a PRO instrument scale, it is emphasized that treatment groups should be balanced in the use of nonantimicrobial therapies to minimize confounding and ensure that a treatment effect on a PRO outcome measure would be attributed to the investigational antibacterial drug over the control (e.g., placebo). Therefore, sponsors should make every attempt to control for potential confounders such as concomitant medications. This can be accomplished through a protocol-specified nonantimicrobial background regimen with the dose and frequency of use similar for all patients in the trial (e.g., bronchodilator treatment, or protocol-specified rules for the addition of nonantimicrobial therapy such as corticosteroids). At a minimum, the protocol should specify appropriate options for nonantimicrobial therapies during the trial.

We anticipate that changes in the use of the following medications will be monitored or specified in an ABECB-COPD trial and should be balanced between treatment groups:

- Changes in the frequency or dose of beta-agonist therapy, or the addition of new beta-agonist therapy (long- or short-acting therapy)

- Changes in the frequency or dose of anticholinergic therapy or the addition of an anticholinergic therapy

- Addition of methylxanthine therapy

- Changes or the addition of systemic corticosteroids; systemic corticosteroids should be administered in a standardized way in the trial (e.g., to all patients with a pre-enrollment FEV1 of < 50% of predicted FEV1)

Assessment of the need for concomitant medications as an endpoint may not be reflective of the persistence of patient signs or symptoms; the presence of such signs or symptoms should be confirmed by a PRO instrument that shows continued signs or symptoms at the time of administration of the concomitant medication.

9. Efficacy Endpoints

a. Evaluation of clinical response

The primary emphasis of the trial should be the effect of the antimicrobial drug on outcomes that are clinically important to patients. A well-defined and reliable method of assessing patient symptoms should be used for ABECB-COPD trials. Accordingly, we recommend use of a valid and reliable PRO instrument as the primary outcome measure.[12] The same PRO instrument also should be used at baseline to define enrollment criteria; the severity level based on the PRO instrument's score should be sufficient to allow observation of a clinically meaningful response (i.e., change on the PRO instrument). The direction and magnitude of change, improvement or worsening, determined to be clinically meaningful (and therefore appropriate for regulatory decisions) should be determined during instrument development and should be discussed with the FDA before trial initiation. Statistically significant differences between comparator regimens may not be sufficient for demonstrating treatment benefit in terms of how a patient feels or functions if response to treatment has not been confirmed to be clinically meaningful to patients. For example, signs or symptoms used to diagnose ABECB-COPD that may be important to a clinician, such as the color of sputum, may not be an important outcome to patients and therefore would not be appropriate as part of the score used in the efficacy endpoint to determine response to treatment.

If an adequate PRO instrument for ABECB-COPD is available for studying ABECB-COPD, it should be incorporated in the entire clinical development program. The use of a PRO instrument in phase 2 trials of patients with ABECB-COPD can provide additional data about clinical activity and can inform the design and use of the PRO instrument in phase 3 clinical development plans (e.g., sample size calculations). If an adequate instrument for studying ABECB-COPD is not available at the outset of the clinical development program, we recommend that the new instrument development process begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol.

Patients with ABECB-COPD are unlikely to be asymptomatic at the end of trial treatment, and may not even return to their baseline status before the onset of the acute episode. Improvement

[12] The use of a well-defined and reliable PRO instrument can yield greater assurance that symptoms are being measured in a consistent manner across patients. For more information regarding the development of PRO measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

of symptoms over time as measured by a well-defined and reliable PRO measure should be the primary efficacy endpoint rather than return to previous baseline.

A fixed time endpoint may not be as sensitive a measure of treatment effect as a time-to-improvement analysis. For example, clinical outcome at greater than 3 weeks after onset of therapy may not show a difference between treatment arms because many patients may have resolution of the acute exacerbation by this time, regardless of the administration of antibacterial drug therapy. Sponsors who choose to use response at a fixed time point as the primary outcome (i.e., as the *test-of-cure* assessment) should provide evidence to support the selection of that specific time point.

An outcome scale can be used for describing categorical responses (e.g., *improvement* or *failure*) at each time point if the criteria for the categories are well-defined and reliable. Overall response should also incorporate survival and the absence of complications of ABECB-COPD as part of the overall response assessment (e.g., the development of pneumonia should be considered a clinical failure). Failure criteria should be defined a priori (e.g., protocol-defined worsening of symptoms, failure to improve at certain time points after treatment onset). Failure should likely mandate a change in treatment, which should include *active* therapy for the placebo arm.

Other measures such as pulmonary function testing or exercise testing (e.g., a *6-minute walk*) can be incorporated into a clinical protocol and should be considered secondary outcome measures.

Patients designated as clinical failures at any time point should be designated as clinical failures for all subsequent follow-up visits.

Early clinical assessment for treatment failure should be performed in a placebo-controlled trial so that *rescue* therapy can be incorporated into the trial design at the time a failure outcome is assigned; this process can serve to mitigate concerns regarding inclusion of a placebo arm in an ABECB-COPD trial.

b. Clinical relapse or recurrence

Patients who initially improve and then experience worsening of signs and symptoms of ABECB-COPD during the trial should be considered as treatment failures because of relapse or recurrence of ABECB-COPD. These patients should be re-evaluated clinically and microbiologically to distinguish between clinical relapse (with persistence of the same bacterial pathogen) and clinical recurrence (infection with a new bacterial pathogen). This distinction may be useful for trials that examine clinical recurrence as a secondary endpoint (i.e., assessment of the prolonged effect from antibacterial treatment of a single episode). Patients who continue to demonstrate clinical improvement during the trial, yet do not return to their baseline COPD status before ABECB-COPD, should not be characterized as clinical relapse or recurrence.

c. Adverse events or receipt of additional antibacterial therapy

Patients who discontinue therapy because of an adverse event should be evaluated at the time of discontinuation of the trial drug therapy. These patients should not be necessarily considered

withdrawn from the trial in terms of overall evaluation; investigators should continue to follow all such patients at scheduled visits and continue to record information on both safety and efficacy outcomes. If at the time trial drug therapy is discontinued the patient is alive, without complications, and does not receive additional antimicrobial therapy, then the patient should be evaluated following the protocol criteria. If a trial patient maintains clinical improvement of ABECB-COPD after discontinuation of therapy because of an adverse event, the patient should not be automatically considered a clinical failure.

Patients who receive another antibacterial drug while on trial drug therapy should be identified because these patients should be considered failures in an efficacy analysis.

d. Microbiological response

Although microbiological outcome may provide useful information regarding the biological activity of antimicrobials, microbiological outcome is not a direct measure of benefit to patients. Microbiological outcome should be viewed as being supportive information, but not as a substitute for clinical outcome in a specific trial.[13]

If follow-up specimens for culture are obtained from patients, the most useful specimens are those obtained at least 72 hours after the completion of drug therapy because negative culture results obtained while on therapy may represent suppression rather than elimination of organisms. Any target pathogens isolated from follow-up specimens should be tested for susceptibility to the antimicrobial used to treat the disease.

All target pathogens isolated from patients during clinical trials should be appropriately saved in the event that there is a need to do additional trials with the bacteria.

10. Clinical Trial Visits and Timing of Assessments

a. Entry visit

At entry, the investigator should evaluate the patient by performing an appropriate history and physical examination. The following information should be recorded on the case report form during the entry examination.

- **History and demographic characteristics**

  - Date of visit.
  - Age, sex, and weight.
  - Underlying medical condition(s).
  - Current medications.

[13] Microbiological outcomes may be valuable in phase 2 trials addressing dosing regimens (i.e., where time to no growth on culture is being used as an outcome to optimize dose and/or dosing frequency).

- Number of distinct and well-documented episodes of acute bronchitis in the past, including how this information is obtained (i.e., chart review or patient recall); dates, treatment regimens, and outcomes should be recorded.

- Detailed history of COPD including results of prior pulmonary function testing. This history is best obtained from objective sources (e.g., patient medical records).

- History of tobacco use.

- Recent or current use of antibacterial drugs, and the indication or reason for use.

- Bacteria previously isolated from sputum during previous exacerbations, with antimicrobial susceptibility profile.

- **Symptoms**

  A well-defined and reliable PRO instrument, as discussed in section III.B.9., Efficacy Endpoints, should be used to assess symptoms at baseline.

- **Signs**

  - Vital signs, including body temperature measurement

  - Posteroanterior and lateral chest X-rays[14]

  - Electrocardiography (to rule out arrhythmia and for safety analysis)

  - Other laboratory tests for evaluation of safety parameters (e.g., complete blood count, serum chemistries)

- **Sputum sample collection**

  The entry visit should include baseline sputum Gram stain with submission of sputum for culture and susceptibility testing. Sponsors should describe in the protocol the methods of obtaining specimens, specimen processing, and culture techniques. For microbiological assessment, the investigator should collect the following information:

  - A description of how the sample was obtained (e.g., expectoration, induced sputum, aspiration), processed, and transported to the laboratory.

[14] Patients should have a baseline chest X-ray to rule out pneumonia and other confounding illnesses such as congestive heart failure, malignancy, or bronchiectasis. Spiral computed tomography and D-dimer testing can be indicated in selected patients to exclude pulmonary embolism.

- The adequacy of the specimen in terms of numbers of polymorphonuclear cells and epithelial cells present.[15]

- Identification of bacterial isolates.

- In vitro susceptibility (preferably minimum inhibitory concentration) testing of the isolates to both the trial and control drugs. In vitro susceptibility testing should be performed by using standardized methods, such as the Clinical and Laboratory Standards Institute methods, unless otherwise justified.

Microbiological information that is not part of the entry criteria (e.g., susceptibility results) should remain blinded to investigators. Previous trials have shown that patients with the following characteristics may be more likely to have bacteria isolated by sputum culture at baseline:

- Purulent sputum
- Patients with more than two episodes of acute bronchitis per year
- Patients with a positive baseline sputum Gram stain

Clinical outcome results should be evaluated by sputum culture data for each pathogen (e.g., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*).

b. On-therapy visits

Each patient should have daily on-therapy assessments of signs and symptoms using a well-defined and reliable PRO instrument. Regardless of how the assessment is conducted (e.g., using an interviewer-administered PRO, interactive voice response via telephone, or electronic capture using a mobile device), the questioning of patients should be performed in a valid, reproducible, and structured way to minimize the potential for inconsistencies in the assessment.[16] The ability to detect differences between therapies for a time-to-improvement endpoint may be increased if assessments are done more often (e.g., twice daily). Therapy should be continued as described in the protocol regardless of whether symptoms have improved. Investigators should attempt to allow a minimum of 72 hours on therapy with the trial drug therapy before classifying a patient as a clinical failure; accordingly, investigators may wish to include a 48- to 72-hour visit to ensure there is no substantial clinical worsening at this time.

Assigning an outcome of clinical failure and permitting use of rescue antibacterial therapy should be reserved for patients who are worsening on their assigned treatment; specific criteria to identify these patients should be included in the protocol. It is important that investigators

[15] Investigators should evaluate the adequacy of sputum samples by ensuring that the specimen is most likely from lower respiratory secretions by use of the following factors: greater than 25 white blood cells per field at 100x magnification (low power, 10x objective) confirming the impression of *sputum purulence* and fewer than 10 squamous epithelial cells at 100x magnification (low power, 10x objective).

[16] When interviews are used they should be standardized; in addition, symptoms recorded from the patient should be recorded without interpretation by the interviewer. See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

distinguish patients who are worsening (i.e., where rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy. The protocol should also specify a failure endpoint if symptoms have not improved by a certain day, even if the symptoms are not clinically worsening at that time; this may be most objective if defined as a score remaining above a certain threshold for a PRO instrument. In general, patients should not be unblinded if a criterion for rescue therapy is met.

In the case of clinical failure, therapy should be changed to include initiation of antibacterial therapy and/or other appropriate therapeutic modifications as necessary. Protocols should define the choice of the antibacterial therapy to be used in the case of clinical failure. If failure is assigned, the investigator should attempt to obtain a repeat sputum culture and the sample should be sent for culture and susceptibility testing. Patients who meet criteria for clinical failure should continue to have the identical protocol-specified assessments as patients who continue to receive their originally assigned treatment.

Investigators should document findings from on-therapy office visits on the case report form (e.g., history, physical examination, and laboratory test results). If the investigator contacts the patient by telephone or by another interactive technology, documentation of the specific questions asked, how they were asked, and the responses given should be captured on the case report form. If a well-defined and reliable diary is used to capture patient symptoms during this visit, this information also should be recorded on the case report form.

Consideration should be given to obtaining blood samples for the measurement of drug concentration (e.g., a sparse sampling strategy). An assessment of drug exposure in phase 3 could help explain trial outcomes related to efficacy and/or safety. It could also be used to assess the relationship between the pharmacokinetic/pharmacodynamic indices and observed clinical outcomes. The protocol should provide a description of the sampling strategy and the proposed analysis plan.

c. Early follow-up visit

The early follow-up visit should occur after completion of all trial drug therapy at a time when the drug is expected to be clear from the infection site (usually at least 5 half-lives). For example, if a drug with a short half-life is administered for 10 days, this visit can occur at completion of trial drug therapy or up to 4 days after completion of therapy; this visit should occur later for drugs with a longer half-life. At this visit, the investigator should perform a directed medical history and physical examination, as well as appropriate laboratory measurements. The investigator also should inquire about adverse events. Depending on the trial design, follow-up sputum culture may be appropriate at this visit.

d. Late follow-up assessment

The late follow-up assessment should occur 10 to 14 days after the completion of all trial drug therapy (e.g., if trial drug is administered for 10 days, this assessment can occur on days 20 to 25 after therapy initiation (unless a drug with a long half-life has been studied)). For patients with adverse events occurring at or after the early follow-up assessment, investigators should perform

an assessment that includes a medical history, a physical examination, appropriate laboratory evaluations, identification of any new adverse events, and follow-up on unresolved adverse events.

e. Safety evaluations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations also may be needed because of the nonclinical and clinical profile of the specific drug under study (e.g., additional electrocardiogram measurements). Longer-term assessment of adverse events after discontinuation or completion of the antibacterial drug therapy also can be considered depending on the specific drug being studied.

All patients should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the test drug has been discontinued.[17] All adverse events should be followed until resolution, even if time on trial would otherwise have been completed.

11. Statistical Considerations

Sponsors should designate the hypotheses to be tested before trial initiation. These hypotheses should be stated in the protocol or statistical analysis plan, and the trial should be powered to detect differences between treatment arms if group differences exist. If sponsors choose to test multiple hypotheses, they should address issues related to the potential increase in obtaining false positive results (type I error) because of multiple comparisons, either by adjusting the type I error or using a stepwise, closed testing strategy for hypothesis testing. If sponsors use a closed testing hypothesis strategy, they should specify the order of hypothesis testing before trial initiation and the method for controlling the overall type I error rate. These issues should be discussed with the FDA in advance of trial enrollment, and should be incorporated into the statistical analysis plan as appropriate.

a. Analysis populations

The following definitions apply to various populations for analyses in ABECB-COPD clinical trials:

- **Safety population —** All patients who receive at least one dose of assigned therapy during the trial.
- **Intent-to-treat (ITT) population** — All patients who are randomized.
- **Microbiological intent-to-treat (micro-ITT) population —** All patients who are randomized and who have a pathogen associated with ABECB-COPD isolated at

[17] For specific safety reporting recommendations during clinical trials, see the ICH guidance for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

baseline. Patients should not be excluded from this population based upon events that are measured after randomization (e.g., loss to follow-up).

- **Per-protocol populations (also referred to as the *clinically evaluable* or *microbiologically evaluable* populations) —** The population of patients who meet the definition for the primary analysis population (ITT or micro-ITT population) and who follow important components of the protocol as specified (e.g., administration of a specified minimum amount of trial drug therapy). Traditionally, adequacy of therapy for a per-protocol analysis population has been defined as patients who have received greater than 80 percent (or within 80 to 120 percent) of the prescribed dose amount and/or dosing regimen. Sponsors should document compliance with dosing (e.g., daily assessment, patient diary, urine testing, or MEMS caps).

To ensure consistency of results, the ITT and/or micro-ITT populations should be evaluated as well as the population of patients who follow important aspects of the protocol (i.e., the per-protocol populations). However, it is also important to note that the per-protocol population analyses are subgroup analyses because they exclude patients based upon events that occur after randomization. Patients in such subgroup analyses may differ by important factors (both measured and unmeasured) other than the drug received; because of this, analyses based on the ITT (or micro-ITT) population should be considered the primary analyses, with analyses based on a per-protocol population reviewed for consistency of results. Results in both populations should provide evidence of effectiveness.

The primary and secondary analyses should be defined in the protocol before trial initiation. Depending on the exact hypothesis being tested, sponsors may prefer to specify either the ITT or micro-ITT population as the primary population for analysis. For example, because an effect of an antibacterial drug is most likely to be seen in patients with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* or other likely bacterial pathogens isolated at baseline, the trial can be powered for the micro-ITT population and this should be the primary analysis population. If it is expected that the investigational drug arm will be superior to the placebo arm for all patients enrolled, even patients who did not have a pathogen isolated, then an ITT population would be the most appropriate primary analysis population. The choice of population (i.e., micro-ITT or ITT) for the primary analysis may guide the details of product labeling if the drug is approved.

b. Noninferiority margins

As previously mentioned, FDA review of previous ABECB-COPD trials has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABECB-COPD with antibacterial drug therapy. Because of this, we do not recommend using noninferiority trials to establish evidence of effectiveness for regulatory approval of a new indication for ABECB-COPD. Sponsors who are considering a noninferiority trial for ABECB-COPD should justify to the FDA the proposed noninferiority margin by data that include reliable estimates of a well-defined efficacy outcome measure. Such justification should be discussed with the FDA as early as possible during protocol development and before trial initiation. For additional information regarding noninferiority trials in general and in antibacterial trials, see ICH E10, the guidance for

industry *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval*, and the draft guidance for industry *Non-Inferiority Clinical Trials*.[18]

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate, and the noninferiority margin (for a noninferiority trial), or the amount by which the trial drug is expected to be superior to the control (in a superiority trial). Sample size should be based upon the number of patients needed to draw conclusions in the ITT or micro-ITT analysis population.

d. Missing data

There is no single optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. Analyses that exclude patients are subgroup analyses, and patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways. Therefore, sponsors should prespecify in the protocol the method of how missing data will be addressed in the analysis of trial results. Sponsors also should present sensitivity analyses in the final report such as including all missing patients as failures, including all missing patients as successes, and including all missing data as successes or failures in each treatment group respectively.

Different rates of missing data or differences in the reasons for missing data across treatment arms can be a cause for concern in the interpretation of a clinical trial. If this occurs, it should be addressed in the final report.

e. Interim analyses and data monitoring committee

If interim (or futility) analyses will be performed, they should be specified in the analysis plan. The purpose of the interim analysis should be stated in the analysis; it is important that the interim analysis not affect trial conduct and thereby compromise trial results. Trial data also should be examined at the time of interim analysis for any emerging safety signals. We encourage sponsors to discuss their plans with the review division before trial initiation to ensure that the overall trial significance tests properly address the effect of interim testing.

Use of a data monitoring committee (DMC) may be appropriate depending on the design of the proposed phase 3 trial and the patient population that the trial will enroll. If a DMC is used, a detailed charter with the composition of the committee members and the operational details should be provided for review.[19]

[18] When final, this guidance will represent the FDA's current thinking on this topic.

[19] For more detailed information, see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

f. Other analyses of interest and secondary endpoints

Analyses of secondary and additional endpoints should be considered exploratory because a trial usually is not designed to address the questions raised by these analyses, either because of multiple comparisons and/or concerns with subgroup analyses. However, the conclusions of such analyses can be strengthened if hypotheses related to these endpoints are prespecified in the protocol, if adjustments for multiple comparisons (maintenance of type I error) are outlined in the protocol, and if the trial is appropriately powered to determine differences between groups related to these variables. Analyses of secondary and additional endpoints can be most helpful for identifying areas for study in future trials.

g. Statistical analysis plan

Before initiation of any phase 3 trial, sponsors should provide a detailed statistical analysis plan with the protocol for the phase 3 trial.

12. Ethical Considerations

Review of previous placebo-controlled trials involving the treatment of ABECB-COPD has shown variable results, with several placebo-controlled trials showing no effect for antimicrobial treatment of exacerbations. Accordingly, for patients with ABECB-COPD of lesser severity, trials have not shown a risk to placebo-treated patients that make future placebo-controlled trials unethical; the risk from placebo treatment may be similar to that associated with antibacterial therapy because low-frequency severe events (e.g., pseudomembranous colitis or serious allergic reactions) have been observed with almost all antibacterial drugs. The occurrence of common but less-severe adverse events (e.g., diarrhea) from antibacterial drugs also can be relevant in assessing the risk-benefit to patients in a placebo-controlled trial where the expected treatment effect may be small. Rescue antibacterial therapy can be incorporated into the trial design so that individual patients are treated at the time a failure outcome is assigned. This addition may serve to mitigate concerns regarding inclusion of a placebo group in an ABECB-COPD trial. All trial designs should provide appropriate provisions for patient safety.

Although results have been varied, some previous ABECB-COPD trials have shown clinically significant benefit in patients with a greater severity of illness (e.g., patients with ABECB-COPD receiving mechanical ventilation). We strongly encourage discussion with the FDA regarding trial design if enrollment will include patients with clinically severe disease (e.g., patients requiring hospitalization or at immediate risk of respiratory failure).

C. Other Considerations

1. Animal Models

There are no animal models for ABECB-COPD. However, animal models for other upper and lower bacterial infections by the same microorganisms implicated as a cause of ABECB-COPD may be useful in determining antimicrobial candidates for further study in the treatment of ABECB-COPD.

2. Labeling Considerations

The following is an example of a labeled indication for the treatment of ABECB-COPD:

> *"[Drug] is indicated in the treatment of acute exacerbations of chronic bronchitis in patients with underlying chronic obstructive pulmonary disease (ABECB-COPD) due to susceptible isolates of [relevant pathogens based on trial results]."*

The labeling should describe the disease severity of patients enrolled in the clinical trials.

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[20] When final, this guidance will represent the FDA's current thinking on this topic.

APPENDIX A: STRATIFIED APPROACH FOR CHARACTERIZING PATIENTS WITH ABECB-COPD IN PLACEBO-CONTROLLED TRIALS

In general, patients with greater severity of ABECB-COPD (i.e., *moderately ill* or *severely ill*) should be offered treatment with an antibacterial drug.[21] Two publications that are addressed in reviews and treatment guidelines showed that antibacterial drug therapy among patients hospitalized for treatment of ABECB-COPD was associated with a decrease in mortality. One of these publications described the results of a placebo-controlled trial in patients who received mechanical ventilation in an intensive care unit for their ABECB-COPD; in this trial, patients randomized to receive an antibacterial drug had a lower mortality rate. The other publication evaluated retrospective data among patients hospitalized for ABECB-COPD and found an association between the use of antibacterial drugs before hospitalization and a lower mortality rate.[22]

Thus, patients who are hospitalized for ABECB-COPD (a population generally considered to have greater severity of ABECB-COPD) should not be enrolled in trials designed with a placebo control; this recommendation is consistent with the public discussions that occurred in 2002.[23]

The reviews and treatment guidelines do not recommend antibacterial drug therapy for patients with mild ABECB-COPD. We evaluated the published placebo-controlled trials that enrolled patients with ABECB-COPD who were managed as outpatients to determine whether there may be an identifiable treatment difference between antibacterial drug therapy and placebo in patients with mild ABECB-COPD.

We identified eight placebo-controlled trials that enrolled outpatients with ABECB-COPD.[24] Among these trials, three used the following outcome measures that did not incorporate information about patient symptoms: (1) mean duration of ABECB-COPD; (2) assessments of observed clinical signs; and (3) pulmonary function testing. None of these three trials demonstrated a difference between antibacterial drugs and placebo with the use of these different outcome measures.

Among the five trials in outpatients that used an outcome measure incorporating patient symptoms, four showed a statistically significant treatment difference from placebo. In addition, one trial evaluated a symptom-based outcome measure earlier in therapy (i.e., at day 5), and showed a treatment difference that was larger than symptom-based outcome measures evaluated at the end of therapy or after therapy had been completed. The results of this trial suggest that outcome measures based on symptom improvement earlier in therapy may be more sensitive predictors of significant differences between investigational therapy and placebo.

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[21] See References, section A., Treatment guidelines and reviews of ABECB-COPD.

[22] See References, section B., Clinical trials evaluating hospitalized patients with ABECB-COPD.

[23] See http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3837t1 htm and http://www regulations.gov/#!documentDetail;D=FDA-2002-N-0319-0003.

[24] See References, section C., Placebo-controlled trials enrolling outpatients with ABECB-COPD.

The types of symptom evaluations incorporated into the outcome measures in these trials were different, and it was not possible to describe a reliable treatment effect based on any particular symptom improvement or scoring system. Among patients randomized to receive placebo, there were no reports of serious infectious complications, and there was a trend toward fewer adverse event reports.

A review of these data demonstrates that patients with ABECB-COPD of lesser severity can be appropriately managed through outpatient care, and can be enrolled in trials designed with a placebo control (see also section III.B.12., Ethical Considerations). A superiority finding of an effective antibacterial drug over placebo may be more likely when the symptom improvement outcome measure is evaluated earlier in therapy, instead of at the end of therapy or at a period of time after completion of therapy.

APPENDIX D: SUMMARY OF THE ABS, ABECB-COPD, AND uUTI INDICATIONS FOR CURRENTLY AVAILABLE FLUOROQUINOLONES

Table of Fluoroquinolones and the Related Indications

	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin	Gemifloxacin
ABS	**X**	**X**	**X**		
ABECB-COPD	**X**	**X**	**X**	**X**	**X**
Acute uncomplicated cystitis	**X**			**X**	
uUTI	**X**	**X**			
Urinary tract infection	**X**				

APPENDIX E: EXAMPLES OF SAFETY WARNINGS IN FLUOROQUINOLONE LABELS

APPENDIX E: EXAMPLES OF SAFETY WARNINGS IN FLUOROQUINOLONE LABELS

Tendinitis and Tendon Rupture Boxed Warning

Boxed Warning: *"Fluoroquinolones, including FQ®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants".*

Warnings and Precautions: *"Fluoroquinolones, including FQ®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. FQ® should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug."*

Medication Guide*: "Tendon rupture or swelling of the tendon (tendinitis).*

- *Tendon problems can happen in people of all ages who take FQ®. Tendons are tough cords of tissue that connect muscles to bones.*

Some tendon problems include pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.

- *The risk of getting tendon problems while you take FQ® is higher if you:*
  - *are over 60 years of age*
  - *are taking steroids (corticosteroids)*
  - *have had a kidney, heart or lung transplant.*
- *Tendon problems can happen in people who do not have the above risk factors when they take FQ®.*
- *Other reasons that can increase your risk of tendon problems can include:*
  - *physical activity or exercise*
  - *kidney failure*
  - *tendon problems in the past, such as in people with rheumatoid arthritis (RA)*
- *Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking FQ® until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area.*

The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the risk of tendon

rupture with continued use of FQ®. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.

- *Tendon rupture can happen while you are taking or after you have finished taking FQ®. Tendon ruptures have happened up to several months after people have finished taking their fluoroquinolone.*
- *Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:*
  - *hear or feel a snap or pop in a tendon area*
  - *bruising right after an injury in a tendon area*
  - *unable to move the affected area or bear weight"*

Central Nervous System (CNS) Effects Warning

Warnings and Precautions: *"Convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri) been reported in patients receiving fluoroquinolones, including FQ®. Fluoroquinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving FQ®, the drug should be discontinued and appropriate measures instituted. As with other fluoroquinolones, FQ® should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold."*

Medication Guide*: "Central Nervous System effects. Seizures have been reported in people who take fluoroquinolone antibiotics including FQ®. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking FQ® will change your risk of having a seizure. Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of FQ®. Talk to your healthcare provider right away if you have any of these side effects, or other changes in mood or behavior:*

- *Feeling dizzy*
- *Seizures*
- *Hear voices, see things, or sense things that are not there (hallucinations)*
- *Feel restless*
- *Tremors*
- *Feel anxious or nervous*
- *Confusion*
- *Depression*
- *Trouble sleeping*
- *Feel more suspicious (paranoia)*
- *Suicidal thoughts or acts*
- *Nightmares*
- *Vision Loss*

Peripheral Neuropathy Warning

Warnings and Precautions: *" Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including FQ®. Symptoms may occur soon after initiation of FQ® and may be irreversible. FQ® should be discontinued immediately if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation."*

Medication Guide*: "Changes in sensation and nerve damage (Peripheral Neuropathy) Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including FQ®.*
Stop FQ® and talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
• Pain
• Burning
• Tingling
• Numbness
• Weakness
The nerve damage may be permanent.

Myasthenia Gravis Exacerbation Warning

Boxed Warning: *"Fluoroquinolones, including FQE®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid FQ® in patients with a known history of myasthenia gravis"*

Warnings and Precautions: *"Fluoroquinolones, including FQ®, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid FQ® in patients with a known history of myasthenia gravis"*

Medication Guide*: "Worsening of myasthenia gravis (a disease which causes muscle weakness). Fluoroquinolones like FQ® may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems."*

QT Prolongation and Torsades De Pointes Warning

Warnings and Precautions: *"Some fluoroquinolones, including FQ®, have been associated with prolongation of the QT interval on the electrocardiogram and cases of arrhythmia. Cases of torsade de pointes have been reported during postmarketing surveillance in patients receiving*

fluoroquinolones, including FQ®. Avoid FQ® in patients with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes (for example, congenital long QT syndrome, uncorrected electrolyte imbalance, such as hypokalemia or hypomagnesemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA antiarrhythmic agents (quinidine, procainamide), or Class III antiarrhythmic agents (amiodarone, sotalol), tricyclic antidepressants, macrolides, and antipsychotics. Elderly patients may also be more susceptible to drug-associated effects on the QT interval."

***Medication Guide**: "Serious heart rhythm changes (QT prolongation and torsade de pointes) Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. AVELOX may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:*
•Who are elderly
•With a family history of prolonged QT interval
•With low blood potassium (hypokalemia)
•Who take certain medicines to control heart rhythm (antiarrhythmics)

Phototoxicity Warning

***Warnings and Precautions:** "Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of fluoroquinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs".*

***Medication Guide**: "FQ® can cause serious side effects, including:*

- *Sensitivity to sunlight (photosensitivity)"*

Hypersensitivity Warning

***Warnings and Precautions:** "Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including FQ®. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, including intubation, as indicated."*

"Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported in patients receiving therapy with quinolones, including FQ®. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- *Fever, rash, or severe dermatologic reactions (for example, toxic epidermal necrolysis, Stevens-Johnson syndrome);*
- *Vasculitis; arthralgia; myalgia; serum sickness;*
- *Allergic pneumonitis;*
- *Interstitial nephritis; acute renal insufficiency or failure;*
- *Hepatitis; jaundice; acute hepatic necrosis or failure;*
- *Anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.*

Discontinue FQ® immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted"

***Medication Guide**: "Serious allergic reactions. Serious allergic reactions, including death, can happen in people taking fluoroquinolones, including FQ®, even after only 1 dose. Stop taking FQ® and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:*

- *hives*
- *trouble breathing or swallowing*
- *swelling of the lips, tongue, face*
- *throat tightness, hoarseness*
- *rapid heartbeat*
- *faint*
- *skin rash*

Skin rash may happen in people taking FQ® even after only 1 dose. Stop taking FQ® at the first sign of a skin rash and call your healthcare provider.
Skin rash may be a sign of a more serious reaction to FQ®.

APPENDIX F: Reviews from the Division of Epidemiology II

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology Review (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Literature Review of Fluoroquinolone-Associated Tendinopathy

Date:	September 23, 2015
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Drug Name:	Fluoroquinolones
Subject	Literature Review of Fluoroquinolone Exposure and the Risk of Tendinopathy
OSE RCM #:	2014-0896

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1 EXECUTIVE SUMMARY

The Division of Anti-Infective Products consulted the Division of Epidemiology II, requesting a literature review of fluoroquinolone-associated adverse events that are currently labeled. This literature review focuses on fluoroquinolone exposure and the risk of tendinopathy.

All fluoroquinolone product labeling includes a boxed warning on the risk of tendinitis and tendon rupture. The boxed warning states that "this risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants".

Four observational studies of higher quality compared the risk of tendinopathy in patients using fluoroquinolones to those without fluoroquinolone exposure. This review did not focus on eight other epidemiologic studies that assessed the association between fluoroquinolones and tendinopathy for reasons outlined in Section 3.

The four studies support the current boxed warning of an increased risk of tendinitis and tendon rupture. These studies suggest that, relative to other subjects, fluoroquinolone-exposed subjects have 2.7 times the risk of tendinopathy (tendon rupture and tendinitis); 1.2 to 11.0 times the risk of tendon rupture; and 2.1 times the risk of tendinitis.

Overall, the four studies provide moderate support of further increased risk in elderly patients and in patients taking corticosteroid drugs. One study found a non-significant elevated association of fluoroquinolone-associated tendinopathy if subjects were both elderly and using corticosteroids. Another study restricted the study population to elderly subjects and found a high risk associated with fluoroquinolone use relative to fluoroquinolone-associated risk observed in the other studies, suggesting an increased risk among elderly patients.

No comment can be made on whether the risk of tendinopathy varies by transplant recipient status because no results were stratified by this risk factor. In any case, immunosuppressive therapy with corticosteroids may predispose transplant recipients to tendinopathy.

One of the most concerning tendinopathy outcomes assessed in the four studies was Achilles tendon rupture, a disabling, serious adverse event sometimes requiring surgery and commonly seen in case-series data. Because the incidence of Achilles tendon rupture is low, a moderately increased relative risk among fluoroquinolone users would only result in a small increased absolute risk. That is, among the general population or among users of non-fluoroquinolone antibiotics, the incidence density ranged from 0.5 to 1.0 per 10,000 person-years. Among fluoroquinolone-exposed persons, the incidence density ranged from 1.3 to 5.6 per 10,000 person-years. Even though Achilles tendon rupture occurs rarely, caution should be exercised when prescribing fluoroquinolones to avoid additional risk.

2 INTRODUCTION

The Division of Ant-Infective Products (DAIP) consulted the Division of Epidemiology II (DEPI II), requesting a literature review of fluoroquinolone-associated adverse events that are currently labeled. DEPI II engaged in three parallel reviews. This review focuses on fluoroquinolone exposure and the risk of tendinopathy.

Fluoroquinolone product labels contain a boxed warning for fluoroquinolone-associated tendinitis and tendon rupture, which was added in 2008 to strengthen the warnings found in other sections of labeling (1). The boxed warning was based on analyses of reports collected by the Adverse Event Reporting System (AERS) and a review of four observational studies (2; 3).

2.1 Background

Epidemiology of tendinopathy

Tendinopathy, including tendinitis and tendon rupture, can be a painful and debilitating condition. Risk factors for tendinopathy include advanced age, male gender, corticosteroid therapy, chronic lung disease, diabetes mellitus, dialysis or renal dysfunction/failure, gout, hypercholesterolemia, hyperparathyroidism, hypoparathyroidism, low bone mineral density/osteoporosis, magnesium deficiency (e.g., alcoholism, dietary deficiency, or renal disease), rheumatic disease, tendon trauma or athletic activity, transplantation, and history of tendinopathy (4-6).

Case-series data on fluoroquinolone-associated tendinopathy suggest that the Achilles tendon is the most frequently affected tendon (4; 5). In context, the annual incidence of Achilles tendon rupture (ATR) ranges from 0.2 to 3.7 per 10,000 population and has increased over time (7-15).

2.2 Product Labeling

All fluoroquinolone labels carry the following boxed warning:

> "Fluoroquinolones, including TRADENAME, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants."

2.3 Fluoroquinolone-induced tendinopathy

Three theories have been postulated on the pathophysiology of fluoroquinolone-induced tendinopathy (4):

- Fluoroquinolones may cause ischemic effects (toxicity) on tendon tissue.
- Fluoroquinolones may cause degradation of tendon matrix.
- Fluoroquinolones may have direct cytotoxic effects on tendon cells.

Case-series data suggest that the onset of fluoroquinolone-induced tendinopathy is acute, with a roughly two-week average onset and a range of 1 to 90 days (4; 5).

3 REVIEW METHODS AND MATERIALS

The following review describes and evaluates studies of fluoroquinolone exposure and the risk of tendinopathy, including the studies that were previously reviewed (2).

Conducted on May 15, 2015, a search of the National Library of Medicine's PubMed database used the following search string: (fluoroquinolone[MeSH]) AND (((“acute kidney injury”[MeSH] OR “anaphylaxis”[MeSH] OR “hypersensitivity”[MeSH] OR “tendinopathy”[MeSH] OR "peripheral nervous system diseases"[MeSH] OR "retinal detachment"[MeSH] OR "arrhythmias, cardiac"[MeSH] OR "death"[MeSH] or "Drug-Related Side Effects and Adverse Reactions"[MeSH]))). The literature search included 722 publications written in English, conducted in humans, and published anytime from January 1, 1986, to the date of the search.

During the process of selecting studies for the three parallel DEPI reviews, publications with the following characteristics were excluded:

- publications that did not mention fluoroquinolones
- case reports and case series
- commentaries and reviews
- methods development studies and studies based on adverse event reports
- QT prolongation studies
- studies with no safety data
- studies where fluoroquinolones were only used by ophthalmic, otic, or topical routes of administration, among pediatric populations, or in the inpatient setting

This literature review was restricted further to studies of fluoroquinolones and tendinopathy outcomes. Additional studies were identified from the selected studies' citations. Lastly, a poster presented by the US Army Pharmacovigilance Center (in collaboration with FDA) at the 2011 International Conference of Pharmacoepidemiology was also included.

This review focuses on studies with the following characteristics: 1) assessment of confirmed cases of tendinopathy and 2) no restriction of the study populations to transplant recipients. This review includes studies with confirmed cases of tendinopathy because tendinitis and tendon rupture have been labeled outcomes, so non-adjudicated cases of tendinopathy may represent false positives (e.g., rule-out diagnoses) in studies using health care claims data. Furthermore, this review aims to provide insight into fluoroquinolone-associated tendinopathy among patient populations with non-severe indications to support the advisory committee meeting in November 2015. For this reason, this review did not focus on studies restricted to transplant recipients. In addition, this review summarizes the indications of fluoroquinolone users when such data were available.

4 REVIEW RESULTS

Twelve studies examined the association between fluoroquinolone use and tendinopathy (16-27). Appendix B summarizes the methods and results of these studies, and Appendix C summarizes findings from these studies, grouped by outcome.

Four studies are the focus of this review:

i. Seeger, J. D., West, W. A., Fife, D., Noel, G. J., Johnson, L. N., & Walker, A. M. (2006). Achilles tendon rupture and its association with fluoroquinolone antibiotics and other potential risk factors in a managed care population. Pharmacoepidemiol.Drug Saf, 15, 784-792.

ii. Wilton, L. V., Pearce, G. L., & Mann, R. D. (1996). A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies. Br J Clin Pharmacol, 41, 277-284.

iii. van der Linden, P. D., van de Lei, J., Nab, H. W., Knol, A., & Stricker, B. H. (1999). Achilles tendinitis associated with fluoroquinolones. Br J Clin Pharmacol, 48, 433-437.

iv. van der Linden, P. D., Sturkenboom, M. C., Herings, R. M., Leufkens, H. M., Rowlands, S., & Stricker, B. H. (2003). Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. Arch Intern.Med, 163, 1801-1807.

4.1 Case-control study by Seeger (19)

Seeger and colleagues conducted a retrospective, claims-based, case-control study to quantify the association between ATR and fluoroquinolone exposure while accounting for other suspected risk factors. The data source for this study was the Ingenix Research Database, which was sourced from UnitedHealthcare and includes information on demographics, enrollment in commercial insurance and Medicare supplement health insurance, and health care claims.

The study included subjects with at least 180 days of enrollment prior to index date, from January 1997 through June 2001. The study did not apply any exclusion criteria.

The study used an algorithm to select cases of ATR not associated with trauma. The algorithm selected subjects with both diagnosis (ICD-9-CM 727.67) and procedural codes (CPT codes 27605, 27606, 27650, 27652, 27654, or 01472) related to ATR. Cases also had one of the following: 1) an ankle sprain diagnosed by specialist or hospital/surgicenter, or 2) an ATR diagnosed by specialist, hospital/surgicenter, or medical professional. The positive predictive value of the algorithm was 91.2%. The index date for cases was the earliest date of any of the diagnostic or procedural codes.

The study aimed to assess whether clinicians conduct more diagnostic work-ups resulting in ATR claims among fluoroquinolone-exposed patients than other patients (diagnostic bias). To do so, the study defined rule-outs as subjects who met one of two definitions: 1) presence of either a diagnosis or procedural code related to ATR, but not both, or 2) presence of both a diagnosis and procedural code related to ATR but no ATR diagnosis by a specialist, hospital/surgicenter, or

medical professional. The rule-out definition included some subjects who were true cases, for a low positive predictive value of 16.4%.

Twenty controls were matched to each case on calendar-day and were also frequency matched to cases' age.

The study examined the following antibiotic exposures occurring 0 to 180 days prior to the index date: fluoroquinolones (including ciprofloxacin, levofloxacin, ofloxacin, and other fluoroquinolones), azithromycin, clarithromycin, and other non-fluoroquinolone antibiotics. Other exposures of interest included oral and injected corticosteroids in the past 180 days. The calculated absorbed dose of fluoroquinolones (dose times bioavailability) was also examined.

Univariate and multivariate unconditional logistic regression analyses compared the estimated odds of fluoroquinolone exposure between cases and controls, as well as between rule-outs and controls. Multivariate analyses incorporated the following covariates: age, sex, obesity, skin and soft tissue infections, oral corticosteroid use, injected corticosteroid use, other non-fluoroquinolone antibiotic use, arthritis, diabetes, and trauma. Analyses also stratified by age and oral corticosteroid use.

During 9.8 million person-years of experience in the study population, 947 cases were identified, for a crude incidence rate of 1.0 ATRs per 10,000 person-years, 95% CI [0.9, 1.1]. These 947 cases were matched to 18,940 controls.

As seen in Table 1, cases and controls had similar fluoroquinolone exposure in the 180 days before index date: adjusted odds ratio (aOR) = 1.2, 95% CI [0.9, 1.7]. The results were similar before and after adjusting for potential covariates. Analyses assessing fluoroquinolone exposure in the 90 days before the index date also yielded a similar finding. A dose response relationship was observed, with cases more likely to have 8 grams or more cumulative fluoroquinolone exposure than controls in the past 180 days, aOR = 1.5, 95% CI [1.0, 2.3].

Table 1: Comparison of antibiotic exposures between cases of Achilles tendon rupture and controls, Seeger et al. (19)

Antibiotic exposure in 0 to 180 days before index date	Number (%) of cases n = 947	Number (%) of controls n = 18,940	Crude odds ratio [95% CI][α]	Adjusted odds ratio [95% CI][β]
Any fluoroquinolone[γ]	49 (5.2%)	751 (4.0%)	1.3 [1.0, 1.8]	1.2 [0.9, 1.7]
--- Ofloxacin	5 (0.5%)	69 (0.4%)	1.5 [0.6, 3.6]	1.4 [0.6, 3.6]
--- Levofloxacin	7 (0.7%)	197 (1.0%)	0.7 [0.3, 1.5]	0.6 [0.3, 1.4]
--- Ciprofloxacin	34 (3.6%)	458 (2.4%)	1.5 [1.1, 2.1]	1.4 [1.0, 2.0]
--- Other fluoroquinolones	6 (0.6%)	61 (0.3%)	2.0 [0.9, 4.6]	1.2 [1.0, 1.4]
Azithromycin	65 (6.9%)	1,102 (5.8%)	1.2 [0.9, 1.5]	1.2 [0.9, 1.6]
Clarithromycin	23 (2.4%)	456 (2.4%)	1.0 [0.7, 1.5]	0.9 [0.6, 1.4]
Other non-fluoroquinolone antibiotic	226 (23.9%)	3,834 (20.2%)	1.2 [1.1, 1.4]	1.2 [1.1, 1.5]

[α] 95% confidence intervals calculated by the Reviewer

[β] Adjusted for age, sex, obesity, skin and soft tissue infections, oral corticosteroid use, injected corticosteroid use, other non-fluoroquinolone antibiotic use, arthritis, diabetes, and trauma

[γ] Ciprofloxacin, levofloxacin, ofloxacin, and other fluoroquinolones. Note: crude odds ratio for fluoroquinolone exposure in 0 to 90 days before index date was 1.3, 95% CI [0.9, 1.9]

Most cases and controls were exposed to ciprofloxacin (34 and 458 subjects, respectively), followed by levofloxacin (7 and 197 subjects), ofloxacin (5 and 69 subjects), and other fluoroquinolones (6 and 61 subjects). Stratified by type of fluoroquinolone, an elevated association was observed for ciprofloxacin and other fluoroquinolones: aOR = 1.4, 95% CI [1.0, 2.0], and aOR = 1.2, 95% CI [1.0, 1.4], respectively. Meanwhile, cases and controls had similar exposure to levofloxacin and ofloxacin.

While age and oral corticosteroid use were not strong effect modifiers by themselves, the study results suggest a three-way interaction between age, oral corticosteroid use, and fluoroquinolone use. That is, among elderly subjects (60 years and older) who used an oral corticosteroid in the past 180 days, cases had more fluoroquinolone exposure than controls: 4 out of 10 cases and 21 out of 95 controls. However, the association was not statistically significant, aOR = 5.8, 95% CI [0.9, 38.6].

Rule-outs were more likely to have fluoroquinolone exposure than controls in the past 180 days (aOR = 1.7, 95% CI [1.4, 2.8]), and in the past 90 days aOR = 1.9, 95% CI [1.5, 3.9]). Based on these results, the investigators concluded that studies that do not adjudicate ATR case status will incorrectly quantify risks.

4.2 Cohort study by Wilton (21)

Wilton and colleagues conducted a retrospective cohort study to examine the safety of ciprofloxacin, norfloxacin, ofloxacin, azithromycin, and cefixime.

The data source for this study was Prescription-Event Monitoring data. The Prescription-Event Monitoring program solicits adverse event reports from doctors who wrote prescriptions for specific drugs. The event reports capture information on patient demographics, indications for the prescribed drug, reasons for discontinuation, effectiveness of the drug, start and stop dates for drug therapy, and events during and after therapy. An event was "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration or improvement in a concurrent illness, any suspected drug reaction, or any complaint which was considered of sufficient importance to enter in the patient's notes."

The study included patients prescribed ciprofloxacin, norfloxacin, ofloxacin, azithromycin, or cefixime. The study timeframe differed for each cohort of patients prescribed these antibiotics:

- Patients prescribed ciprofloxacin during November 1988 to January 1989
- Patients prescribed norfloxacin during October 1990 to October 1991
- Patients prescribed ofloxacin during May 1990 to December 1991
- Patients prescribed azithromycin during March 1992 to June 1993
- Patients prescribed cefixime during September 1990 to May 1991

The study outcomes were reported adverse events, including tendinitis and tendon rupture occurring within 2 months of onset of therapy.

The analyses were descriptive in nature, so no formal statistical tests were performed.

The Prescription-Event Monitoring program sent roughly 133,900 questionnaires to physicians, and around 63,500 questionnaires were returned. A minority of forms were considered void, yielding cohort sizes of roughly 11,000 patients per antibiotic.

The cohorts had similar demographics, with a few exceptions. The average age of the fluoroquinolone cohorts was roughly 55 years, while the other cohorts' average ages were in the late 30s. Roughly 60% of patients were female for each of the cohorts, except for the norfloxacin cohort which was roughly 80% female. This finding is consistent with the indications for use. Most patients who were prescribed norfloxacin used it for urinary tract infection, while the majority of patients prescribed the other four antibiotics used them for respiratory tract infections (Table 2).

Table 2: Proportion of patients using selected antibiotics for specific sites of infection, Wilton et al. (21)

Site of infection	Ciprofloxacin n = 11,477	Norfloxacin n = 11,110	Ofloxacin n = 11,033	Azithromycin n = 11,275	Cefixime n = 11,250
Urinary tract	17.9%	87.6%	11.9%	0.7%	4.4%
Respiratory tract	53.2%		61.0%	63.6%	61.9%
Various or other	22.0%	12.4%	15.7%	24.6%	23.5%
Not reported	6.8%		11.4%	11.1%	10.2%

Fifteen mutually exclusive cases of tendinitis or tendon rupture were reported, of which twelve occurred among users of fluoroquinolones and three occurred among users of azithromycin or cefixime (Table 3). Under the assumption that the cohorts are mutually exclusive, the Reviewer calculated the two-month risk of tendinitis or tendon rupture to be 3.6 per 10,000 patients treated with fluoroquinolones and 1.8 per 10,000 patients treated with azithromycin or cefixime, crude relative risk (cRR) = 2.7, 95% CI [0.8, 9.5].

Table 3: Comparison of incidence of tendinitis and tendon rupture between users of selected fluoroquinolones and other antibiotics, Wilton et al. (21)

Antibiotic	Patients experiencing adverse event[α]		Patient cohort size	Incidence per 10K patients[α,β]		Estimated incidence rate per 10K PYs[α,β]		Crude relative risk [95% CI] for tendinitis or tendon rupture[β]
	Tendinitis or tendon rupture	Tendon rupture		Tendinitis or tendon rupture	Tendon rupture	Tendinitis or tendon rupture	Tendon rupture	
Ciprofloxacin, norfloxacin, or ofloxacin	12	4	33,620	3.6	1.2	21.4	7.1	2.7 [0.8, 9.5]
---Ciprofloxacin	1	0	11,477	0.9	0.0	5.2	0.0	0.7 [0.1, 6.3]
---Norfloxacin	3	1	11,110	2.7	0.9	16.2	5.4	2.0 [0.4, 10.0]
---Ofloxacin	8	3	11,033	7.3	2.7	43.5	16.3	5.4 [1.4, 20.5]
Azithromycin or cefixime	3	0	22,525	1.3	0.0	8.0	0.0	Ref
--- Azithromycin	1	0	11,275	0.9	0.0	5.3	0.0	N/A
--- Cefixime	2	0	11,250	1.8	0.0	10.7	0.0	N/A

[α] Tendinitis and tendon rupture occurred within 2 months of onset of antibiotic therapy

[β] Measures of incidence and relative risks were calculated by the Reviewer.

Most tendinitis and tendon ruptures occurred among users of ofloxacin (n = 8 cases), with norfloxacin (n = 3) and ciprofloxacin (n = 1) having a minority of cases.

4.3 Cohort study by van der Linden (23)

Van der Linden and colleagues conducted a retrospective, claims-based cohort study to assess whether there is an association between use of fluoroquinolones and tendinitis and to determine the incidence and relative risk of tendinitis across different fluoroquinolones. The data source for this study was the Integrated Primary Care Information system which contains computerized patient records.

The study included patients 15 years old and older who were prescribed selected antibiotics within 41 general practices in Netherlands, years 1995 and 1996. All patients had 3 or more months of computer-recorded history prior to the start of their antibiotic regimen. The study excluded patients with unknown gender, age, or antibiotic dosage, patients who used the selected antibiotics for more than 60 days in 1 year, patients with history of inflammatory joint disease,

Reiter's syndrome, polymyalgia rheumatica, gout or AIDS, and patients with concomitant use of fluoroquinolones with other antibiotics of interest in the risk period.

Two cohorts were constructed from the study population: 1) users of fluoroquinolones (ofloxacin, ciprofloxacin, and norfloxacin), and 2) users of other antibiotics (amoxicillin, trimethoprim, cotrimoxazole, or nitrofurantoin). All antibiotics of interest were non-dermatological and non-ocular preparations. Cohort entry was the date of the first antibiotic prescription. The exposure period was the sum of the duration of use (i.e., prescribed drug divided by daily dose), corrected for refill prescriptions. The risk period was the exposure period plus one month.

Although the outcome definition initially included tendinitis and tendon rupture, the investigators only analyzed adjudicated incident cases of tendinitis. Tendinitis included Achilles tendinitis and other sites of tendinitis. Cases were initially identified using selected International Classification for Primary Care (ICPC) diagnosis codes in the series L81 (other musculoskeletal injuries), L92 (shoulder syndrome), L93 (epicondylitis), and L99 (other diseases of the musculoskeletal system). Additional potential cases were identified using text string searches using the following search terms: "tendinitis," "tendon disorder," "tendon rupture," "coup de fouet," "and "pain upper leg". The outcome definition excluded tendinitis associated with trauma. Patients were censored at the diagnosis of the outcome, transfer to another practice, death, or at the end of the study period.

Only the first identified outcome was analyzed. The incidence density was expressed as the number of outcomes per total risk period. Poisson regression was used to estimate rate ratios, unadjusted and adjusted for gender, age, number of general practitioner visits, and concurrent corticosteroid use. The risk difference was the difference in incidence densities. Stratified analyses considered the site of tendinitis and risk of tendinitis for each fluoroquinolone.

During the study period, roughly 11,800 patients 15 years and older were prescribed the study drugs. There were 1,012 patients excluded from the study population, including a small number of patients who used the selected antibiotics for more than 60 days in one year (n = 99).

Of the remaining 10,800 patients in the study population, 1,841 patients used fluoroquinolones and 9,406 patients used other antibacterial drugs, for an average duration of 9 and 7 days, respectively. Roughly 450 patients were included in both cohorts because the risk window for fluoroquinolone use and risk window for use of other antibacterial drugs did not overlap. The investigators claimed that most antibiotics were prescribed for urinary or respiratory tract infections, with no significant difference in indications between users of fluoroquinolones and users of other antibiotics. However, the publication did not quantify the indications. The cohorts had a similar proportion of concomitant corticosteroid use, but fluoroquinolone users were more likely to be male, be older, have greater number of GP visits, and have renal failure.

Of the twenty-two cases identified, seven cases occurred among fluoroquinolone users and fifteen cases occurred among other antibiotic users. No cases had renal failure. The incidence density of tendinitis was twice as high among fluoroquinolone users than other antibiotic users: 7.7 cases per 100,000 days at risk versus 3.3 cases per 100,000 days at risk, respectively. However, the

rate ratio was not statistically significant: aRR = 2.1, 95% CI [0.8, 5.1]. Crude and adjusted analyses' findings were similar.

Table 4: Comparison of incidence densities (ID) for tendinitis among users of fluoroquinolones vs. other antibiotics, overall and stratified for Achilles tendinitis and other sites of tendinitis, van der Linden et al. (23)

	Cases	*Risk period*	*ID/100 000 days*	*RR_{crude}*	*(95% CI)*	*$RR_{adjusted}$*	*(95% CI)*
All tendinitis							
Reference drugs*	15	458 484	3.27	1.0	–	1.0	–
Fluoroquinolones	7	90 435	7.74	2.4	(0.96–5.80)	2.1[#]	(0.83–5.09)
Ofloxacin	4	18 944	21.11	6.5	(2.14–19.45)	4.9[#]	(1.57–15.06)
Ciprofloxacin	2	20 487	9.76	3.0	(0.68–13.05)	2.2[#]	(0.50–9.88)
Norfloxacin	1	51 004	1.96	0.6	(0.08–4.54)	0.6[#]	(0.08–4.59)
Achilles tendinitis							
Reference drugs*	4	458 237	0.87	1.0	–	1.0	–
Fluoroquinolones	4	90 371	4.43	5.1	(1.27–20.27)	3.7[#]	(0.93–15.14)
Ofloxacin	3	18 929	15.85	18.2	(4.06–81.12)	10.1[#]	(2.20–46.04)
Ciprofloxacin	1	20 461	4.89	5.6	(0.63–50.09)	2.8[#]	(0.30–25.18)
Norfloxacin	0	50 981	–	–	–	–	–
Other tendinopathies							
Reference drugs*	11	458 426	2.40	1.0	–	1.0	–
Fluoroquinolones	3	90 362	3.32	1.4	(0.39–4.96)	1.3[$]	(0.36–4.71)
Ofloxacin	1	18 886	5.29	2.2	(0.28–17.10)	2.0[$]	(0.25–16.08)
Ciprofloxacin	1	20 472	4.88	2.0	(0.26–15.77)	1.8[$]	(0.23–14.41)
Norfloxacin	1	51 004	1.96	0.8	(0.11–6.31)	0.8[$]	(0.10–6.05)

[#]Adjusted for age, gender, GP visits and concomitant corticosteroid use.
[$]Adjusted for age, gender and GP visits.

*Amoxicillin, cotrimoxazol, nitrofurantoin, or trimethoprim

Note: Table taken from the publication by van der Linden et al. (23)

Stratification by type of fluoroquinolone revealed higher rates of tendinitis among ofloxacin users, but not for among ciprofloxacin or norfloxacin users: aRR for ofloxacin = 4.9, 95% CI [1.6, 15.1], aRR for ciprofloxacin = 2.2, 95% CI [0.5, 9.9], and aRR for norfloxacin = 0.6, 95% CI [0.1, 4.6]. These rates are not robust because the number of exposed cases was small: four cases among ofloxacin users, two cases among ciprofloxacin users, and one case among norfloxacin users. Analyses stratified by site of tendinitis also found a small number of cases per stratum.

The investigators commented that the association between fluoroquinolones and tendinitis was only recently widely recognized, so confounding by indication may not play a major role in this study since fluoroquinolone use may not be contraindicated with other risk factors (e.g., physical training) during the study period.

4.4 Case-control study by van der Linden (26)

Van der Linden and colleagues conducted a retrospective, electronic medical record (EMR)-based case-control study to quantify the risk of ATR from quinolones and to study the role of concomitant risk factors. The data source for this study was the General Practice Research

Database, which includes data on patient demographics, symptoms, diagnoses, referrals, hospitalizations, and vital status.

The study population included subjects 18 to 95 years old, from January 1, 1988, to January 1, 1999. Subjects were excluded if they had less than 18 months of standard history, had a history of cancer, drug abuse, alcoholism, or AIDS, or had a hospital admission in the month prior to the index date.

Cases were subjects with a first-time, adjudicated diagnosis of ATR not associated with trauma, identified using Oxford Medical Information System (OXMIS) codes 845 B, 7339 E, and 7339 TT. The case index date was the date of ATR diagnosis. Controls were 50,000 subjects randomly selected from practices where cases were registered, and the controls' index dates were randomly selected dates during the study period.

The study examined current exposure to oral and parenteral quinolones as well as six other antibiotics: tetracyclines, amoxicillin, penicillins, amoxicillin-clavulanate potassium, trimethoprim and sulfonamides, and macrolides. However, only sensitivity analyses examined fluoroquinolones separately from the non-fluoroquinolone quinolone, nalidixic acid. In these analyses, the investigators assessed current exposure to ofloxacin, ciprofloxacin, and norfloxacin among cases and controls. Current exposure was defined as an overlap of the index date with the exposure window (treatment length plus 30 days).

The sensitivity analyses were conducted using unconditional logistic regression, unadjusted and adjusted for age, sex, oral corticosteroid use, musculoskeletal-related disorders, disorders of lipid metabolism, and transplants or dialysis. Users and non-users of quinolones differed with respect to other covariates, but these other covariates were not incorporated into analyses.

The investigators claimed that cases and controls had similar indications for quinolone use, with most courses of quinolones given for respiratory tract or urinary tract infections. However, they did not quantify indications for quinolone use.

Except for statistically significant increased odds of trimethoprim and sulfonamide exposure among cases, the odds of current exposure to non-quinolone antibiotics were similar between cases and controls among all subjects of any age.

All quinolone-exposed cases were 60 years old or older, so sensitivity analyses were restricted to elderly subjects. The absolute risk of ATR among subjects aged 60 to 79 years old and 80+ years was 5.5 and 3.5 per 100,000 person-years, respectively.

The sensitivity analyses found greater odds of current fluoroquinolone use among 290 cases than among 12,658 controls. Specifically, five cases and five controls had used ofloxacin; six cases and forty controls used ciprofloxacin; and one case and five controls used norfloxacin. The corresponding adjusted odds ratios ranged from 3.6 to 28.4 for these three fluoroquinolones. Although not provided in the published paper, the Reviewer calculated the odds of exposure to these three fluoroquinolones combined as cOR = 11.0, 95% CI [5.8, 20.8].

Table 5: Comparison of antibiotic exposures between cases of Achilles tendon rupture and controls, van der Linden et al. (26)

Exposure	Number (%) of cases[α] n = 290	Number (%) of controls[α] n = 12,658	Crude odds ratio [95% CI][α]	Adjusted odds ratio [95% CI][β]
No quinolone exposure	276 (95.2%)	12,608 (99.6%)	Ref	Ref
Ciprofloxacin, ofloxacin, or norfloxacin exposure	12 (4.1%)	50 (0.4%)	11.0 [5.8, 20.8]	Not reported
Ciprofloxacin	6 (2.0%)	40 (0.3%)	6.9 [2.9, 16.3]	3.6 [1.4, 9.1]
Norfloxacin	1 (0.3%)	5 (<0.1%)	9.1 [1.1, 78.5]	14.2 [1.6, 128.6]
Ofloxacin	5 (1.7%)	5 (<0.1%)	45.7 [13.1, 158.7]	28.4 [7.0, 115.3]
Nalidixic acid	2 (0.7%)	0 (0.0%)	N/A	N/A

[α] The Reviewer calculated 95% confidence intervals for the crude odds ratios, the percentages, and the crude odds ratio for the three fluoroquinolones combined.

[β] All adjusted odds ratios were adjusted for age, sex, corticosteroid use, musculoskeletal-related disorders, disorders of lipid metabolism, and transplants or dialysis.

Sensitivity analyses conducted on quinolone exposure (including fluoroquinolones and nalidixic acid) suggested that current and recent oral corticosteroid use among the elderly may be an effect modifier, with adjusted odds ratios of roughly 18.0 when subjects use oral corticosteroids, and adjusted odds ratios of roughly 5.0 in the absence of oral corticosteroid use.

4.5 Summary

Overall, the four studies suggested an increased risk of tendinopathy associated with exposure to any fluoroquinolones, but did not provide consistent evidence of differential risk across the fluoroquinolone class (Table 6). For example, the cohort and case-control studies by van der Linden disagreed on whether norfloxacin was associated with any increased risk. Furthermore, tendinopathy risk for the fluoroquinolone class varied across studies, and confidence intervals were wide enough to include no association. The other eight studies, which are summarized in Appendix B and C, also consistently demonstrated an elevated risk of tendinopathy for the fluoroquinolone class, but also did not agree on whether there was a differential risk within this class. Several factors may have contributed to the different results among the studies:

- The study designs differed (e.g., the assumed risk period of fluoroquinolone-induced tendinopathy varied across studies).
- Risk factors across the study populations and users of different fluoroquinolones may differ across studies. Furthermore, the studies varied in how they accounted for various risk factors. For example, analyses in the 2003 study by van der Linden were restricted to elderly subjects, while the other three studies did not have this restriction.
- The outcomes differed, with two studies assessing only ATR, one study only assessing tendinitis, and another study assessing both tendinitis and tendon rupture. Still, even the two studies assessing ATR did not numerically agree.

- The specific fluoroquinolones varied across these studies. More importantly, the prevalence of fluoroquinolone use and incidence of outcomes was low, precluding a sufficiently powered formal analysis of differences in risk within the fluoroquinolone class.

Table 6: Inconsistent association between fluoroquinolones and tendinopathy across four selected studies (19; 21; 23; 26)

Fluoroquinolone[α]	Relative risk [95% CI][β]			
	Case-control study of ATR by Seeger et al. Ref: Absence of fluoroquinolone in 180 days before index date	Cohort study of tendinitis and tendon rupture by Wilton et al. Ref: Non-fluoroquinolone antibiotics[γ]	Cohort study of tendinitis by van der Linden et al. (1999) Ref: Non-fluoroquinolone antibiotics[δ]	Case-control study of ATR by van der Linden et al. (2003) Ref: Not current user of fluoroquinolone
All	1.2 [0.9, 1.7]	2.7 [0.8, 9.5]	2.1 [0.8, 5.1]	11.0 [5.8, 20.8]
Ciprofloxacin	1.4 [1.0, 2.0]	0.7 [0.1, 6.3]	2.2 [0.5, 9.9]	3.6 [1.4, 9.1]
Levofloxacin	0.6 [0.3, 1.4]			
Norfloxacin		2.0 [0.4, 10.0]	0.6 [0.1, 4.6]	14.2 [1.6, 128.6]
Ofloxacin	1.4 [0.6, 3.6]	5.4 [1.4, 20.5]	4.9 [1.6, 15.1]	28.4 [7.0, 115.3]
Other	1.2 [1.0, 1.4]			

[α] The following fluoroquinolones were studied in at least one study: ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, and ofloxacin. Only fluoroquinolones examined individually are listed in the table above. The 'other fluoroquinolones' in the Seeger et al. was not specified.

[β] The Reviewer calculated the crude relative risk estimate for fluoroquinolones overall for the 2003 study by van der Linden et al. The Reviewer also calculated all the crude relative risk estimates for the study by Wilton et al. All other estimates are the adjusted relative risk provided within the publications. The odds ratio from case-control studies approximates the relative risk for rare outcomes. The hazard ratio is the relative risk assuming that the proportional hazards assumption is met. Lower confidence intervals that are ≤1.0 denote lack of statistical significance.

[γ] Non-fluoroquinolone antibiotics include azithromycin and cefixime

[δ] Non-fluoroquinolone antibiotics include amoxicillin, trimethoprim, cotrimoxazole, and nitrofurantoin

Consistent with the acute onset of fluoroquinolone-induced tendinopathy observed in case-series data (4; 5), studies that assessed tendinopathy occurring soon after fluoroquinolone exposure found stronger associations. The two studies by van der Linden et al. assessed current fluoroquinolone use, with the exposure risk window being the duration of fluoroquinolone therapy plus 30 days, and the study by Wilton et al. identified tendinopathy cases occurring within two months of onset of therapy. These three studies found higher point estimates than the study by Seeger et al. which assessed a larger risk window (180 days) --- see Table 6.

The study by Wilton et al. was the only one that did not account for potential confounding. In this study, fluoroquinolone users were older than users of other antibiotics, which may partly explain why fluoroquinolone users had a higher risk of tendinopathy. Sex differences among fluoroquinolone users also arose: norfloxacin users were more likely to be female (i.e., may have lower risk of tendinopathy). Despite these differences, norfloxacin users still had an elevated risk of tendinopathy compared to ciprofloxacin users. Alternatively, the higher prevalence of female

patients exposed to norfloxacin may be concealing an even higher risk associated with norfloxacin.

Although they adjusted for confounding, the other three studies may have incorporated more covariates than should have been incorporated given the small number of (exposed) cases. In any case, the adjusted and crude estimates consistently suggest an elevated risk of tendinopathy associated with fluoroquinolone exposure.

The four studies had other notable findings:

- The association between fluoroquinolone use and tendinopathy may be stronger among elderly patients and patients who use corticosteroids, a finding observed in other epidemiological studies (17; 20; 25; 27).
- Tendinopathy risk may be specific to fluoroquinolones.
- Fluoroquinolones were used primarily for respiratory or urinary tract infections.
- Using health claims to identify tendinopathy cases data may yield false positives.
- The incidence of ATR is low, even among fluoroquinolone-exposed patients.

Assessment of effect modification differed across the four studies. Effect modification by oral corticosteroid use among the elderly was observed in the study by Seeger et al.. Van der Linden et al. (2003) observed effect modification of oral corticosteroid use when examining the association between quinolones (including nalidixic acid) and tendinopathy, but neither study by van der Linden et al. specifically assessed effect modification by corticosteroid exposure for fluoroquinolones (without nalidixic acid). The 2003 study by van der Linden also restricted the study population to elderly subjects, which seemed necessary since all quinolone-exposed cases were older. Relative to the other studies, this study found a stronger association with fluoroquinolone use, suggesting an increased risk associated with fluoroquinolone use among elderly patients --- see Table 6. The study by Wilton et al. did not control for age or corticosteroid use. Lastly, none of the four studies assessed transplant status as a potential effect modifier.

One case-control study with active comparators suggested that tendinopathy risk was specific to fluoroquinolones. Both case-control studies by Seeger et al. and van der Linden et al. assessed cases' and controls' exposure to fluoroquinolones, to non-fluoroquinolone comparator antibiotics, and to no antibiotic exposure. In the studies, the odds of comparator antibiotic exposure and the odds of no antibiotic exposure were similar between cases and controls. However, only the study by van der Linden et al. found a statistically significant association between fluoroquinolone use and ATR, suggesting that tendinopathy risk is specific to fluoroquinolones. In the study by Seeger et al., the association between fluoroquinolones and ATR was not statistically significant, so the findings did not suggest that the risk of tendinopathy was specific to fluoroquinolones. By design, the cohort studies by Wilton et al. and van der Linden et al. compared the risk of tendinopathy between fluoroquinolone users and other antibiotic users, so they could not examine the risk of tendinopathy associated with no antibiotic exposure.

The case-control study by Seeger et al. and the cohort study by van der Linden et al. suggested that identification of tendinopathy from administrative claims data may yield many false positives

in the absence of outcome adjudication. Seeger et al. found that ICD-9-CM diagnosis or CPT procedural codes alone were insufficient for identifying cases of ATR not related to trauma. Similarly, although 97 patients in the cohort study by van der Linden had administrative claims codes and narrative text fields indicating tendinopathy, only a small percentage of these patients could be confirmed to have tendinopathy (all tendinitis). However, the case-control study by van der Linden et al. found that roughly 90% of ATR cases initially identified through OXMIS/READ EMR encounters were eventually confirmed cases. Differences in the positive predictive value of administrative claims codes and EMR coded data to identify tendinopathy may reflect differences in the accuracy of various coding schemes and/or variations in practices geographically or across time.

The study by Wilton et al. and the two studies by van der Linden et al. found that fluoroquinolones/quinolones were used primarily for respiratory or urinary tract infections. However, none of these studies described specific types of infections or the severity of the infections, so these studies did not quantify the relative or absolute risk of tendinopathy by specific indication or severity.

As described above in Section 2.1, the incidence of ATR is low, so a moderately increased relative risk of ATR among fluoroquinolone users would result in a small increased absolute risk. The study by Seeger et al. and the 2003 study by van der Linden et al. provided sufficient information to quantify the incidence of ATR among persons exposed versus unexposed to fluoroquinolones. Among the general population or among users of non-fluoroquinolone antibiotics, the incidence density ranged from 0.5 to 1.0 per 10,000 person-years. Meanwhile, among fluoroquinolone-exposed persons, the incidence density ranged from 1.3 to 5.6 per 10,000 person-years.

Table 7: Estimated incidence of Achilles tendon rupture (ATR) in studies of fluoroquinolone-associated tendinopathy (19; 26)

First Author, Year	Comparator Group	Incidence rate of ATR per 10K person-years	
		Comparator group	Fluoroquinolone-exposed group
Seeger, 2006	General population	1.0 [0.9, 1.1]	1.3 [1.0, 1.7][α]
van der Linden, 2003	General population, ages 60+	0.5[β]	5.6 [3.0, 10.6][α]

[α] Incidence rate of ATR estimated by the Reviewer under rare disease assumption, i.e., $IR_{exposed} = IR_{unexposed} \times OR$

[β] Incidence rate of ATR estimated by the Reviewer as the average rate between non-users 60 to 79 years and non-users 80+

5 DISCUSSION

The four studies selected for in-depth review support the current boxed warning of an increased risk of tendinitis and tendon rupture. These studies suggest that, relative to other subjects, fluoroquinolone-exposed subjects have 2.7 times the risk of tendinopathy (tendon rupture and tendinitis); 1.2 to 11.0 times the risk of tendon rupture; and 2.1 times the risk of tendinitis.

Overall, the four studies provide moderate support of further increased risk in elderly patients and patients taking corticosteroid drugs. One study found a non-significant elevation of fluoroquinolone-associated tendinopathy if subjects were both elderly and using corticosteroids. Another study found that corticosteroid use among elderly patients increased the risk of tendinopathy for quinolones as a class (including nalidixic acid); this study's analyses of elderly subjects found a higher risk associated with fluoroquinolone exposure relative to the other three studies that did not restrict on age. The remaining two studies did not assess effect modification by age or corticosteroid use.

No comment can be made on whether the risk of tendinopathy varies by transplant recipient status. None of the four studies were designed to examine this issue; that is, no analyses were stratified by transplant recipient status. Because immunosuppressive therapy with corticosteroids may predispose transplant recipients to tendinopathy, it may be difficult to study transplantation and corticosteroid use as independent risk factors for tendinopathy. Indeed, in the two studies that included only transplant recipients, all patients were treated with steroids.

While it is clear from the epidemiological literature that there is an increased risk of tendinopathy among patients exposed to fluoroquinolones, the four studies of higher quality did not agree on the magnitude of risk within the fluoroquinolone class. None of the studies were designed or powered to assess variations in risk across different fluoroquinolones, precluding conclusions about variation in risk by fluoroquinolone type. Furthermore, no conclusions can be drawn on the risk of tendinopathy by specific indication or severity of infection.

The most concerning tendinopathy outcome assessed in the four studies is ATR because it is a disabling, serious adverse event sometimes requiring surgery and is commonly seen in case-series data (4; 5). Still, the overall incidence of ATR is low, so a moderate relative increase of rupture among fluoroquinolone-exposed patients only increases the absolute risk of ATR by a small amount.

6 CONCLUSION

Overall, the four epidemiological studies of higher quality support the current boxed warning of an increased risk of tendinitis and tendon rupture. The studies also provide moderate support for further increased risk of fluoroquinolone-associated tendinopathy among elderly patients and patients who use corticosteroids. No comment can be made on whether the risk of tendinopathy varies by transplant recipient status because no results were stratified by this risk factor. Patients with organ transplants undergo steroid therapy which may predispose them to a higher risk of tendinopathy irrespective of their transplant status.

The most concerning tendinopathy outcome assessed in the four studies is ATR because it is a disabling, serious adverse event sometimes requiring surgery and is commonly seen in case-series data. Even though it occurs rarely, caution should be exercised when prescribing fluoroquinolones to avoid additional risk.

7 RECOMMENDATIONS

No recommendations at this time.

8 APPENDIX A: REFERENCES

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9 APPENDIX B: SUMMARY OF STUDIES – FLUOROQUINOLONES AND TENDINOPATHY BY STUDY DESIGN

Table 8: Ecological study of fluoroquinolones and tendinopathy

Selection Criteria	*Exposure Definition*	*Outcome Definition*	*Sample Size and Analytical Approach*	*Findings*
(24) van der Linden (2001), ecological study				
Inclusion criteria: Inhabitants of selected cities in Netherlands, years 1991 through 1996 Exclusion criteria: None stated	Dispensed fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, or pefloxacin), coded as J01MA in the Anatomical Therapeutic Chemical (ATC) classification system and recorded in the PHARMO drug database	Hospitalized tendon ruptures not related to trauma, presented in clinical and day-care settings, and recorded as principal discharge code ICD-9-CM 727.6 in the Dutch Centre for Health Care Information (SIG)	Approximately 300,000 inhabitants Descriptive analysis of trends of incident fluoroquinolone episodes and hospitalized non-traumatic tendon ruptures, overall and stratified by gender and age	Corresponding increase in incidence of fluoroquinolone use and incidence of tendon ruptures from years 1991 through 1996, stratified by gender and age - Overall fluoroquinolone use per 1K inhabitants: 8.1 in 1991 to 20.5 in 1996 - Tendon ruptures per 100K inhabitants: 5.1 in 1991 to 6.3 in 1996 - Both incidences driven by elderly inhabitants (≥60 y/o)

Table 9: Cohort studies of fluoroquinolones and tendinopathy

Selection Criteria	*Exposure Definition and Cohorts*	*Outcome Definition*	*Sample Size and Analytical Approach*	*Findings*
(16) Chhajed (2002), retrospective cohort study				
Inclusion criteria: Living lung transplant recipients from Australia, all who received post-transplantation cyclosporine / tacrolimus, azathioprine, and prednisolone, and responded to a questionnaire, study time period not stated Exclusion criteria: None stated	Exposure: Ciprofloxacin for treatment of lower respiratory tract infection (pseudomonas or atypical mycobacteria) Cohort 1: Lung transplant recipients treated with ciprofloxacin Cohort 2: Lung transplant recipients not treated with ciprofloxacin	Achilles tendon disease, consisting of Achilles tendinitis (defined as "presence of pain over the tendon with walking or on palpation") and Achilles tendon rupture (confirmed by positive Thompson's test)	Sample size: 101 (67.3%) respondents among 150 surveyed Univariate logistic regression Dose-response analysis: Mann-Whitney U-test for comparison of mean cumulative ciprofloxacin dose between exposed lung transplant recipients with vs. without Achilles tendon disease	Higher risk of Achilles tendon disease among exposed - Reviewer calculated: cRR = 4.0, 95% CI [1.0, 16.1] - Exposed: 20/72 (27.8%) - Unexposed: 2/29 (6.9%) Inverse dose-response relationship - Average dose (std) --- ATD cases: 17.6 (12.7) g --- Non-cases: 135.2 (313.7) g Short onset of Achilles tendon disease among exposed - Average (std): 10.8 (5) days - Range: 2 to 20 days

Selection Criteria	*Exposure Definition and Cohorts*	*Outcome Definition*	*Sample Size and Analytical Approach*	*Findings*
(18) Donck (1994), retrospective cohort study				
Inclusion criteria: Cadaveric kidney transplant recipients treated with cyclosporine and steroids, with or without treatment with azathioprine, years 1991 through 1992, with follow-up through February 1993 Exclusion criteria: None stated	Exposure: Use of fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, and pefloxacin) according to medical records Exposure risk window: Exposure period plus 15 days Cohort 1: Kidney transplant recipients treated with fluoroquinolones Cohort 2: Kidney transplant recipients not treated with fluoroquinolones	Achilles tendinopathy (tendinitis and/or rupture) according to medical records	Sample size: 230 patients, with 90 treated with fluoroquinolones (131 treatment episodes) Student's t test, chi-squared test, and Fisher's exact tests	Higher risk of Achilles tendinopathy among exposed - Reviewer calculated: cRR = 3.4, 95% CI [1.2, 9.5] - Exposed: 11/90 (12.2%) - Unexposed: 5/140 (3.6%) Higher risk of Achilles tendinopathy among users of pefloxacin - Pefloxacin: 10 cases per 51 treatment episodes - Norfloxacin: 1 case per 50 treatment episodes - Ciprofloxacin and ofloxacin: 0 cases per 10 and 20 treatment episodes, respectively

Selection Criteria	*Exposure Definition and Cohorts*	*Outcome Definition*	*Sample Size and Analytical Approach*	*Findings*
(27) Moeny (2011), retrospective, claims-based cohort study				
Inclusion criteria: Patients 17 years and older, who were new users of selected oral antibiotics, according to data from the Military Healthcare System, from January 2005 through April 2010. Exclusion criteria: No antibiotic exposure or Achilles tendon rupture (ATR) in 180 days before index prescription	Exposure: Dispensed oral antibiotics Exposure window: Days of supply plus 60 days. Cohort 1: Patients dispensed fluoroquinolones, including ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin Cohort 2: Patients dispensed other antibiotics, including amoxicillin/clavulanate, azithromycin, and sulfamethoxazole-trimethoprim	Achilles tendon rupture (ATR), ICD-9-CM code 727.67. Censoring: First occurrence of ATR, the end of index exposure plus 60 days, disenrollment, or end of study period.	~1.1M fluoroquinolone users (59.5% on ciprofloxacin and 49.2% on levofloxacin) --- fluoroquinolone users could be exposed to more than one type fluoroquinolones. ~2.3M users of other antibiotics Comparison of rates (specific analytical technique not stated), adjusted for age and gender Stratification by oral corticosteroid use anytime during the 30 days prior to index date through the drug exposure era (proximal use).	57 ATRs among fluoroquinolone users and 81 ATRs among users of other antibiotics Fluoroquinolone users had higher rate of ATR, aHR = 1.4, 95% CI [1.1, 1.8] - Similar findings when stratified by age - Highest aRR for elderly (65+): 2.1, 95% CI [1.4, 3.0] With no corticosteroid stratification, higher ATR rate with use of levofloxacin than for ciprofloxacin - Levofloxacin: aHR = 2.0, 95% CI [1.4, 2.7] - Ciprofloxacin: aHR = 0.8, 95% CI [0.5, 1.3] - Proximal corticosteroid use was an effect modifier for levofloxacin --- w/ proximal corticosteroid use: aHR = 4.2, 95% CI [2.2, 7.3] --- w/o proximal corticosteroid use: aHR = 1.8, 95% CI [1.2, 2.6]

Selection Criteria	*Exposure Definition and Cohorts*	*Outcome Definition*	*Sample Size and Analytical Approach*	*Findings*
(20) Sode (2006), retrospective, claims-based cohort study --- see also Sode (2006) for case-crossover analysis				
Inclusion: Residents of Funen County, Denmark, where health care utilization is recorded in the Patient Administrative System (inpatient and outpatient), and the Odense University Pharmacoepidemiological Database (reimbursed prescriptions), from January 1, 1991 through May 17, 1999 Exclusion: Non-residents at time of Achilles tendon rupture or at time of redeemed prescription	Exposure: First dispensed antibiotic prescriptions Exposure risk window: 90-days for each prescription Cohort 1: Persons dispensed fluoroquinolones Cohort 2: Persons dispensed other antibiotics (tetracyclines, penicillins, cephalosporins, sulfonamides, macrolides, aminoglycosides, and glycopeptides)	Discharge codes for Achilles tendon rupture (ICD-8 code 90810 and ICD-10 code S860)	Absolute risk calculated as the 90-day cumulative incidence proportion per 100K prescriptions Calculation of standardized incidence ratio by indirect standardization for gender and 10-year age intervals, using Poisson regression Risk difference, assumed by the Reviewer to be calculated as the difference between the background population's standardized incidence rate and standardized incidence rate for the antibiotic cohorts	Higher 90-day risk per 100K prescriptions among fluoroquinolone exposed vs. persons exposed to other antibiotics - Reviewer calculated: cRR = 3.4, 95% CI [1.3, 9.0] - Fluoroquinolone: 90-day risk = 17.7, 95% CI [5.7, 41.3], per 100K prescriptions - Other antibiotics: 90-day risk = 5.2, 95% CI [3.2, 8.0], per 100K prescription Relative to background incidence rate, higher standardized incidence ratio among fluoroquinolone users during 90-day risk window - Fluoroquinolone: 3.1, 95% CI [1.0, 7.3] - Other antibiotics: 0.8, 95% CI [0.5, 1.3] Note: 30-day risk window yielded RR = 3.6, and 180-day risk window yielded RR = 2.7 Age-stratified results suggest higher risk among elderly (60+) Relative to background incidence, higher risk difference among fluoroquinolone users - Fluoroquinolone: 12.0, 95% CI [0.0, 35.6] - Other antibiotics: -1.0, 95% CI [-2.9, 1.8]

Selection Criteria	*Exposure Definition and Cohorts*	*Outcome Definition*	*Sample Size and Analytical Approach*	*Findings*
(21) Wilton (1996), retrospective cohort study				
Inclusion criteria: Patients who were prescribed fluoroquinolones or other antibiotics, and whose prescribers responded to the Prescription-Event Monitoring questionnaires and wrote the prescriptions during selected timeframes (see exposure on right) Exclusion criteria: None stated	Exposure: Antibiotics prescribed during selected timeframes: - Ciprofloxacin prescribed during November 1988 to January 1989 - Norfloxacin prescribed during October 1990 to October 1991 - Ofloxacin prescribed during May 1990 to December 1991 - Azithromycin prescribed during March 1992 to June 1993 - Cefixime prescribed during September 1990 to May 1991 Exposure risk period: 60 days for each prescription	Outcome: Adverse events – including tendinitis and tendon rupture – reported by prescribers, occurring within 2 months of onset of therapy, and defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration or improvement in a concurrent illness, any suspected drug reaction, or any complaint considered of sufficient importance to enter in the patient notes. See publication for other adverse events.	Sample size: - Fluoroquinolones: 11,477, 11,110, and 11,033 patients prescribed ciprofloxacin, norfloxacin, and ofloxacin, respectively - Other antibiotics: 11,275 and 11,250 patients prescribed azithromycin and cefixime, respectively No formal statistical tests performed Reviewer's calculations of incidence proportion and relative risk assumed mutually exclusive cohorts	According to Reviewer's calculations, similar absolute 2-month risk for tendinitis or tendon rupture between the two antibiotic cohorts - Crude relative risk: 2.7, 95% CI [0.8, 9.5] - All fluoroquinolones: 12 reports, 3.6 per 10K patients --- Ciprofloxacin: 1 report (0 ruptures), 0.9 per 10K patients --- Norfloxacin: 3 reports (1 rupture), 2.7 per 10K patients --- Ofloxacin: 8 reports (3 ruptures), 7.3 per 10K patients - Azithromycin and cefixime: 3 reports, 1.3 per 10K patients --- Azithromycin: 1 report (0 ruptures), 0.9 per 10K patients --- Cefixime: 2 reports (0 ruptures), 1.8 per 10K patients Indications: Fluoroquinolones generally used for respiratory or urinary tract infections See publication for other adverse events.

Selection Criteria	*Exposure Definition and Cohorts*	*Outcome Definition*	*Sample Size and Analytical Approach*	*Findings*
(23) van der Linden (1999), retrospective, claims-based cohort study				
Inclusion criteria: Patients ages ≥15 years, having ≥3 months of computer-recorded history, treated with selected antibiotics within 41 general practices that contributed data to the Integrated Primary Care Information systems research database, in Netherlands, years 1995 and 1996 Study entry was index prescription for first antibiotic Exclusion criteria: Patients with unknown gender, age, or study drug dosage, patients who used study drugs >60 days in 1 year, patients with history of inflammatory joint disease, Reiter's syndrome, polymyalgia rheumatica, gout or AIDS, and patients with concomitant use of fluoroquinolones with other study drugs in risk period	Exposure: Use of non-dermatological / non-ocular preparations of selected antibiotics, with the exposure period being the sum of the duration of use (i.e., prescribed drug divided by daily dose) corrected for refill prescriptions Exposure risk period: Exposure period plus 1 month Cohort 1: Patients treated with fluoroquinolones (ofloxacin, ciprofloxacin, or norfloxacin) Cohort 2: Patients treated with amoxicillin, trimethoprim, co-trimoxazole, or nitrofurantoin	Adjudicated, incident cases of tendinitis not related to trauma, including Achilles tendinitis and non-Achilles tendinitis, initially identified using International Classification for Primary Care (ICPC) diagnosis codes in series L81 (other musculoskeletal injuries), L92 (shoulder syndrome), L93 (epicondylitis), and L99 (other diseases of the musculoskeletal system) Note: Before validation, case definition included tendinitis and tendon rupture Censoring criteria: Outcome, transfer to another practice, death, or end of study period	10,800 patients - 1,841 patients treated with fluoroquinolones, with 9 days average duration --- Ofloxacin: 418 patients --- Ciprofloxacin: 456 patients --- Norfloxacin: 1,362 patients - 9,406 patients treated with other antibiotics, with 7 days average duration *Note: 447 patients treated with fluoroquinolones during different risk periods than treatment with other antibiotics Calculation of rate ratios using Poisson regression, unadjusted and adjusted for gender, age, number of general practitioner visits, and concurrent corticosteroid use. Risk difference calculated as difference in incidence density	Similar rates for all tendinitis - aRR = 2.1, 95% CI [0.8, 5.1] - Fluoroquinolone: 7.7 / 100K days - Other antibiotics: 3.3 / 100K days - Risk difference: ~4 / 100K days Similar rate for Achilles tendinitis - aRR = 3.7, 95% CI [0.9, 15.1] - Fluoroquinolone: 4.4 / 100K days - Other antibiotics: 0.9 / 100K days - Risk difference: ~4 / 100K days Ofloxacin with higher rates for all tendinitis and Achilles tendinitis, while ciprofloxacin and norfloxacin had similar rates vs. other antibiotics - Ofloxacin, all tendinitis: aRR = 4.9, 95% CI [1.6, 15.1] - Ofloxacin, Achilles tendinitis: aRR = 10.1, 95% CI [2.2, 46.0] No elevated rate for non-Achilles tendinitis for all and each fluoroquinolone vs. other antibiotics Similar indications for fluoroquinolones and other antibiotics, most being for urinary or respiratory tract infections Note: Use of corticosteroids was not related to tendinitis in this study.

Table 10: Case-based studies of fluoroquinolones and tendinopathy

Selection Criteria	*Case and Control Definitions*	*Exposure Definition*	*Sample Size and Analytical Approach*	*Findings*
(17) Corrao (2006), retrospective, claims-based case-control study				
Inclusion criteria: Residents ages ≥18 years in Lombardia, Italy, where demographic, prescription, and hospital discharge data are recorded in National Health Service databases Exclusion criteria: Residents with any of the following: cancer, diabetes mellitus, gout, renal failure, thyroid disease, other diseases of the musculoskeletal system and connective tissue, or history of tendon disorders	Cases: Subjects hospitalized with tendon disorders (ICD-9 code 727.0), Achilles tendon rupture not related to trauma (727.67), and rupture of other tendon sites not related to trauma (727.6x, excluding 727.67). Index date was first hospitalization of tendon disorder Controls: Up to five subjects matched to cases on sex, age, municipality of residence, and index date	Fluoroquinolones coded as J01MA in the Anatomic-Therapeutic-Chemical classification (ATC) system Exposure windows: Dispensing date plus estimated duration of use Each exposure window categorized as one of the following mutually exclusive groups relative to index date: current use (within 15 days prior), recent use (15-30 days prior), past use (30-90 days prior), and non-use (no exposure within 90 days prior) Other drug exposure windows categorized as: recent use (≤30 days prior), non-use (no exposure within 30 days prior)	Cases: 22,194 subjects - 14,993 with tendon disorders - 6,361 with non-traumatic non-Achilles tendon rupture - 840 with non-traumatic Achilles tendon rupture Controls: 104,906 subjects Analyses to test differences in drug exposure between cases and controls: - Chi-square test - Conditional logistic regression for each category of exposure (non-use as reference), unadjusted and adjusted for concurrent exposure to other antibacterials, corticosteroids, and other drugs Test of homogeneity of odds ratios across age classes (<60 and ≥60 years) conducted with Mantel-Haenszel test	Higher odds of fluoroquinolone use - aOR for tendon disorders --- Current: 1.7, 95% CI [1.4, 2.0] --- Recent: 1.3, 95% CI [1.1, 1.6] --- Past: 1.1, 95% CI [0.9, 1.2] - aOR for tendon rupture --- Current: 1.3, 95% CI [1.0, 1.8] --- Recent: 1.7, 95% CI [1.2, 2.3] --- Past: 1.1, 95% CI [0.9, 1.3] - aOR for Achilles tendon rupture --- Current: 4.1, 95% CI [1.8, 9.6] --- Recent: 1.9, 95% CI [0.5, 7.5] --- Past: 1.1, 95% CI [0.5, 2.2] Higher odds of fluoroquinolone use only for Achilles tendon rupture among elderly (≥60 years) vs. non-elderly (p = 0.009) Highest odds with past 30-day corticosteroid and fluoroquinolone use - Tendon disorder: aOR = 1.8, 95% CI [1.1, 2.9] - Non-Achilles tendon rupture: aOR = 3.1, 95% CI [1.5, 6.3] - Achilles tendon rupture: aOR = 43.2, 95% CI [5.5, 341.1] Note: Past 30-day corticosteroid use was independent risk factor for each outcome 16 day average onset from fluoroquinolone dispensing date to index date 70% of fluoroquinolone-exposed controls used ciprofloxacin or levofloxacin, with no evidence of heterogeneity of effects

Selection Criteria	*Case and Control Definitions*	*Exposure Definition*	*Sample Size and Analytical Approach*	*Findings*
(19) Seeger (2006), retrospective, claims-based, case-control study				
Inclusion criteria: Persons with commercial and Medicare supplement health insurance, selected from the Ingenix Research Database, enrolled for at least 180 days prior to index date, from January 1997 through June 2001 Exclusion criteria: None stated	Cases: Persons with both a diagnosis and surgical or non-surgical procedure code related to Achilles tendon rupture (ATR) not related to trauma: ICD-9 codes (assumed by the Reviewer to be 727.67) and a CPT code (27605, 27606, 27650, 27652, 27654, or 01472). Cases had one of the following: 1) Ankle sprain diagnosed by specialist or hospital/surgicenter 2) Achilles tendon rupture diagnosed by specialist, hospital/surgicenter, or medical professional Positive predictive values for case definition was 91.2% Index date was date of case diagnosis. Controls: 20 subjects matched to cases on index date and frequency matched to cases on age	Fluoroquinolone antibiotics use in the following windows relative to index date: - 180 days prior - 0 to 90 days prior - 91 to 180 days prior Cumulative fluoroquinolone use (referred to as absorbed dose) in the 180 days prior to index date calculated as dose times bioavailability Fluoroquinolones included ciprofloxacin, levofloxacin, ofloxacin, and other	947 cases of Achilles tendon rupture among 9.8M person-years, incidence rate of 1.0 per 10K person years Note: Based on 20-to-1 control-to-case ratio, the Reviewer calculates 18,940 controls Unconditional logistic regression, adjusted for age, sex, and the following covariates ascertained in 180 days prior to index date: obesity, skin and soft tissue infection, oral or injected corticosteroid use, non-fluoroquinolone antibiotic use, arthritis, diabetes, and trauma	Similar odds of fluoroquinolone use vs. no use, with the following aOR for risk windows prior to index date: - 180 days: 1.2, 95% CI [0.9, 1.7] - 0-90 days: 1.3, 95% CI [0.8, 1.8] - 91-180 days: 1.3, 95% CI [0.8, 2.0] Slight increased odds of past-180 day ciprofloxacin or 'other' fluoroquinolone use, aOR: - Ciprofloxacin: 1.4, 95% CI [1.0, 2.0] - Levofloxacin: 0.6, 95% CI [0.3, 1.4] - Ofloxacin: 1.4, 95% CI [0.6, 3.6] - Other fluoroquinolones: 1.2, 95% CI [1.0, 1.4] Moderately higher odds of for higher cumulative fluoroquinolone doses, aOR: - <4 g: 1.1, 95% CI [0.5, 2.2] - 4 to 8 g: 1.0, 95% CI [0.6, 1.8] - >8 g: 1.5, 95% CI [1.0, 2.3] No increased odds for fluoroquinolone use stratified by age and oral corticosteroid use, although suggested highest odds for fluoroquinolone use among elderly (≥60 years) subjects with oral corticosteroid use - cOR = 2.7, 95% CI [0.7, 10.4]

Selection Criteria	*Case and Control Definitions*	*Exposure Definition*	*Sample Size and Analytical Approach*	*Findings*
(20) Sode (2006), retrospective, claims-based, case-crossover study– see also Sode (2006) for cohort analysis				
Inclusion criteria: Residents ages ≥18 of Funen County, Denmark, where health care utilization is recorded in the Patient Administrative System (inpatient and outpatient), and the Odense University Pharmacoepidemiological Database (reimbursed prescriptions), between July 1, 1992, and May 17, 1999, with residency for at least 18 months prior to index date Exclusion criteria: Non-residents at time of Achilles tendon rupture or at time of redeemed prescription	Cases: Residents with discharge codes for first-time Achilles tendon rupture (ICD-8 code 90810 and ICD-10 code S860 Index date was the case diagnosis date. Case window: 90 days prior to index date Control window: 90 day period prior to 1 year prior to the index date	Primary exposure: Fluoroquinolone dispensed within case or control windows Comparator exposure: Other antibiotics, including teracyclines, chloramphenicols, penicillins, cephalosporins, sulfonamides, macrolides, aminoglycocides and glycopeptides, dispensed within case or control windows	911 patients with first-time Achilles tendon rupture Odds ratio, assumed by the Reviewer to be the McNemar estimate	Similar odds of fluoroquinolone exposure between case and control windows, OR = 1.8, 95% CI [0.5, 6.9] Similar odds of exposure to other antibiotics between case and control windows, OR = 0.9, 95% CI [0.6, 1.2]

Selection Criteria	*Case and Control Definitions*	*Exposure Definition*	*Sample Size and Analytical Approach*	*Findings*
(22) Wise (2012), retrospective, claims-based, case-crossover disease				
Inclusion criteria: U.K. residents selected from The Health Improvement Network (THIN) database, from January 1, 1986, to November 31, 2009 Exclusion criteria: Achilles tendinitis or tendon rupture diagnosed within two years of entry into the THIN database	Cases: Subjects with first-time diagnosis of Achilles tendinitis or tendon rupture (case identification procedures not specified) Index date was the case diagnosis date. Case window: 30 days prior to index date Control window: 30 day period that was 1 year prior to the index date	Note: Secondary analyses focused specifically on oral or parental fluoroquinolone use (claim codes not stated. See publication for findings for quinolones, the primary exposure of interest Comparator exposures - trimethoprim, amoxicillin, or nitrofurantoin	Incident cases - Achilles tendinitis: 28,907 cases, with baseline rate of 92 per 100K person-years - Achilles tendon rupture: 7,685, with baseline rate of 24 per 100K person-years Rate difference calculated as the difference between the product of baseline incidence rate times odds ratio minus the baseline incidence rate: (IR * OR) – IR Estimation of 30-day risk of Achilles tendinitis or tendon rupture per 10K new fluoroquinolone prescriptions	Following results are for fluoroquinolones only. See publication for results on quinolones Rate difference for fluoroquinolone exposed versus baseline rate: - Achilles tendinitis: 30.2 per 10K person-years - Achilles tendon rupture: 2.4 per 10K person-years Reviewer calculated: 30-day incidence rates for fluoroquinolone users: - Achilles tendinitis: 39.4 per 10K person-years - Achilles tendon rupture: 4.8 per 10K person-years 30-day risk - Achilles tendinitis: 4.8 per 10K new fluoroquinolone prescriptions - Achilles tendon rupture: 0.6 per 10K new fluoroquinolone prescriptions

Selection Criteria	*Case and Control Definitions*	*Exposure Definition*	*Sample Size and Analytical Approach*	*Findings*
(25) van der Linden (2002), retrospective, claims-based, nested case-control study				
Inclusion criteria: Patients ages ≥18 years who received a fluoroquinolone prescription, selected from the IMS Health Database (UK MediPlus), from July 1992 through June 1998 Exclusion criteria: History of Achilles tendon disorders, cancer, AIDS, illicit drug use, or alcohol misuse	Cases: Patients with Achilles tendon disorders (health claim codes not stated) not related to trauma, including Achilles tendinitis and Achilles tendon rupture The Reviewer assumes that the index date was diagnosis date. Controls: Random sample of 10K patients from study population	Exposure window: Prescription length plus 30 days Each exposure window categorized as one of the following mutually exclusive groups relative to index date: current use (within 30 days prior), recent use (30-90 days prior), past use (>90 days prior). No use before index date requires that fluoroquinolones be dispensed after index date, given study selection criteria	46,776 fluoroquinolone users, with 704 patients having Achilles tendinitis and 38 having Achilles tendon rupture Estimation of relative risk through unconditional logistic regression, unadjusted and adjusted for age, sex, number of visits to general practitioners, corticosteroid use, calendar year, obesity, and history of musculoskeletal disorders, with no use as the reference	Higher risk of any Achilles tendon disorder for current use, aRR: - Current use: 1.9, 95% CI [1.3, 2.6] - Risk similar for recent, past, and no use (not quantified) Increased risk of any Achilles tendon disorder among elderly (≥60 years), but not non-elderly - aRR among elderly for current use --- Any: 3.2, 95% CI [2.1, 4.9] --- Rupture: 7.1, 95% CI [1.7, 29.1] --- Tendinitis: 3.1, 95% CI [2.0, 4.8] - Similar risk among elderly for recent, past, and no use, as was risk among non-elderly for any window - Increased risk with concurrent corticosteroid and fluoroquinolone use, RR = 6.2, 95% CI [3.0, 12.8] Cases and controls had similar indications for fluoroquinolone use (indications not stated)

Selection Criteria	*Case and Control Definitions*	*Exposure Definition*	*Sample Size and Analytical Approach*	*Findings*
(26) van der Linden (2003), retrospective, claims-based case-control study				
Inclusion criteria: Subjects aged 18 to 95 with permanent registration status at index date and 18 months of standard history, selected from the General Practice Research Database, from January 1, 1988, to January 1, 1999 Analyses of fluoroquinolones were restricted to subjects 60 years and older. Exclusion criteria: History of cancer, drug abuse, alcoholism, or AIDS, or hospital admission in month prior to index date	Cases: First-time diagnosis of Achilles tendon rupture (ATR, OXMIS codes 845B, 7339E, 7339TT) not related to trauma, verified through medical record review Controls: Randomly selected persons from practices where cases were registered Index date for cases was the case diagnosis date, and index date for controls was randomly selected during the study period	Sensitivity analyses focused specifically on oral or parental fluoroquinolone use of ofloxacin, ciprofloxacin, or norfloxacin. See publication for findings for quinolones (including nalidixic acid), the primary exposure of interest Exposure window was the prescription length plus 30 days, and current exposure was an overlap of the index date with the exposure window	Cases: 290 subjects Controls: 12,658 subjects Unconditional logistic regression, unadjusted and adjusted for age, sex, oral corticosteroid use, musculoskeletal disorders, lipid metabolism disorders, and organ transplants or hemodialysis	The following results are for fluoroquinolones only. See publication for results on the quinolone nalidixic acid Increased odds of <u>current</u> fluoroquinolone use, cOR - Reviewer calculated: cOR = 11.0, 95% CI [5.8, 20.8] Highest odds for ofloxacin, aOR: - Ofloxacin: 28.4, 95% CI [7.0, 115.3] - Ciprofloxacin: 3.6, 95% CI [1.4, 9.1] - Norfloxacin: 14.2, 95% CI [1.6, 128.6] Most courses for quinolones (including fluoroquinolones and nalidixic acid) given for urinary or respiratory tract infection, with no significant difference in indications between cases and controls ($p>0.05$)

10 APPENDIX C: SUMMARY OF STUDY FINDINGS – FOREST PLOTS

Figure 1a: Increased risk[α] of tendinopathy (tendinitis or tendon rupture) among fluoroquinolone-exposed subjects

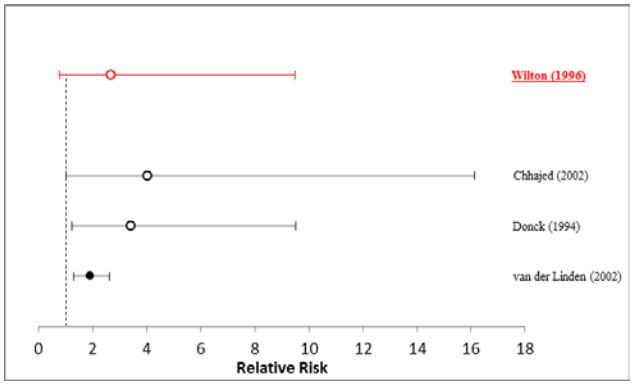


Figure 1b: Increased risk[α] of tendon rupture among fluoroquinolone-exposed subjects

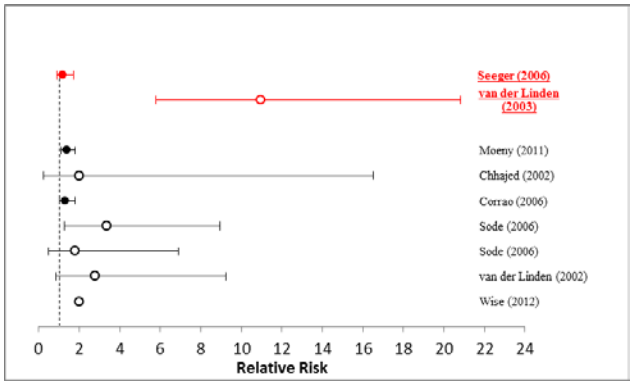
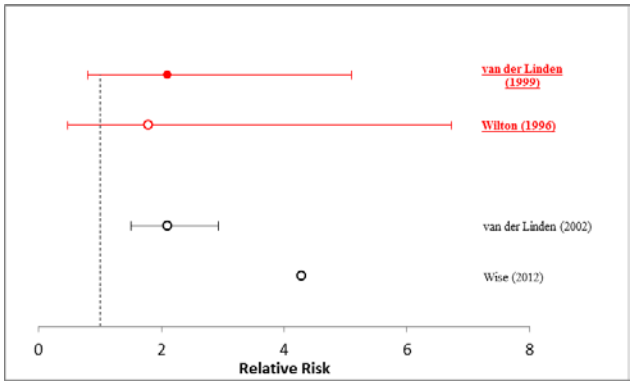


Figure 1c: Increased risk[α] of tendinitis among fluoroquinolone-exposed subjects



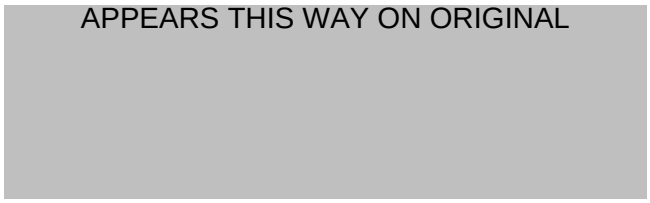
Four studies with in-depth review are in red, with the first author and year bolded and underlined.

Estimates calculated with multivariate regression are in filled circles, and estimates calculated without multivariate regression are in open circles.

Data was insufficient to calculate confidence intervals for the study by Wise et al.

For more information on the studies' design, see Appendix B.

[α] The odds ratio from case-control studies approximates the relative risk for rare outcomes. The hazard ratio is the relative risk assuming that the proportional hazards assumption is met. Comparator group differs across studies. Cohort studies compared fluoroquinolone exposure to exposure to other antibiotics or no fluoroquinolone exposure. Case-control studies generally assessed the presence vs. absence of fluoroquinolone exposure between cases and controls.


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Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology Review (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of post-marketing safety studies on fluoroquinolones and serious cardiac arrhythmias

Date:	September 23, 2015
Reviewer(s):	Chih-Ying Chen, Ph.D. Division of Epidemiology II
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Division Director	Judy A. Staffa, Ph.D., R.Ph Division of Epidemiology II
Drug Name(s):	Fluoroquinolones
Subject:	Review of post-marketing safety studies on fluoroquinolones and serious cardiac arrhythmias
OSE RCM #:	2015-896

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EXECUTIVE SUMMARY

The Division of Anti-Infective Products (DAIP) is planning a Joint Advisory Committee meeting to discuss the benefits and risks of the systemic fluoroquinolone antibacterial drugs for the treatment of three "milder" indications—acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections. DAIP requested that the Division of Epidemiology II (DEPI II) conduct an epidemiological review of publications to characterize the incidence and relative risks of selected labeled adverse reactions associated with systemic fluoroquinolone antibacterial drugs. This document describes the literature review of published epidemiologic studies that investigated the risk of serious cardiac arrhythmias among fluoroquinolone users, which could be the consequence of fluoroquinolone-associated QT prolongation.

DEPI II identified eight observational studies that focused on serious cardiac arrhythmias (that could potentially be the result of QT prolongation, such as cardiac arrhythmia) or death that were included in an in-depth review. The quality of the evidence provided in each study was evaluated according to 1) the appropriateness of the risk window to evaluate fluoroquinolone-associated serious cardiac arrhythmia risk, 2) the sufficiency of the approach to account for confounding by indications and other covariates, and 3) the adequacy of the outcome ascertainment.

Only two of the eight studies were deemed sufficient to quantify fluoroquinolone-associated serious cardiac arrhythmia risk. Reasons for exclusion of the other six studies are provided in section 3. Both studies used population-level data reflecting the real-world antibiotic user population. They also attempted to control for confounding using an active comparator antibiotic and advanced analytical approaches to adjust for confounding. However, these studies lacked sufficient adjustment for confounding by indication. Although they both found an increased risk of serious cardiac arrhythmias associated with fluoroquinolone use, and one suggested a difference in risk of serious cardiac arrhythmias between individual fluoroquinolones, definitive conclusions cannot be made based on these two observational studies. The absolute risk of serious cardiac arrhythmias associated with fluoroquinolone use is likely to be low, ranging between 15-57 per 100,000 users of fluoroquinolones, compared to 9-12 per 100,000 users of amoxicillin or amoxicillin-clavulanate. Fluoroquinolone users with underlying cardiovascular disease appeared to have a higher baseline risk for serious cardiac arrhythmias than those without. The absolute risk of serious cardiac arrhythmias ranged from 46-85 per 100,000 users with cardiovascular diseases versus 5-44 per 100,000 users without cardiovascular diseases.

DEPI-II does not recommend a regulatory action at this time, due to the limitations of the existing studies in determining absolute and relative risk of fluoroquinolone-associated serious cardiac arrhythmia risk. It appears that the absolute risk is low, but further investigation is warranted to examine the comparative cardiac safety between fluoroquinolones and other antibiotics and to explore the difference in serious cardiac arrhythmia risk associated with individual fluoroquinolones and effect modification by presence of underlying cardiovascular disease. To advance from existing evidence, future studies will need to capture the indication of antibiotic use with better clinical granularity and include deaths that are the direct consequence of QT prolongation (i.e. cardiac or sudden cardiac deaths) in the outcome definition.

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1 INTRODUCTION

The Division of Anti-Infective Products (DAIP) is planning a Joint Advisory Committee meeting to discuss the benefits and risks of the systemic fluoroquinolone antibacterial drugs for the treatment of three "milder" indications—acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections. DAIP requested that the Division of Epidemiology II (DEPI II) conduct an epidemiological review of publications to characterize the incidence and relative risks of labeled adverse reactions associated with systemic fluoroquinolone antibacterial drugs. This document describes the literature review of existing epidemiologic studies that investigated the risk of serious adverse cardiac outcomes among fluoroquinolone users which could be the consequences of the fluoroquinolone-associated QT prolongation.

1.1 Drug-induced QT prolongation

The QT interval on the electrocardiogram is the time required for ventricular repolarization during a single cardiac cycle.[1] It represents the summation of action potential of ventricular myocytes.[2] The action potential reflects the flow of ion currents across a cell membrane through specialized protein channels.[2] Malfunction of these protein channels can lead to increases in the action potential duration and hence QT interval prolongation.[2] QT prolongation is separated into two general categories: 1) inherited long QT syndrome resulting from loss-of-function mutations in several cardiac potassium channels;[1] and 2) acquired long QT syndrome which is commonly induced by drug therapy, caused by the direct blockage of the potassium channel.[1] Long QT syndrome increases the risk of torsades de pointes, a polymorphic ventricular tachycardia.[1;3] Torsades de pointes can either terminate spontaneously, or degenerate into lethal ventricular fibrillation, or sudden cardiac death.[1] Examples of drugs that are generally considered to confer a risk of QT prolongation or torsades de pointes are listed below:[1;2]

- Antiarrhythmic drugs
  - Class Ia: quinidine, procainamide, disopyramide
  - Class III: amiodarone, sotalol, ibutilide, dofetilide, berpridil
- Non-antiarrhythmic drugs
  - Cisapride
  - Antihistamines: Terfenadine[a], Astemizole[a]
  - Antipsychotics:
    - Neuroleptic: haloperidol, droperidol, thioridazine, chlorpromazine
    - Atypical antipsychotics: sertindole[a], ziprasidone, risperidone, zimeldine, citalopram
  - Antidepressants: amitriptyline, desipramine, omipramine, maprotiline, doxepin, fluoxetin
  - Antibiotics
    - Quinolone: sparfloxacin[a], levofloxacin, moxifloxacin, grepafloxacin[a]
    - Macrolide: erythromycin, clarithomycin
  - Antimalarial: quinine, halofantrine
  - Antiprotozoal: Pentamidine
  - Antifungal (Azole group)
  - Methadone
  - Digitalis
  - Diuretics

[a] Withdrawn from market or discontinued

Other risk factors that have been associated with drug-induced QT prolongation or torsades de pointes includes:[2;3]

- Demographic characteristics
  - Female sex
  - Advanced age
- Clinical characteristics (comorbidities)
  - Electrolyte disturbances
  - Hepatic and renal dysfunction
  - Bradycardia
  - Congenital long QT syndrome
  - Prior QT prolongation
  - Underlying heart disease, such as heart failure, left ventricular hypertrophy and myocardial infarction

Long QT syndrome affects an estimated 1 in 5,000–10,000 people worldwide.[1] Drug-induced torsades de pointes by the antiarrhythmic drug quinidine is a relatively frequent side effect, affecting 2–9% of treated patients.[4] However, induction of torsades de pointes by drugs other than antiarrhythmic agents is rare.[1] For example, cisapride-induced torsades de pointes was estimated to occur between 1 per 12,000 patients and 1 per 120,000 patients prescribed this medication.[5]

1.2 Fluoroquinolones and QT prolongation

Fluoroquinolones have a variable effect on QT interval with very rare incidence of Torsades de Pointes.[2] Grepafloxacin and sparfloxacin delay repolarization more profoundly than gatifloxacin, levofloxacin, and moxifloxacin, with ciprofloxacin and ofloxacin causing the least effect.[6] Grepafloxacin was withdrawn from the market because it lengthened the QT interval leading to cardiac events and sudden death.[7] Sparfloxacin has been associated with 145 post-marketing reports of QT-related events among 49,000 patients,[8] although there is no official report that it was withdrawn due to safety reasons.[9] With minor variations, the current labeling of fluoroquinolones in the U.S. all carry similar warning of the known association with QT prolongation and infrequent cases of arrhythmia, and/or isolated (rare) cases of Torsade de pointes. All labels recommend avoidance or cautious use of fluoroquinolones among

- patients with known prolongation of the QT interval,
- patients with uncorrected hypokalemia,
- patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents, or other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants,
- elderly patients who may be more susceptible to drug-associated effects on the QT interval, and
- patients with proarrhythmic conditions such as clinically significant bradycardia or acute myocardial ischemia.

2 REVIEW MATERIALS

Conducted on May 15, 2015, a search of the National Library of Medicine's PubMed database used following search string: (fluoroquinolone[MeSH]) AND (((“acute kidney injury”[MeSH] OR “anaphylaxis”[Mesh] OR “hypersensitivity”[MeSH] OR “tendinopathy”[MeSH] OR "peripheral nervous system diseases"[Mesh] OR "retinal detachment"[MeSH] OR "arrhythmias, cardiac"[MeSH] OR "death"[MeSH] or "Drug-Related Side Effects and Adverse Reactions"[MeSH]))). The literature search included 722 publications written in English, dealing with humans, and published anytime from January 1, 1986 to the date of the search. We then excluded:

- publications that did not mention fluoroquinolones
- case reports and case series
- commentaries and reviews
- methods development studies and studies based on adverse event reports
- QT prolongation studies
- studies with no safety data
- studies were fluoroquinolones were only used by ophthalmic, otic, or topical routes of administration, among pediatric populations, or in the inpatient setting

DEPI II identified thirteen studies on fluoroquinolone-associated serious cardiac arrhythmia risk from the aforementioned PubMed search.

3 REVIEW RESULTS

Among the thirteen identified studies, we excluded four studies[10-13] that only examined QT prolongation (but not serious arrhythmia or sudden [cardiac] death) as the outcome. We further excluded one pooled-analysis of randomized control trials.[14] We evaluated the quality of the eight remaining observational studies[15-22] by the following criteria:

- Appropriateness of the risk window to evaluate fluoroquinolone-associated cardiac arrhythmia: Given that drug-induced QT prolongation is caused by the direct blockage of the cardiac potassium channel,[1] we expect the cardiac adverse events would occur while patients are exposed to fluoroquinolone, or within the elimination half-life of the drug. A short risk window (that closely corresponds to the treatment duration) is more appropriate than a long risk window.

- Sufficiency of the approach to account for “confounding by indications” and other confounders: Indications such as pneumonia or acute exacerbation of chronic bronchitis (or chronic obstructive pulmonary disease [COPD]) are potential risk factors for cardiac arrhythmia. It is crucial 1) to use an active comparison group to examine fluoroquinolone-associated cardiac risk and 2) to capture the information on the indication for antibiotic use in the study to account for potential differences in indication among fluoroquinolone(s) users and the active comparator. Studies

should also account for other important confounders, such as comorbidities and co-medications that could increase drug-induced arrhythmia or drug-induced Torsades de Pointes risk (see section 1.1).

- Adequacy of the outcome ascertainment
  The study should be able to capture all serious clinical consequences of QT prolongation, such as inpatient or emergency visit for cardiac arrhythmia, cardiac arrest, and sudden (cardiac) death. The study should also provide evidence of outcome measure validity.

Applying the above criteria, six articles were deemed to be strongly insufficient to inform absolute or relative risk due to

- a longer than 30-day risk window or a risk window that was not clearly specified;[19-22]
- no capture or adjustment for the indication of antibiotic use;[17-21]
- no adjustment for comorbidities or most co-medications that could cause drug-induced arrhythmia or torsades de pointes (see section 1.1)
  - Carrao et al. (2005) accounted for gender, age, calendar time, use of other antibiotics and cumulative number of antibiotic prescriptions[20]
  - Carrao et al. (2006) only accounted for gender, age, and calendar time[21]
- the outcome measure was inadequate to capture clinically significant arrhythmia events or was likely to suffer from misclassification bias;
  - Clark et al. used a physician survey to capture outcomes, but the response rate was low (between 38-55%) and the validity of the physician-reported outcome was not reported. Physician-reported outcomes would likely under-ascertain cardiac adverse events that were not brought to medical attention.[22] For example, it would miss patients who died before they reached a clinic or hospital.
  - Carrao et al. (2005) used the prescription of anti-arrhythmia drugs as a surrogate for arrhythmia[20] which would miss the more severe events where patients died before drug treatment was initiated.

We briefly describe the two studies that are of better quality to inform the absolute and/or relative cardiac risk associated with fluoroquinolones in Section 3.1 and 3.2. Further detail about the design, data sources, methods, and main findings are in Appendix Tables 1 and 2. More details of the Chou et al. study are provided because Chou et al. included more detail about their study methods than did Rao et al.

3.1 Rao 2014[16]

Rao et al.[16] conducted a retrospective cohort study to test the hypothesis that taking azithromycin or levofloxacin would increase the risk of mortality and cardiac arrhythmia compared with persons taking amoxicillin. The study was based on the information at 140 Veteran Affairs (VA) Medical Centers and 600 community-based outpatient clinics between September 1, 1999 and April 30, 2012. National VA electronic health record data were searched to obtain patient-level information on demographics, administrative claims, vital signs, mortality, laboratory results, and pharmacy dispensation. The study included patients (30-74 years-old) who received only one of three targeted oral antibiotics—azithromycin, levofloxacin, or amoxicillin (including amoxicillin-clavulanate) within 30 days after a VA outpatient visit. Each patient could have had more than one clinical treatment cycle as long as the cycles were at least 30 days apart. The study excluded patients who had diagnosis of life-threatening noncardiovascular illness or drug abuse during the previous year, those who resided in nursing home

during the previous year, those who had hospitalization in the preceding 30 days, those who had another antibiotic prescription in the previous 29 days, those who had no enrollment in VA care in the preceding year, and those who had more outpatient visit counts per year than 95% of all included patients. Primary and secondary endpoints were all-cause mortality and serious cardiac arrhythmia. The authors did not provide an operational definition for mortality; they stated that the information was available from the VA data. Serious cardiac arrhythmia was defined as any inpatient or emergency department encounter/utilization for cardiac arrhythmia according to International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Follow-up times were separated into the first five days and days six through ten after antibiotics were dispensed, with day one being the first day the drug was dispensed. The authors did not specifically mention any censoring criteria for follow-up time. To control for confounding, inverse probability treatment weights (IPTW) were commuted based on several covariates including demographics, indication for antibiotics, comorbidities, laboratory findings and concurrent medications(see Appendix Table 1 for all the covariates included in the analyses). Kaplan Meier-survival curves were generated for both outcomes, with and without IPTW. Hazard ratios (HRs) for comparison were derived using an IPTW-weighted Cox proportional hazards model, with adjustment for multiple comparisons (Bonferroni adjustment).

For the purpose of the review, we only summarized the findings related to levofloxacin use, although the study also examined azithromycin.[b] In this cohort of US veterans (mean age 57 years) who received an outpatient dispensation of either amoxicillin (n = 979,380) or levofloxacin (n = 201,798) the numbers of deaths and serious arrhythmia events per 100,000 antibiotics dispensed at the end of day five were 15 and nine for amoxicillin and 38 and 28 for levofloxacin, respectively (Appendix Table 3, Table 3-1). A short-course (5-day) of levofloxacin had statistically significant adjusted HRs of 2.49 (95% confidence interval [CI] =1.70-3.64) for mortality risk and 3.13 (95% CI=2.03-4.84) for serious arrhythmia risk (Table 3-1); the increased risk with levofloxacin continued to be statistically significant during days 6 to 10.

3.2 Chou 2015[15]

Chou et al.[15] used the Taiwan National Health Insurance Database to perform a nationwide, population-based retrospective cohort study comparing the risks of ventricular arrhythmia and cardiovascular death among users of macrolides (azithromycin, clarithromycin) and fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) with users of amoxicillin-clavulanate. Taiwan National Health Insurance is a government-operated, mandatory-enrollment, single-payer system. The database includes complete outpatient visits, hospital admissions, prescriptions, diagnoses, and healthcare procedures for all beneficiaries. The author linked the insurance database with the National Death Registry to ascertain the survival status and cause of death of each patient.

The authors identified new users of oral fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), macrolides (azithromycin, clarithromycin), or amoxicillin-clavulanate from 1 January 2001 through 30 November 2011. The date of first prescription of study antibiotics was defined as the index date. To ensure patients were new users, those who had received any oral or injectable form of amoxicillin-clavulanate, fluoroquinolones, or macrolides (including erythromycin, azithromycin, and clarithromycin) within 6 months before the index date or those who had been prescribed antibiotics refills for chronic

[b] For further information about FDA's work on azithromycin and cardiac arrhythmias, please see the Drug Safety Communication issued on March 2013 (http://www.fda.gov/Drugs/DrugSafety/ucm341822.htm)

illness were excluded. The primary outcome of this study was severe ventricular arrhythmia, defined by the inpatient or outpatient (including emergency department visit) diagnosis of ventricular arrhythmia, sudden death, sudden cardiac arrest, or cardiopulmonary resuscitation (identified by ICD-9-CM codes and specific payment code 47029C for cardiopulmonary resuscitation in Taiwan). The diagnosis also needed to be accompanied by a new prescription for amiodarone, lidocaine, magnesium sulfate, or sotalol. The secondary outcomes were cardiovascular death and the composite outcome of ventricular arrhythmia or cardiovascular death. To ascertain cause of death, cardiovascular-related deaths were identified from the death registry using ICD-9-CM codes and ICD-10-CM codes. The above adverse cardiac outcomes were evaluated within seven days after the initiation of antibiotic therapy. All individuals were followed until (1) the earliest episode of ventricular arrhythmia or cardiovascular death, (2) the time point at which the patient switched to another study antibiotic, or (3) the end of the study period. Each patient was only included in the study once. Propensity scores for each of the studied drugs were calculated using multinomial logistic regression by considering covariates, including indications of antibiotic use, comorbidities, concomitant medication, and health resource utilization. Inpatient and outpatient diagnosis files and prescription files during the one-year period before the index date were used to ascertain each patient's history of comorbidities, use of concomitant medications and health resource utilization (see Appendix Table 1 for all covariates included in the analyses). The indications for antibiotic use were classified as respiratory tract infection, urinary tract infection, and other infections based on the diagnosis of the index prescription. The estimated propensity scores were then included in the multivariable logistic regression analysis to estimate the crude and adjusted odds ratios (ORs), as well as the 95% confidence interval (CI) for the association between antibiotics and the risk of ventricular arrhythmia or cardiovascular death. Stratified analysis was performed to evaluate potential effect modification by (1) the underlying cardiovascular disease, (2) sex, (3) age (>65 or <65 years), and (4) whether patients were treated for a respiratory tract infection or another indication.

For the purpose of the review, we only summarized the findings related to fluoroquinolone use, although the study also examined two macrolides (azithromycin and clarithromycin).[c] A total of 1,102,358 users of amoxicillin-clavulanate, 205,205 users of ciprofloxacin, 117,352 users of levofloxacin, and 38,833 users of moxifloxacin were included in the final analysis (Appendix Table 3). The absolute risk of ventricular arrhythmia per 100,000 individuals was 12 for amoxicillin-clavulanate, 15 for ciprofloxacin, 26 for levofloxacin, and 57 for moxifloxacin; the absolute risk of cardiovascular death per 100,000 individuals was 13 for amoxicillin-clavulanate, 12 for ciprofloxacin, 39 for levofloxacin, and 46 for moxifloxacin (Table 3-1). For patients with underlying cardiovascular (CV) disease, the absolute risk of adverse cardiac outcomes appeared to be higher than those without underlying CV disease (Table 3-2).

Compared to amoxicillin-clavulanate, levofloxacin and moxifloxacin were each associated with a higher risk of adverse cardiac outcomes than ciprofloxacin (Table 3-1). The adjusted ORs for ventricular arrhythmia were 3.30 (95% CI, 2.07–5.25) for moxifloxacin, and 1.41 (95% CI, .91–2.18) for levofloxacin. For cardiovascular death, the adjusted ORs for moxifloxacin and levofloxacin were 2.31 (95% CI, 1.39–3.84), and 1.77 (95% CI, 1.22–2.59), respectively. No association was noted between ciprofloxacin and adverse cardiac outcomes. The trend of within class difference was observed in most of

[c] For further information about FDA's work on azithromycin and cardiac arrhythmias, please see the Drug Safety Communication issued on March 2013 (http://www.fda.gov/Drugs/DrugSafety/ucm341822.htm)

the subgroups that were examined in the study (Table 3-2), although the confidence intervals of the risk estimates were wide and many risk estimates were not statistically significant.

Table 3-1 Summary of the main findings on the relative risk of adverse cardiac events associated with fluoroquinolone use in Rao et al.[16] and Chou et al.[15] studies

Study	Outcomes	Groups	Incidence rate†	Crude OR/HR	Adj. OR/HR
Rao 2014[16]	5-day all-cause mortality	Amoxicillin	15	1.00	1.00
		Levofloxacin	38	2.92*(2.00-4.26)	2.49*(1.70-3.64)
	5-day serious arrhythmia events	Amoxicillin	9	1.00	1.00
		Levofloxacin	28	2.43*(1.56-3.79)	3.13*(2.03-4.84)
Chou 2015[15]	7-day serious arrhythmia	Amoxicillin-clavulanate	12	1.00	1.00
		Fluoroquinolones	23	1.97*(1.49-2.60)	2.07*(1.56-2.76)
		Moxifloxacin	57	4.92*(3.13-7.74)	3.30*(2.07-5.25)
		Ciprofloxacin	15	1.27(0.85-1.89)	1.07(0.69-1.66)
		Levofloxacin	26	2.22*(1.49-3.30)	1.41(0.91-2.18)
	7-day cardiovascular death	Amoxicillin-clavulanate	13	1.00	1.00
		Fluoroquinolones	24	1.89*(1.45-2.49)	1.97*(1.49-2.59)
		Moxifloxacin	46	3.60*(2.20-5.88)	2.31*(1.39-3.84)
		Ciprofloxacin	12	0.91(0.59-1.40)	0.70(0.44-1.12)
		Levofloxacin	39	3.04*(2.18-4.25)	1.77*(1.22-2.59)

OR: odds ratio; HR: hazard ratio

*$p<0.05$

†Unit of Incidence rate was **per 100,000 prescriptions** in Rao et al.[16] study, and **per 100,000 patients** in Chou et al.[15] study.

Table 3-2 Main findings of the stratified analyses of Chou et al.[15] study

Outcomes	Group	Adjusted risk estimates		Incidence rate per 100,000 patients	
		With underlying CV diseases	**No underlying CV diseases**	**With underlying CV diseases**	**No underlying CV diseases**
Serious arrhythmia	Amoxicillin-clavulanate	1.00	1.00	42	5
	Moxifloxacin	1.40 (0.72-2.72)	6.93* (3.57-13.47)	85	44
	Ciprofloxacin	1.04 (0.62-1.75)	1.03 (0.49-2.29)	46	5
	Levofloxacin	0.91 (0.52-1.58)	2.55* (1.30-5.02)	51	16
CV death	Amoxicillin-clavulanate	1.00	1.00	50	5
	Moxifloxacin	1.42 (0.77-2.59)	3.10* (1.25-7.70)	102	22
	Ciprofloxacin	0.67 (0.03-1.13)	0.71 (0.27-1.87)	40	3
	Levofloxacin	1.32 (0.86-2.03)	2.89* (1.47-5.67)	95	17
		Male	**Female**	**Male**	**Female**
Serious arrhythmia	Amoxicillin-clavulanate	1.00	1.00	NA	NA
	Moxifloxacin	2.53* (1.43-4.47)	4.14* (1.84-9.32)		
	Ciprofloxacin	0.78 (0.42-1.43)	1.63 (0.85-3.13)		
	Levofloxacin	1.21 (0.70-2.09)	1.70 (0.83-3.49)		
CV death	Amoxicillin-clavulanate	1.00	1.00	NA	NA
	Moxifloxacin	1.83 (0.92-3.64)	2.81* (1.34-5.91)		
	Ciprofloxacin	0.66 (0.34-1.29)	0.71 (0.37-1.38)		
	Levofloxacin	1.89* (1.15-3.10)	1.48 (0.83-2.63)		
		Age < 65	**Age >65**	**Age < 65**	**Age >65**
Serious arrhythmia	Amoxicillin-clavulanate	1.00	1.00	NA	NA
	Moxifloxacin	6.19* (2.68-14.30)	1.57 (0.90-2.74)		
	Ciprofloxacin	1.59 (0.75-3.38)	0.88 (0.52-1.48)		

	Levofloxacin	1.97 (0.83-4.69)	1.04 (0.64-1.67)		
CV death	Amoxicillin-clavulanate Moxifloxacin Ciprofloxacin Levofloxacin	1.00 3.04 (0.65-14.22) 0.22 (0.03-1.75) 2.41 (0.83-6.97)	1.00 1.27 (0.75-2.15) 0.73 (0.46-1.18) 1.34 (0.92-1.95)	NA	NA
		Respiratory tract infection	**Other infections**	**Respiratory tract infection**	**Other infections**
Serious arrhythmia	Amoxicillin-clavulanate Moxifloxacin Ciprofloxacin Levofloxacin	1.00 1.47 (0.67-3.26) 0.87 (0.32-2.39) 2.84* (1.59-5.08)	1.00 1.52 (0.74-3.09) 0.50 (0.16-1.59) 2.03* (1.14-3.63)	NA	NA
CV death	Amoxicillin-clavulanate Moxifloxacin Ciprofloxacin Levofloxacin	1.00 5.71* (3.22-10.15) 1.05 (0.66-1.66) 0.80 (0.44-1.43)	1.00 3.32* (1.61-6.84) 0.75 (0.45-1.23) 1.54 (0.99-2.41)	NA	NA

CV: cardiovascular; NA: not available

*$p<0.05$

4 DISCUSSION

The two observational studies that are of better quality both used population-level data reflecting the real-world antibiotic user population. They also both attempted to control for confounding by using another antibiotic as an active comparator and by employing advanced analytical approaches, such as IPTW or propensity score adjustment. The absolute risk of serious arrhythmic events associated with fluoroquinolone use reported in the two studies were low (Figure 4-1), ranging between 15-57 per 100,000 users of fluoroquinolones, compared to 9-12 per 100,000 users of amoxicillin or amoxicillin-clavulanate. Fluoroquinolone users with underlying cardiovascular disease appear to have a higher baseline risk for serious cardiac adverse events than those without (the absolute risk of serious arrhythmia ranges from 46-85 per 100,000 users with cardiovascular diseases versus 5-44 per 100,000 users without cardiovascular diseases, Figure 4-2). Both studies found an increased risk of serious cardiac arrhythmia associated with fluoroquinolone use, and one reported a difference in the risk between individual fluoroquinolones, however, these two observational studies were not able to provide conclusive evidence because of methodologic limitations as described in sections 4.1 and 4.2.

Figure 4-1 Comparison of serious arrhythmia incidence between Rao et al.[16] (unit: events per 100,000 prescriptions) and Chou et al.[15] (unit: events per 100,000 patients) studies (Reference group: amoxicillin or amoxicillin-clavulanate)

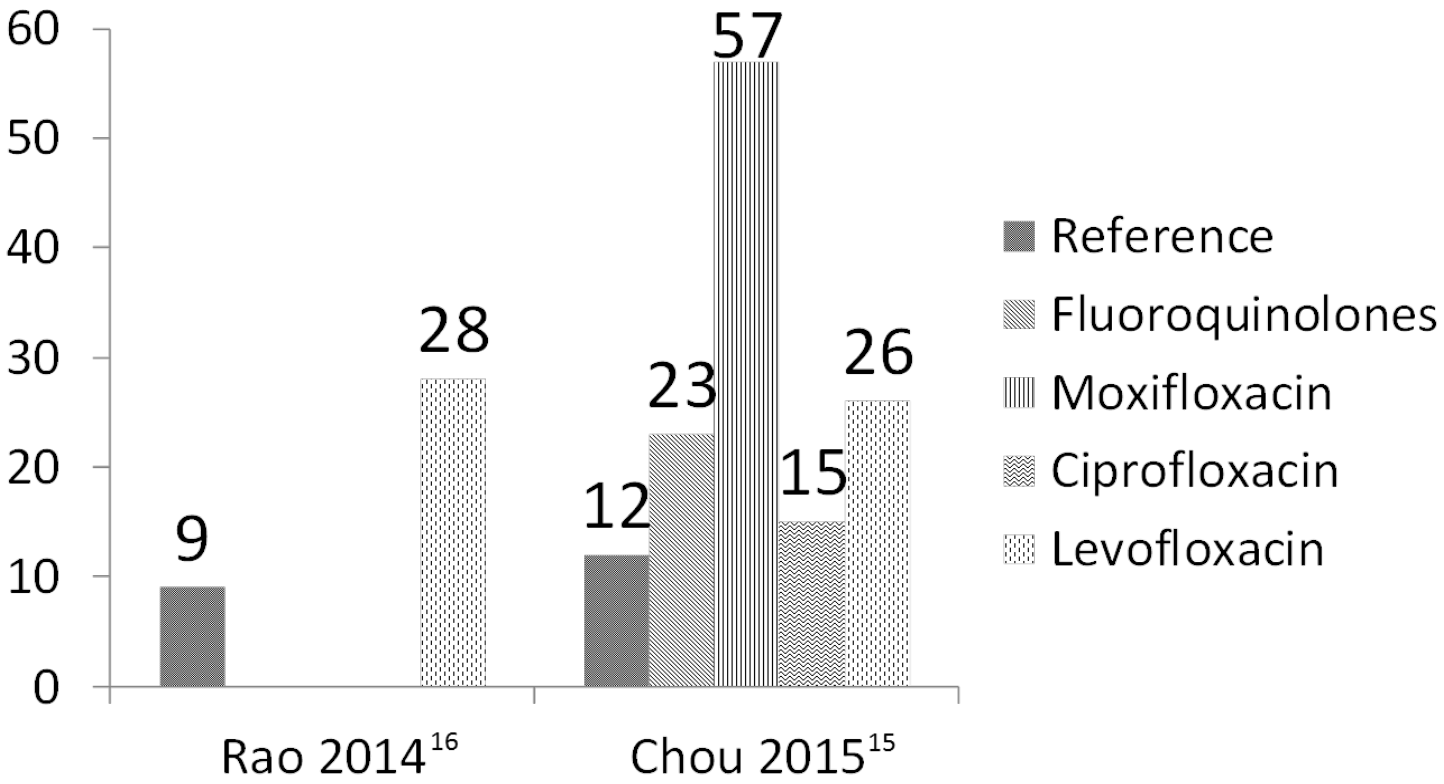
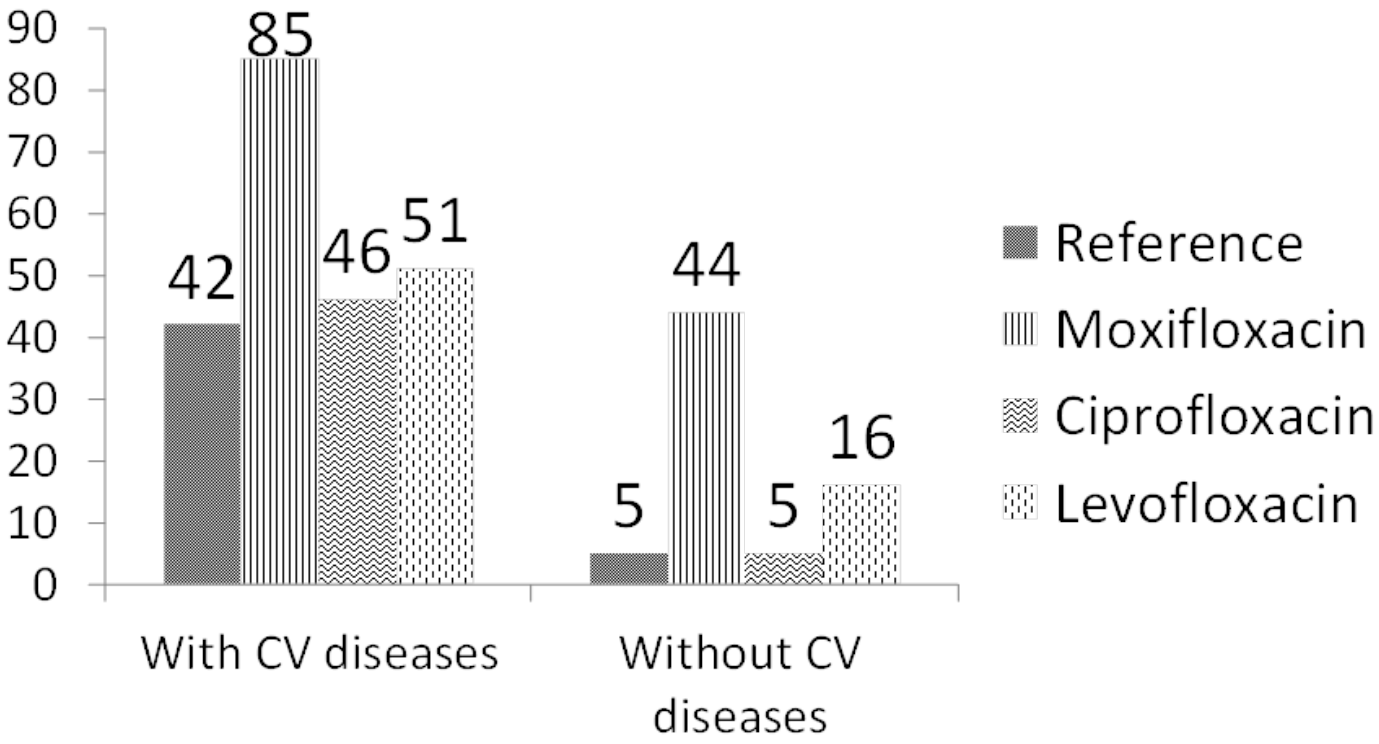


Figure 4-2 Comparison of serious arrhythmia incidence between patients with and without underlying cardiovascular (CV) diseases in Chou et al.[15] (unit: events per 100,000 patients) studies (Reference group: amoxicillin-clavulanate)



4.1 Concern with the measurement of indication for antibiotic use

In most administrative claims data, diagnosis is not linked to dispensing information. Investigators usually need to develop an algorithm to search for diagnostic information from medical encounter claims on or close to the time that a patient received a prescription. In other words, the indication of drug use from most claims data is a surrogate, instead of direct information. One would need to know the algorithm for identifying indication of use to evaluate the quality of such information.

Rao et al.[16] considered infections identified from up to 1 year before the date of antibiotic dispensation as indication for antibiotic use. Because of the long look-back period, the captured diagnoses may have been related to an earlier condition rather than the indication for fluoroquinolone use. In addition, a significant proportion (close to half) of antibiotic users did not have a diagnosis of an infectious disease documented in claims data, even with the one-year look-back period. The potential measurement error of the indication led to the concern that the relative risk estimates of outcomes could still reflect the differences of serious cardiac arrhythmia risk that could be attributable to the difference in indication of use between the study antibiotics.

Chou et al.[15] stated that they identified the indication of antibiotic use based on "*the diagnosis of the index prescription*", but did not address how they ascertained the diagnosis of index prescription from their data source. Therefore, the reviewer is not able to comment on how well the study actually captured the indication. (The reviewer contacted the authors for clarification, but has not heard back from them) Furthermore, the categories of indication used in the Chou et al. study (i.e. respiratory tract infection, urinary tract infection, or other infection) did not provide sufficient clinical granularity to assess whether and how the three studied fluoroquinolones were used differently. For example, close to 50% of the ciprofloxacin users and levofloxacin users were in the "other infection" category, which consists of three different infections: otitis media, septicemia and colitis (Appendix Table 2). The category of "respiratory tract infection" also should be refined to distinguish pneumonia and exacerbation of COPD from other respiratory tract infections, because the former are the indications that could increase arrhythmia risk irrespective of fluoroquinolone use.

4.2 Concern with the measurement of outcome events

In Rao et al.,[16] the primary outcome, mortality, was not specific enough to inform risk of fluoroquinolone-associated cardiac adverse events. The secondary outcome, inpatient or emergency department encounter for serious arrhythmia, is more specific, however, it would miss events if patients died from serious arrhythmia before reaching the hospital, which leads to an underestimate of the absolute risk of serious arrhythmic events. This misclassification of outcome would bias the relative risk estimate toward the null, if the same proportion of the events were missed in the fluoroquinolones and the comparator groups, or make the drug(s) that cause more cardiac arrest/arrhythmia deaths look safer than the others.

The primary outcome of the Chou et al. study[15] included arrhythmic events that were diagnosed during the inpatient/emergency department encounters or in the outpatient setting. The validity of an outpatient-diagnosed arrhythmia event has not been investigated. The study could over-estimate the absolute risk of severe arrhythmia by including outpatient-diagnosed events, because those events might not reach the same severity as those diagnosed in hospital or emergency department. The secondary outcome used by Chou et al.[15] (i.e. cardiovascular deaths, identified by ICD-9-CM codes 401– 449 and ICD-10-CM codes I10–I79) could also over-estimate the absolute risk in those using fluoroquinolones because it included deaths due to non-cardiac causes, such as pulmonary embolism (ICD-9-CM 415.1 or ICD-10 I26), that are not likely due to fluoroquinolone's proarrhythmic effect.

5 CONCLUSION

Epidemiologic data to quantify the risk of fluoroquinolone-associated serious cardiac arrhythmia are limited. In our literature review, the two studies that were deemed to be of better quality still did not adequately control for confounding by indication. Although both studies found an increased risk of serious cardiac arrhythmia associated with fluoroquinolone use, and one reported a difference in the risk between individual fluoroquinolones, definitive conclusions cannot be made due to inadequate control for indication for antibiotic use and the potential measurement errors in capturing outcome event (by either not including deaths attributable to QT prolongation [i.e. death due to serious arrhythmia], or, including events that were not likely due to QT prolongation [i.e non-cardiac deaths]). Despite the methodological issues noted for the outcome measures from each study, the absolute risk of serious arrhythmic events associated with fluoroquinolone use is likely to be low, ranging between 15-57 per 100,000 users of

fluoroquinolones, compared to 9-12 per 100,000 users of amoxicillin or amoxicillin-clavulanate. Fluoroquinolone users with underlying cardiovascular disease appear to have a higher baseline risk for serious cardiac adverse events than those without (the absolute risk of serious arrhythmia ranges from 46-85 per 100,000 users with cardiovascular diseases versus 5-44 per 100,000 users without cardiovascular diseases).

6 RECOMMENDATIONS

The available evidence is not sufficient to support any regulatory action. However, future research is warranted to explore the potential difference of serious cardiac arrhythmia risk between individual fluoroquinolones and the effect modification by presence of underlying cardiovascular disease. To advance from existing evidence, such a study will need to capture the indication of antibiotic use more comprehensively and with better clinical granularity, and to include deaths that are the direct consequence of QT prolongation (i.e. cardiac or sudden cardiac deaths) in the outcome definition.

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8 APPENDIX

Table 1 Summary of methods of the Rao et al.[16] and Chou et al.[15] studies

	Rao 2014[16]	**Chou 2015[15]**
Data source	VA health care system	Taiwan National Health Insurance Data linked to the National Death Registry
Time frame	Sep. 1 1999 to Apr. 30 2012	Jan. 1 2001 to Nov. 30 2011
Target population	Users of oral antibiotics (excluded those who received another antibiotic in the previous 29 days)	New users of oral antibiotics (6-months look-back)
Age	30-74 years	20-100 years
Index date	The date of first dispensed record of study antibiotics	The date of first dispensed record of study antibiotics
Exclusions	Users who • were treated with multiple study antibiotics • hospitalized in the preceding 30 days • residing in a nursing home during the previous year • had life-threatening non-CV illness, diagnosis of drug abuse, more outpatient visit counts per year than 95% of all included patients • Not having 1 year look-back period	Users who • were treated with multiple study antibiotics • hospitalized in the preceding 30 days • were prescribed antibiotic refills for chronic illnesses within 1 year preceding the index date • diagnosis of ventricular arrhythmia, sudden cardiac arrest, any malignancy, human immunodeficiency virus infection, or treatment with any antiarrhythmic agents within 1 year preceding the index date
Target fluoroquinolone	Levofloxacin	Moxifloxacin, ciprofloxacin, levofloxacin
Reference	Amoxicillin or amoxicillin-clavulanate	amoxicillin-clavulanate

Risk-window	5 days after exposure	7 days after exposure
Outcomes	1) <u>All-cause mortality</u> 2) <u>Serious ventricular arrhythmia:</u> inpatient or ED encounter for long QT syndrome (ICD-9: 426.82), ventricular tachycardia (427.0, 427.1, 427.2), ventricular fibrillation (427.41), ventricular flutter (427.42), or cardiac arrest (427.5)	1) <u>Severe ventricular arrhythmia:</u> In-/outpatient, or ED visit for ventricular arrhythmia (427.1, 427.4), cardiac arrest (427.5, V12.53), sudden death (798.1, 798.2, 798.9), or cardiopulmonary resuscitation (specific payment code 47029C) AND any prescription for antiarrhythmic agents, including amiodarone, lidocaine, magnesium sulfate, or sotalol 2) <u>Cardiovascular deaths</u> 3) <u>1) or 2)</u>
Indication for use	Diagnosis of infection within 1 year prior to index date	Classified as **respiratory tract infection, urinary tract infection** and **other infections (otitis media, septicemia, and colitis)** based on diagnosis of the index prescription; however, no information was provided with regard to how diagnosis of the index prescription was determined
Confounding adjustment	Inverse probability weighting accounting for indication of antibiotic use, comorbidities, concomitant medications, health resource utilization (it's unclear how the covariates were identified from the data sources)	Propensity score adjustment accounting for indication of antibiotic use, comorbidities, concomitant medications, healthcare resource utilization (identified from both in- and out-patient claims)
Covariates included in the analyses	**Antibiotic indication** Infection due to chronic obstructive pulmonary disease (COPD) and bronchiectasis Pneumonia Other respiratory infection Ear-nose-throat infection	**Antibiotic indication** Respiratory tract infections Urinary tract infections Other infections (Otitis media, septicemia and colitis) **Demographic characteristics** Age

	Gastrointestinal infection Genitourinary infection Wound infection Other serious infection **Demographic characteristics** Age Gender Race/ethnicity **Body mass index** **Smoking status** **Comorbidities** COPD and bronchiectasis Diabetes with/without complications Essential hypertension/Hypertension with complications and secondary hypertension Congestive heart failure Acute myocardial infarction	Gender **Comorbidities in prior year** Cardiovascular disease Peripheral vascular disease Cerebrovascular disease Chronic kidney disease Chronic liver disease Chronic lung disease Diabetes Congestive heart failure Depression Dementia Rheumatologic disease Ulcer disease **Medication use in prior year** Oral hypoglycemic agents Insulin

	Cardiac arrhythmia	Digoxin
	Occlusion or stenosis of precerebral arteries	Angiotensin-converting enzyme inhibitor
	Acute cerebrovascular disease	Angiotensin receptor blocker
	Peripheral and visceral atherosclerosis	β-adrenergic antagonists
	Transient cerebral ischemia	Thiazide diuretics
	Late effects of cerebrovascular disease	Sulfonamides
	Other and ill-defined cerebrovascular disease	Statin
	Chronic renal failure	Fibrate
	Hepatitis	Glucocorticoids
	Personality disorders	Nonsteroidal anti-inflammatory drugs
	Mood disorders	Aspirin
	Medication use	β-agonist
	Insulin	Cisapride
	Oral hypoglycemic	Antihistamines
	Antipsychotics	Antipsychotics
	β-Agonists	Antidepressant
	β –Blockers	Diphenylpropylamine derivatives

	Calcium channel blockers	Other non-study antibiotics
	Digoxin	**Health care utilizations in prior year**
	Diuretic (Loop or non-loop)	No. of outpatient visits to cardiologist
	Angiotensin-converting enzyme inhibitor	No. of outpatient visits to general internist
	Angiotensin receptor blocker	No. of outpatient visits to infectious physicians
	Antiarrhythmic	No. of outpatient visits to chest medicine physicians
	Anticoagulant	Total cost for outpatient visits (thousands)
	Antiplatelet	No. of hospitalizations
	Anti-anginal	Duration of hospital stay
	Anti-lipid	Total cost for hospitalization (thousands)
	Systematic corticosteroids	
	Laboratory values	
	Albumin	
	Alanine transaminase	
	Aspartate transaminase	
	Serum creatinine	
	Hemoglobin A1C	

	High-density lipoprotein Hemoglobin International normalized ratio Low-density lipoprotein Platelet count Potassium	

Table 2 Summary of demographic and clinical characteristics of the Rao et al.[8] and Chou et al [7] studies (Figures are percentages unless otherwise specified)

	Rao 2014[16]		**Chou 2015[15]**			
	Amoxicillin (N=979,380)	Levofloxacin (N=201,798)	Amoxicillin-clavulanate (N=1,102,358)	Ciprofloxacin (N=205,205)	Levofloxacin (N=117,352)	Moxifloxacin (N=38,833)
Demographic						
Mean Age (Standard deviation)	57 (10)	59 (10)	44 (17)	47 (18)	51 (19)	52 (20)
Male	89	91	47	42	44	53%
Race	71% White		74% White		100% Asian	
Indication of antibiotic use						
Respiratory tract infection	-	-	63	24	27	72
Chronic obstructive pulmonary disease (COPD) and bronchiectasis	8	16	-	-	-	-
Pneumonia	0.1	3	-	-	-	-
Other respiratory infection	12	6	-	-	-	-
Ear-nose-throat infection	24	16	-	-	-	-
Gastrointestinal infection	0.0	0.2	-	-	-	-
Genitourinary infection	5.3	28	1.8	27	26	1.3
Wound infection	2.3	3.5	-	-	-	-
Other serious infection	0.2	0.1	-	-	-	-

Other infections (Otitis media, septicemia and colitis)	-	-	36	50	47	27
Selected comorbidities						
Cardiovascular disease	-	-	18	23	29	30
Hypertension	5.1	5.6	-	-	-	-
Cardiac arrhythmia	0.5	0.6	-	-	-	-
Heart failure	0.4	0.6	1.1	1.5	2.4	3.1
Chronic kidney disease	0.2 (CRF)	0.3 (CRF)	13	28	33	16
Diabetes	4.5	4.8	8	11	13	12
Cerebral vascular disease	~0.6	~0.8	3	5	7	7
Chronic lung disease	1.1 (COPD)	2.6 (COPD)	9	8	13	20
Ulcer	-	-	8	10	12	11
Selected medication use						
Oral hypoglycemic	3.2	3.5	6	8	10	10
Insulin	1.5	1.5	1.2	2	3	2
Digoxin	0.3	0.5	0.6	0.8	1.4	1.8
ACE	4	4	4	6	8	8
ARB	0.5	0.3	6	8	10	11
Beta-blockers	3	4	12	15	17	17
Beta-agonist	2	3	44	38	41	53
Antipsychotics	2	1	9	11	12	10
Statin	5	5	5	6	7	7
Fibrate			2	2	3	3
Diuretics	3.1	3.6	-	-	-	-
Thiazides	-	-	5	7	9	10
Sulfonamides	-	-	3	5	7	7
NSAID	-	-	78	77	76	75

Aspirin	-	-	10	12	17	17
Antihistamine	-	-	68	65	64	68
Antidepressant	-	-	6	7	9	7
Other non-study antibiotics	-	-	70	70	71	60
Glucocorticoids	-	-	25	24	26	27

CRF: Chronic renal failure; ACE: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blockers; NSAID: nonsteroidal anti-inflammatory drug

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Observational Study of Cardiovascular Events with Azithromycin and Levofloxacin

Date:	August 18, 2015
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Subject	Two observational studies of azithromycin and cardiac arrhythmia
Drug Name(s):	Azithromycin (Zithromax and generics)
Application Type/Number:	NDA 50-711 et al.
Applicant/sponsor:	Pfizer (innovator)
OSE RCM #:	2012-1106
TSI #:	**1321**

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EXECUTIVE SUMMARY

The purpose of this review is to evaluate two published observational studies of arrhythmia and mortality with use of azithromycin. The Rao study was a retrospective observational study in the Veteran's Administration (VA) database examining death from any cause and cardiac arrhythmias with use of azithromycin, levofloxacin, and amoxicillin, in a sample of mostly older, mostly male patients. The study found an excess risk for both death and arrhythmia with levofloxacin and azithromycin versus amoxicillin, during the time of antibacterial use; adjusting for the indication of pneumonia did not materially alter the results. The Chou study examined arrhythmias and cardiovascular deaths in the nation of Taiwan associated with outpatient use of azithromycin, levofloxacin, ciprofloxacin, clarithromycin, and moxifloxacin (with amoxicillin-clavulanate as the comparator), finding associations with azithromycin, moxifloxacin, and levofloxacin.

The findings reinforce the existing concerns regarding pro-arrhythmic effects of these antibiotics, presumably mediated by QT prolongation. The estimated numbers needed to harm indicate a level of risk that is meaningful from both a public health and clinical standpoint (compared to use of amoxicillin, in the Rao study, one excess death per 10,204 azithromycin uses and per 2,564 levofloxacin uses, and in the Chou study, one excess cardiovascular death per 1724 azithromycin uses, 1389 moxifloxacin uses, and 2631 levofloxacin uses.). For comparison, the risk of tendon rupture from fluoroquinolones (the subject of a boxed warning) has been estimated at 1 in 6,000. As there appears to be growing evidence of the arrhythmogenic effects of these antibiotics, some recommendations are offered.

- The impact of arrhythmogenic effects on the risk-benefit balance for nonserious infections needs to be considered. This of course must be weighed against the benefits of antibiotics in the treatment of severe infections (e.g., some data indicate macrolides provide a survival benefit in outpatients with CAP).
- Pfizer should continue its efforts to conduct an observational study (or studies) of cardiovascular risks with azithromycin, as their study should be able to address limitations of both of the studies reviewed here.
    - Specifically, neither the Rao study nor the Chou study featured adjudication of endpoints, which will be a part of the Pfizer study.
    - The Rao study analyzed only all-cause mortality, though cardiac-related mortality is more relevant and specific to the concerns regarding arrhythmogenic effects. The Pfizer study will analyze cardiovascular mortality.
    - The Pfizer study will have better information on indication for the antibiotics, a major potential confounder that both the Rao study and the Chou study attempted to control for, but their strategies may not have been fully successful.
- The QT Interdisciplinary Review Team should evaluate the available QT data for levofloxacin and ciprofloxacin. Regarding ciprofloxacin, it has been proposed that ciprofloxacin conveys a lower risk of QT prolongation than other fluoroquinolones, and existing observational data have not shown an association with such cardiovascular events for ciprofloxacin. (The QT-prolonging effects of moxifloxacin are well-described in its label.)
- Enhancements to the existing labeling regarding arrhythmogenic effects for both macrolides and fluoroquinolones would be appropriate. For fluoroquinolones, it would be appropriate to add the current warning regarding QT prolongation to the existing boxed

Reference ID: 3807786

warning. For azithromycin and other macrolides it would similarly be appropriate to box the existing labeling regarding QT prolongation. (This reviewer previously recommended this for azithromycin, based on the findings from the Vanderbilt study (Ray et al. NEJM 2012), which provides a higher quality of evidence than the present two studies.)

- A more comprehensive literature review focused on pro-arrhythmic effects of fluoroquinolones is beyond the scope of the present review, but should be undertaken.

1 INTRODUCTION

Cardiovascular deaths and arrhythmias with azithromycin are the subject of Tracked Safety Issue# 1321 and were also the topic of a Drug Safety Communication in 2013. The purpose of this review is to evaluate two new observational studies of arrhythmia and mortality with use of azithromycin.

1.1 BACKGROUND

Azithromycin is an oral or intravenously administered macrolide compound, widely used for outpatient treatment of a variety of gram-positive and gram-negative bacterial infections. It is less subject than other macrolides to cytochrome P450 3A drug interactions. Previous data have linked the macrolide class to QT prolongation and cardiac arrhythmias[1,2] and all drugs in the class have labeling about this effect. An observational study of Tennessee Medicaid patients treated with erythromycin found an increased risk of sudden death, apparently exacerbated by cytochrome P450 3A drug interactions.[3] More recently, another observational study in Tennessee Medicaid patients found an increase in cardiovascular death and sudden cardiac death with azithromycin, with the time course of the excess risk corresponding to the typical 5-day azithromycin treatment course; patients with cardiovascular risk factors were at greater absolute risk.[4] Tracked Safety Issue #1321 addressed this signal for azithromycin, leading to a Drug Safety Communication and updated labeling for azithromycin regarding QT prolongation.[5] In addition, FDA requested an observational study of azithromycin and cardiovascular death in a Post Marketing Requirement letter issued April 29, 2014 to the brand name sponsor, Pfizer. In 2013, a Danish observational study of a somewhat younger, healthier population failed to reproduce the association between azithromycin and cardiovascular death, consistent with the hypothesis that patients with cardiac risk factors have more risk.[6] In 2014 another observational study from the same Danish data source reported an association between clarithromycin and cardiovascular death.[7]

More recently, an observational study of mortality in hospitalized elderly pneumonia patients showed lower overall mortality with azithromycin compared to other antibiotics, but an increased risk of certain cardiovascular events (though not specifically arrhythmias).[8] In this propensity score matched cohort study of veterans 65 years old and older hospitalized for pneumonia, 90-day mortality with azithromycin was lower compared to other antibiotics (odds ratio 0.73; 95%CI, 0.70-0.76) but the risk of myocardial infarction was increased (odds ratio 1.17; 95%CI, 1.08-1.25). However, heart failure and cardiac arrhythmias were not more frequent with azithromycin. The authors speculated that azithromycin may provide a survival benefit because of its immune modulating properties.

With respect to levofloxacin, a published study has shown that, like azithromycin, it increases the QTc interval in a plasma concentration-dependent manner.[9]

The ICH E14 guideline on clinical evaluation of drug effects on the QT interval states the following regarding the risk of torsades de pointes (TdP) with drug-induced QT prolongation.[10]

Reference ID: 3807786

Drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause TdP. Whether this signifies that no increased risk exists for these compounds or simply that the increased risk has been too small to detect is not clear. The data on drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic, and might have clinical arrhythmic events captured during drug development.

1.2 REGULATORY HISTORY

FDA approved azithromycin in 1991. It is currently available in tablet, oral suspension and IV formulations. There are many generic azithromycin products.

1.3 PRODUCT LABELING

The current azithromycin labeling regarding arrhythmogenic effects is shown below.

Warnings: QT Prolongation Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, aminodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Clinical Pharmacology: Pharmacodynamics/Cardiac Electrophysiology QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose-and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

The current levofloxacin labeling regarding QT prolongation is reproduced below.

5.9 Prolongation of the QT Interval

Some fluoroquinolones, including LEVAQUIN®, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during postmarketing surveillance in patients receiving fluoroquinolones, including LEVAQUIN®. LEVAQUIN® should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

The current moxifloxacin labeling regarding QT prolongation is reproduced below.

[Highlights of Prescribing Information] Prolongation of the QT interval and isolated cases of torsade de pointes has been reported. Avoid use in patients with known prolongation, hypokalemia, and with drugs that prolong the QT interval. Use caution in patients with proarrhythmic conditions such as clinically significant bradycardia or acute myocardial ischemia. (5.3)

5.3 QT Prolongation

AVELOX has been shown to prolong the QT interval of the electrocardiogram in some patients. Following oral dosing with 400 mg of AVELOX the mean (± SD) change in QTc from the predose value at the time of maximum drug concentration was 6 msec (± 26) (n = 787). Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 10 msec (±22) on Day 1 (n=667) and 7 msec (± 24) on Day 3 (n = 667). The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (for example, quinidine, procainamide) or Class III (for example, amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.

Pharmacokinetic studies between AVELOX and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of AVELOX and these drugs cannot be excluded; therefore caution should be exercised when AVELOX is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 AVELOX and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

AVELOX should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of infusion of the intravenous formulation. Therefore the recommended dose or infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. No excess in cardiovascular morbidity or mortality attributable to QTc prolongation occurred with AVELOX treatment in over 15,500 patients in controlled clinical studies, including 759 patients who were hypokalemic at the start of treatment, and there was no increase in mortality in over 18,000 AVELOX tablet treated patients in a postmarketing observational study in which ECGs were not performed. Elderly patients using IV AVELOX may be more susceptible to drug-associated QT prolongation. [see Use In Specific Populations, (8.5).] In addition, AVELOX should be used with caution in patients with mild, moderate, or severe liver cirrhosis.[see Clinical Pharmacology (12.3) and Patient Counseling Information (17.3).]

2 REVIEW METHODS AND MATERIALS

This review covers two publications:

Rao GA, Mann JR, Shoaibi A, et al. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. Ann Fam Med 2014;12:121-7.

Chou H, Wang J, Chang C, Lai C, Lai M, Chan KA. Risks of Cardiac Arrhythmia and Mortality Among Patients Using New-Generation Macrolides, Fluoroquinolones, and β-Lactam/β-Lactamase Inhibitors: A Taiwanese Nationwide Study. Clin Infect Dis. 2014 Nov 18. pii: ciu914 (epub).

There was no access to complete study reports, (b) (4)

3 REVIEW RESULTS

3.1 RAO ET AL.

This was a retrospective observational study in the Veteran's Administration (VA) database examining death from any cause and malignant cardiac arrhythmia with use of azithromycin, levofloxacin, and amoxicillin, in a sample of mostly older, mostly male patients. The study found an excess risk for both outcomes with levofloxacin and azithromycin versus amoxicillin, during the time of antibacterial use.

- *Author, publication year and affiliation/funding*

The lead author was affiliated with the University of South Carolina and the Columbia, SC Veteran's Affairs medical center. Funding support was not specified. The study was published in 2014.

- *Objectives*

The purpose of this study was to test the hypothesis that patients taking azithromycin or levofloxacin would have a higher risk for death or cardiac arrhythmia compared to users of amoxicillin.

- *Design*

This was a retrospective cohort study.

- *Methods*

  - Population & Time Period

The sample comprised U.S. veterans treated as outpatients from September 1, 1999 to April 30, 2012.

  - Selection, Inclusion and Exclusion Criteria

Subjects were aged 30-74 years, enrolled in the VA healthcare system with evidence of utilization in the past year (either clinical, laboratory or pharmacy). Exclusionary criteria were life-threatening cardiovascular illness, drug abuse, nursing home residence, an antibiotic prescription in the previous 29 days, inpatient care in the previous 30 days, and being in the top 5th percentile with respect to outpatient encounters per year. The baseline assessment period was 1 year.

  - Outcomes

The primary outcome was death from any cause, determined from the VA Vital Status File. The secondary outcome was serious cardiac arrhythmia, defined as inpatient or emergency department care for one of the following ICD-9 codes:

Long QT syndrome	426.82
Ventricular tachycardia	427.0, 427.1, 427.2
Ventricular fibrillation	427.41
Ventricular flutter	427.32
Cardiac arrest	427.5

It was unclear whether these codes had to be primary discharge diagnosis codes. There was no mention of chart review for the outcome of serious cardiac arrhythmia.

  - Exposure

Eligible subjects received an azithromycin, an amoxicillin or amoxicillin/clavulanate combination, or a levofloxacin prescription within 30 days of an outpatient encounter. Subjects could have repeat exposures providing the prescriptions were at least 30 days apart. The risk windows were the 5 days and 10 days after the prescription (day 1 = date of prescription).

Reference ID: 3807786

- Covariates

There was a one year baseline period for collecting data on demographic and clinical characteristics, including antibacterial indication and concomitant medications and laboratory values. The investigators classified comorbidities according to the Clinical Classifications Software (CCS) for ICD-9-CM created by the Agency for Healthcare Research and Quality.[11] The following diagnoses and diagnostic codes (apparently from an outpatient visit within 30 days prior to the antibacterial prescription) were assumed to be indications for the antibiotic.

Chronic obstructive pulmonary disease and bronchiectasis	(490-496)
Pneumonia	(480-486)
Other respiratory infection	(470-478)
Ear nose throat infection	(460-466)
Gastrointestinal infection	(001-009)
Genitourinary infection	(580-629)
Wound infection	(800-999)
Other serious infection	(031-040)

- Sample Size/Power

The following lists the numbers of patients prescribed the study drugs. Individual patients may be counted with more than one exposure.

Amoxicillin	n=979,380
Azithromycin	n=594,792
Levofloxacin	n=201,798

- Statistical Analysis

The investigators calculated propensity scores for receiving one of the three study drugs, using multinomial logistic modeling with all available baseline characteristics as covariates, including indication. Kaplan-Meier plots and Cox proportional hazard analyses used inverse probability of treatment weighting (IPTW), excluding patients with IPTWs more than 2 standard deviations away from the smallest group. The authors reported that after weighting, all covariates had acceptable standardized differences (< 10%).

- Ethics

The institutional review board for the William J. B. Dorn VA Medical Center, Columbia, SC, approved this study.

- *Results*

Mean age of the subjects ranged from 56-59 years in all three cohorts, and all three cohorts were predominantly white and male. A relatively small percent of patients in each cohort had diagnoses of cardiovascular illness or used cardiovascular medications. The three groups appeared balanced with respect to most baseline comorbidities except for the indications of COPD in the azithromycin cohort and pneumonia in the levofloxacin cohort. For example, roughly 5% of patients in each cohort used anti-lipid medication, and roughly 4% used angiotensin converting enzyme inhibitors. There were no extreme differences between cohorts with respect to body mass index, smoking status, or laboratory values (including potassium).

The following table, adapted from the publication's on-line supplement, shows the presumed indications for each antibiotic. Ear, nose and throat infections were the most frequent indication for amoxicillin and azithromycin, while genitourinary infections were most frequent for levofloxacin. Nearly half of the amoxicillin prescriptions were missing presumed indications.

Reference ID: 3807786

The modal duration of use was 10 days for amoxicillin (58% of prescriptions), 5 days for azithromycin (81% of prescriptions), and 10 days for levofloxacin (42% of prescriptions).

Antibiotic indication, No. (%)	Amoxicillin (n=979,380)	Azithromycin (n=594,792)	Levofloxacin (n =201,798)
Chronic obstructive pulmonary disease and bronchiectasis	75,073 (7.7)	144,404 (24.3)	31,987 (15.9)
Pneumonia	637 (0.1)	11,044 (1.9)	(b) (4)
Other respiratory infection	119,452 (12.2)	72,522 (12.2)	12,358 (6.1)
Ear-nose-throat infection	234,815 (24.0)	254,892 (42.9)	32,698 (16.2)
Gastrointestinal infection	362 (0.0)	328 (0.1)	336 (0.2)
Genitourinary infection	51,461 (5.3)	29,147 (4.9)	56,092 (27.8)
Wound infection	22,087 (2.3)	12,483 (2.1)	7,161 (3.5)
Other serious infection	1,540 (0.2)	1,185 (0.2)	281 (0.1)
No indication	473,953 (48.4)	68,787 (11.6)	54,230 (26.9)

(b) (4)

The IPTW-calculated rates of deaths per million antibiotic prescriptions are shown below for 5 day and 10 day risk windows.

Deaths from any cause per million prescriptions (weighted estimates)

Drug	Days 1-5	Days 1-10
Amoxicillin	154	324
Azithromycin	228	422
Levofloxacin	384	714

From these data one may calculate the number needed to harm (NNH) for a death from any cause in comparison to an amoxicillin prescription, though confidence limits cannot be calculated from the data in the publication. Over days 1-10, in comparison to amoxicillin, there was one excess death per 10,200 azithromycin prescriptions and per 2,560 levofloxacin prescriptions. A caveat regarding these estimates is that the authors did not provide the raw numerators and denominators used to calculate the incidence rates listed above.

The following table displays the hazard ratios and 95% confidence intervals for deaths and serious arrhythmias.

Outcome	Drug	Hazard Ratio (95% CI) (reference=amoxicillin)	
		Day 1-5	Day 6-10
Death, any cause	Azithromycin	1.48 (1.05-2.09)	1.14 (0.81-1.62)
	Levofloxacin	2.49 (1.70-3.64)	1.95 (1.32-2.88)
Serious arrhythmia	Azithromycin	1.77 (1.20-2.62)	1.37 (0.91-2.05)
	Levofloxacin	2.43 (1.56-3.79)	1.75 (1.09-2.82)

Azithromycin and levofloxacin both had elevated risks for death and serious arrhythmias in the first five days (relative to amoxicillin). In the second five day period only levofloxacin had significantly elevated hazard ratios.

Pneumonia is likely to have one of the higher mortality rates among the listed indications; Asadi et al. found a 30-day mortality for community acquired pneumonia treated on an outpatient basis of around one percent.[12] As the risk estimates parallel the proportion of patients with pneumonia in each cohort (i.e., levofloxacin>azithithromycin>amoxicillin), this reviewer asked the corresponding author on the publication whether their analysis had examined confounding by the indication of pneumonia. (b) (4)

(b) (4)

- *Strengths and limitations*

Some limitations to the study should be noted.

- Total mortality is less specific for assessing malignant ventricular arrhythmias than cardiovascular-related death, the outcome in the Ray et al. Tennessee Medicaid study.
- Pneumonia was the only individual indication directly controlled for in the analysis of all cause mortality. Residual confounding by indication for other indications could have biased the results, though pneumonia is the indication most likely to be related to mortality (and the adjustment for pneumonia did not change the risk estimates substantially).
- Many patients did not have a documented indication for the antibiotic. (This was also the case in the Ray et al. study.)
- The outcome of serious arrhythmia was not validated by medical record review. However, a recent Medicaid study (cited by Chou et al., as noted below) reported a positive predictive value of 74% for principal diagnoses similar to those used here.[13] Additionally, nondifferential misclassification of outcomes would be expected to bias the risk estimate toward rather than away from a null finding.

- The exposure cohorts were balanced for baseline comorbidities, with the exception of the indications of COPD in the azithromycin cohort and pneumonia in the levofloxacin cohort. There is the possibility of bias if comorbidities affect choice of antibiotic, though the authors excluded patients at an obviously high risk for death during the study period.
- The azithromycin cohort had the highest percentage of patients with COPD as the indication (see table above). Recent studies have found COPD to be associated with atrial and ventricular arrhythmias,[14] and higher all-cause mortality,[15] so COPD could be a confounder for the azithromycin cohort. However, the fact that with azithromycin the elevated risks were no longer seen after day 5 is inconsistent with confounding by a chronic condition. Also, COPD was most common in the azithromycin group, which had lower risk estimates than levofloxacin.

Specific strengths of the study include the following.

- While residual confounding is always possible, the IPTW method resulted in standardized mean differences under 10% among the treatment groups for all covariates (although details were not provided). Additionally, data on covariates such as laboratory values, body mass index, and tobacco use were available for this analysis which are not usually present in healthcare claims data.
- As was seen in the Ray et al. study, the elevated risk for azithromycin was limited temporally to the duration of the prescription.

- *Conclusions*

While generally speaking this study had more limitations than the Ray et al. study, the results for azithromycin are entirely consistent with the results of Ray et al., and extend the finding of risk to levofloxacin (which in the Ray study showed elevated risk as well, but not to a statistically significant degree).

3.2 CHOU ET AL.

This was a retrospective observational study in the Taiwan National Health Insurance Database examining ventricular arrhythmia and cardiovascular death with use of azithromycin, levofloxacin, moxifloxacin, clarithromycin , and ciprofloxacin, with amoxicillin-clauvunate as the reference. The study found an excess risk for both outcomes with moxifloxacin and azithromycin, and an excess risk for cardiovascular death with levofloxacin.

- *Author, publication year and affiliation/funding*

The authors are affiliated with National Taiwan University. The study was e-published December 22, 2014, and was funded by the Department of Statistics, Ministry of Health and Welfare, Taiwan.

- *Objectives*

The purpose of this study was to define the risks of cardiovascular death and ventricular arrhythmia with azithromycin, clarithromycin, ciprofloxacin, levofloxacin, and moxifloxacin, compared to amoxicillin-clavunate.

- *Design*

This was a retrospective cohort study.

- *Methods*
    - Population & Time Period

Reference ID: 3807786

The Taiwan National Health Insurance program enrolls 99% of the population of Taiwan, and provided the sample for this study. The time period was January 2001 to November 2011.

- Selection, Inclusion and Exclusion Criteria

The sample consisted of patients with prescriptions for oral preparations of any of the six study drugs (azithromycin, clarithromycin, ciprofloxacin, levofloxacin, moxifloxacin, amoxicillin-clavunate) from January 1, 2001 to November 30, 2011. Eligible patients were 20-100 years old with a recorded gender. The following were exclusion criteria: use of a study drug in the previous 6 months, refills of antibiotics for chronic illness, simultaneous prescriptions for more than one study drug, hospitalization within 30 days, ventricular arrhythmia or use of antiarrhythmic drugs in the past year, past cardiac arrest, malignancy, or human immunodeficiency virus infection.

- Outcomes

The primary outcome was "severe ventricular arrhythmia" identified by a prescription for amiodarone, lidocaine, MgSO4, or sotalol, plus a hospital, outpatient or emergency room diagnosis of the following (ICD9 codes except where indicated):

427.1 Paroxysmal ventricular tachycardia
427.4 Ventricular fibrillation and flutter
427.5 Cardiac arrest
798.1 Instantaneous death
798.2 Death (within 24 hours of symptoms, etc.)
708.9 Unattended death
V12.53 History of sudden cardiac arrest
Taiwan payment code 47029C for cardiopulmonary resuscitation

Outcomes were measured within the 7 day period following index date, with sensitivity analyses based on 14 and 30 day periods following the index date.

A secondary outcome was cardiovascular death, defined as causes of death indicated with ICD9 codes 401-449 and ICD10 codes I10-I79, and determined from a linkage to the Taiwan National Death Registry. It should be noted that these causes of death include other cardiovascular events in addition to ventricular arrhythmias. A third outcome was a composite of ventricular arrhythmia and cardiovascular death.

In support of their primary outcome definition, the authors cited a Medicaid study that used chart reviews to validate a similar (but not identical) list of hospital and emergency department diagnoses of sudden death and ventricular arrhythmia (specifically, ICD9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 798, 798.1, and 798.2). This study found a positive predictive value of 85% for these diagnoses.[16]

- Exposure

Exposure was an outpatient prescription for an oral study drug (azithromycin, clarithromycin, ciprofloxacin, levofloxacin, moxifloxacin, amoxicillin-clavunate), with the date of the prescription being the index date. The unexposed control group was patients with respiratory infections (see under Covariates) without an antibiotic prescription.

- Covariates

Reference ID: 3807786

There were three categories of indications: respiratory (having ICD9 codes for sinusitis, pneumonia, bronchitis, or acute respiratory infections), urinary tract (urinary tract infections, cystitis, pyelonephritis), and other. For the year preceding the index date, the investigators determined comorbidities (from inpatient and outpatient records), concomitant medications (from prescription records), and the patient's health care utilization; these parameters were propensity score covariates.

- Sample Size/Power

The following table, reproduced from the publication, shows the sample size.

Study population	N = 1 923 736
Amoxicillin/clavulanate	N = 1 102 358
Azithromycin	N = 66 745
Clarithromycin	N = 393 243
Ciprofloxacin	N = 205 205
Levofloxacin	N = 117 352
Moxifloxacin	N = 38 833

- Statistical Analysis

The authors used multinomial logistic regression to calculate multiple propensity scores for each cohort from baseline covariates describing indication, comorbidities, health care utilization, and concomitant drugs. Odds ratios (ORs) were adjusted for the propensity score. For the main analysis amoxicillin-clavulanate was the reference group. Secondary analyses involved stratification by selected baseline parameters, and within-class (i.e., macrolides, quinolones) comparisons.

- Ethics

The National Taiwan University Hospital ethics review board approved this study, which used anonymous health data.

- *Results*

The size of the study population is shown above. With respect to baseline characteristics, the youngest cohort was amoxicillin-clavulanate (mean age 44 years) and the oldest moxifloxacin (mean age 52 years); ciprofloxacin had the most females (58%) and moxifloxacin the most males (53%). Cardiovascular comorbidities were more common in the moxifloxacin cohort (30%) followed by the levofloxacin cohort (29%), while only 18% of the amoxicillin-clavulanate cohort had cardiovascular disease. The moxifloxacin cohort also had the highest proportion of patients with chronic lung disease and congestive heart failure, while the clarithromycin cohort was notable for a high percentage of patients with ulcer disease (perhaps reflecting use for H. pylori).

The following table displays the indications for each study drug. Azithromycin was used most frequently for respiratory tract infections, followed by moxifloxacin.

Reference ID: 3807786

Indication	Amoxicillin-clavulanate	Azithromycin	Clarithromycin	Ciprofloxacin	Levofloxacin	Moxifloxacin
Respiratory tract infection	62.5	80.7	51.6	23.7	26.7	72.2
Urinary tract infection	1.8	0.9	0.3	26.6	26	1.3
Other infection (includes otitis, sepsis, colitis)	35.7	18.4	48.1	49.7	47.3	26.5

The primary outcome, ventricular arrhythmia, was associated with use of azithromycin and moxifloxacin. An increase in events with levofloxacin did not reach statistical significance. For brevity only the adjusted ORs are shown here; in general, adjusting the OR tended to bring the OR closer to unity.

	No.	Events, No.	7-day incidence, per 1000	OR for ventricular arrhythmia, PS adjusted (95% CI)
Amoxicillin-clavulanate	1 102 358	127	0.12	1 (reference)
Azithromycin	66 745	35	0.52	4.32 (2.95–6.33)
Clarithromycin	393 243	31	0.08	0.72 (.48–1.08)
Moxifloxacin	38 833	22	0.57	3.30 (2.07–5.25)
Ciprofloxacin	205 205	30	0.15	1.07 (.69–1.66)
Levofloxacin	117 352	30	0.26	1.41 (.91–2.18)

The next tables display results for ventricular arrhythmia plus cardiovascular death, and cardiovascular death alone; both were associated with azithromycin, moxifloxacin and levofloxacin. Clarithromycin showed a reduced risk relative to amoxicillin-clavulanate.

	N	Events, N	7-day incidence per 1000	PS adjusted odds ratio for ventricular arrhythmia or cardiovascular death, (95% CI)
Amoxicillin-clavulanate	1 102 358	249	0.23	1 (reference)
Azithromycin	66 745	54	0.81	3.40 (2.52–4.59)
Clarithromycin	393 243	53	0.13	0.62 (.45–.84)
Moxifloxacin	38 833	37	0.95	2.74 (1.92–3.90)
Ciprofloxacin	205 205	49	0.24	0.85 (.61–1.18)
Levofloxacin	117 352	71	0.61	1.62 (1.20–2.17)

Reference ID: 3807786

	N	Events, N	7-day incidence per 1000	PS adjusted odds ratio for cardiovascular death, (95% CI)
Amoxicillin-clavulanate	1 102 358	142	0.13	1 (reference)
Azithromycin	66 745	24	0.36	2.62 (1.69–4.06)
Clarithromycin	393 243	25	0.06	0.51 (.33–.80)
Moxifloxacin	38 833	18	0.46	2.31 (1.39–3.84)
Ciprofloxacin	205 205	24	0.12	0.70 (.44–1.12)
Levofloxacin	117 352	46	0.39	1.77 (1.22–2.59)

From the crude incidence rates for cardiovascular death, one can calculate the unadjusted numbers-needed-to-harm. Relative to use of amoxicillin-clavulanate, the results indicate one excess cardiovascular death for every 1724 patients treated with azithromycin, 1389 patients treated with moxifloxacin, and 2631 patients treated with levofloxacin. Adjustment might have increased the numbers-needed-to-harm, since it tended to decrease the point estimates. Note that the cardiovascular death number-needed-to-harm for azithromycin versus amoxicillin in the Ray et al. study was much higher (approximately 21,000 overall and about 4,000 in the highest cardiovascular risk subgroup.)

In a supplemental analysis limited to patients with respiratory infections, amoxicillin-clavulanate had a higher risk of ventricular arrhythmia and cardiovascular death than no antibiotic. Direct comparisons between antibiotics in the same class showed an adjusted OR for ventricular arrhythmia, for azithromycin versus clarithromycin, of 6.13 (3.68-10.24); with ciprofloxacin as the reference fluoroquinolone, the adjusted OR for ventricular arrhythmia with moxifloxacin was 2.51 (1.28-4.94) and with levofloxacin 2.36 (1.43-3.90). Longer risk windows of 14 days and 30 days tended to attenuate the risks; the study did not include any analyses limited to follow-up time solely after use of the antibiotic. Subgrouping the patients according to whether the indication was a respiratory infection or another infection showed that the risk estimate for levofloxacin was higher in respiratory infections, but for azithromycin and moxifloxacin was higher in other infections. These results are reproduced below.

		Composite outcome		
	N	PS adjusted OR (95% CI)		
Respiratory tract infection		OR	Lower	Upper
Amoxicillin-clavulanate	689,466	1		
Azithromycin	53,857	2.63	1.75	3.95
Clarithromycin	203,010	0.71	0.47	1.09
Moxifloxacin	28,034	1.38	0.78	2.43
Ciprofloxacin	48,695	0.60	0.27	1.38
Levofloxacin	31,330	2.34	1.52	3.59
Infection other than respiratory tract infection				
Amoxicillin-clavulanate	412,892	1		
Azithromycin	12,888	5.83	3.75	9.08
Clarithromycin	190,233	0.59	0.37	0.95

Reference ID: 3807786

Moxifloxacin	10,799	4.80	3.03	7.58
Ciprofloxacin	156,510	0.88	0.62	1.25
Levofloxacin	86,022	1.23	0.86	1.77

Reference ID: 3807786

Finally, OR estimates tended to be higher in patients younger than 65 years, and in patients without cardiovascular comorbidity.

- *Strengths and limitations*

Strengths of the study include the following.

- It was national in scope.
- Sample sizes were large for several study antibiotics.
- Cardiovascular death was an outcome rather than death from any cause.
- Multinomial propensity scores allowed comparisons of more than just two cohorts to each other.

Limitations of the study should also be noted.

- The categories for indication were relatively broad.
- The endpoints were not adjudicated. The authors cited precedents for their endpoints from the literature, but it is not clear if these examples from North America are fully applicable to Taiwan's database.
- It is not certain that the strategy of propensity-score adjustment was fully successful in making the cohorts comparable, since details were not provided in the paper. This is somewhat mitigated by the largely consistent results obtained when the sample was stratified by confounders such as age and indication.
- There is not an obvious explanation for the lower risks observed with clarithromycin.
- *Conclusions*

The authors concluded that use of azithromycin and moxifloxacin increased ventricular arrhythmia and cardiovascular death relative to amoxicillin, but that further research was needed to establish whether the higher risks were causally related to the antibiotics or the infections. As with the Rao study, the methodology for this study had more limitations than the previous study by Ray et al., but the results are entirely consistent with that study, and extend the concerns to moxifloxacin and levofloxacin.

4 DISCUSSION

In comparison to the Ray et al. azithromycin study, the population in the Rao study tended to have a lower prevalence of relevant comorbidities despite a somewhat higher mean age (the mean age in the Ray et al. study was below 52 years in all cohorts, versus upper 50's in this study). Nineteen percent of amoxicillin users in the Ray et al. study received a statin in the past year, while 5% of amoxicillin users in the VA sample received anti-lipid medication in the past year. Similarly, calcium channel blockers were used by roughly 20% of subjects in the Ray et al. cohorts, versus 2-3% in the present study cohorts. With respect to comorbidities, 4% of amoxicillin users in the Ray et al. study had heart failure, compared to 0.4% in the present study. Despite the apparently lesser cardiovascular vulnerability of the VA sample, it should be noted that the rates of death per million antibiotic prescriptions over 5 or 10 days were generally higher in this study than in the Ray et al. sample, as can be seen by comparing figures in the two publications. In the Svanstrom et al. study, which failed to find any association between azithromycin and cardiovascular death, the mean age was lower, roughly 40 years. It may be that

Reference ID: 3807786

age per se is an important vulnerability factor. In the Chou et al. study, the cardiovascular death rate following an azithromycin prescription was higher (approximately 19 per 1000 patient-years, from the data in Table 3) than in the Ray study (about 6 per 1000 patient-years) despite a slightly younger mean age, though 20% of azithromycin users in the Chou study had some cardiovascular disease (not otherwise specified), so possibly the Taiwan study subjects had greater cardiovascular vulnerability.

As there are a growing number of observational studies of cardiovascular outcomes with antibiotics suspected to be arrhythmogenic, this seems like an opportune time for a high-level examination of recent findings. The following table summarizes observational studies of selected antibiotics, with respect to the outcomes of cardiovascular death or all-cause mortality, over the shortest risk window from each study, in comparison to a penicillin. In brief, 3 studies have shown associations with azithromycin, though a fourth did not; 2 studies found risks with levofloxacin (and results from a third approached statistical significance); results have been mixed for clarithromycin; 2 studies did not find any association for ciprofloxacin; and moxifloxacin showed an association in the single observational study of it to date. (Not listed is the previously mentioned Vanderbilt study showing an association with erythromycin, because it had no penicillin reference group.)

Cardiovascular death risk vs penicillin comparator		All-cause death risk vs. penicillin comparator	
Ray et al.		Ray et al.	
Azithromycin	**2.49 (1.38- 4.50)**	**Azithromycin**	**2.02 (1.24-3.3)**
Levofloxacin	1.99 (0.93- 4.23)	Levofloxacin	1.70 (0.95-3.03)
Ciprofloxacin	0.85 (0.36- 2.01)	Ciprofloxacin	1.36 (0.78 2.36)
Svanstrom et al. 2013		Svanstrom et al. 2013	
Azithromycin	0.93 (0.56–1.55)	not reported	
Chou et al.		Chou et al.	
Azithromycin	**2.62 (1.69–4.06)**	not reported	
Moxifloxacin	**2.31 (1.39–3.84)**		
Levofloxacin	**1.77 (1.22–2.59)**		
Ciprofloxacin	0.70 (.44–1.12)		
Clarithromycin	**0.51 (.33–.80)**		
Rao et al.		Rao et al.	
not reported		**Azithromycin**	**1.48 (1.05-2.09)**
		Levofloxacin	**2.49 (1.70-3.64)**
Svanstrom et al. 2014		Svanstrom et al. 2014	
Clarithromycin	**1.76 (1.08 -2.85)**	(b) (4)	**(unpublished data)**

(b) (4)

However, in the Ray study, the risk of cardiovascular death for azithromycin was significantly higher versus ciprofloxacin. Some authors have proposed that among fluoroquinolones, ciprofloxacin carries a relatively lower risk of QT prolongation.[17]

Reference ID: 3807786

Finally, concerns about arrhythmogenic risks of antibiotics must be balanced with their benefits for the treatment of severe infections; some data indicate macrolides provide a survival benefit in outpatients with CAP.[11]

5 CONCLUSION

Both the Rao study and the Chou study have limitations but provide evidence consistent with a risk of arrhythmia and death in outpatients receiving azithromycin and levofloxacin (relative to amoxicillin). In addition, the Chou study showed such a risk with moxifloxacin, the first time that compound has been studied in this way. The presumed mechanism is QT prolongation, and these results are consistent with the hypothesis that compounds which prolong the QTc interval in a concentration-dependent manner can increase serious arrhythmias, especially in a vulnerable population, even when the magnitude of QTc prolongation is relatively modest on average. The estimated number needed to harm, if valid, indicates a level of risk that is meaningful from both a public health and clinical standpoint (compared to use of amoxicillin, in the Rao study, one excess death per 10,204 azithromycin uses and per 2,564 levofloxacin uses, and in the Chou study, one excess cardiovascular death per 1724 azithromycin uses, 1389 moxifloxacin uses, and 2631 levofloxacin uses.). For context, the number needed to harm for Achilles tendon rupture with fluoroquinolones, a risk currently described in a boxed warning, has been estimated at around 6,000.[18]

In addition, the Rao study provides evidence that a study of cardiovascular death associated with azithromycin (b) (4), as currently being considered by Pfizer, should be feasible.

6 RECOMMENDATIONS

As there appears to be growing evidence of the arrhythmogenic effects of these antibiotics, some recommendations are offered.

- The impact of arrhythmogenic effects on the risk-benefit balance for nonserious infections needs to be considered. This of course must be weighed against the benefits of antibiotics in the treatment of severe infections (e.g., some data indicate macrolides provide a survival benefit in outpatients with CAP).
- Pfizer should continue its efforts to conduct an observational study (or studies) of cardiovascular risks with azithromycin, as their study should be able to address limitations of both of the studies reviewed here.
    - Specifically, neither the Rao study nor the Chou study featured adjudication of endpoints, which will be a part of the Pfizer study.
    - The Rao study analyzed only all-cause mortality, though cardiac-related mortality is more relevant and specific to the concerns regarding arrhythmogenic effects. The Pfizer study will analyze cardiovascular mortality.
    - The Pfizer study will have better information on indication for the antibiotics, a major potential confounder that both the Rao study and the Chou study attempted to control for, but their strategies may not have been fully successful.
- The QT Interdisciplinary Review Team should evaluate the available QT data for levofloxacin and ciprofloxacin. Regarding ciprofloxacin, it has been proposed that ciprofloxacin conveys a lower risk of QT prolongation than other fluoroquinolones, and existing observational data have not shown an association with such cardiovascular events for ciprofloxacin. (The QT-prolonging effects of moxifloxacin are well-described in its label.)

- Enhancements to the existing labeling regarding arrhythmogenic effects for both macrolides and fluoroquinolones would be appropriate. For fluoroquinolones, it would be appropriate to add the current warning regarding QT prolongation to the existing boxed warning. For azithromycin and other macrolides it would similarly be appropriate to box recommended this for azithromycin, based on the findings from the Vanderbilt study the existing labeling regarding QT prolongation. (This reviewer previously recommended this for azithromycin, based on the findings from the Vanderbilt study (Ray et al. NEJM 2012)), which provides a higher quality of evidence than the present two studies.)
- A more comprehensive literature review focused on pro-arrhythmic effects of fluoroquinolones is beyond the scope of the present review, but should be undertaken.

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/s/

ANDREW D MOSHOLDER

08/18/2015

Please note that Beth Maloney (Team Leader) and Judy Staffa (Division Director) do not concur with this review and so have not signed it. Their views will be recorded in a separate memo. Thank you, AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 21, 2015
To:	Sumathi Nambiar, Director, Division of Anti-Infective Drug Products, OND
From:	Judy Staffa, Ph.D., R.Ph., Director, Division of Epidemiology II (DEPI-II), OSE
	Elizabeth Maloney, M.S., Dr.P.H., Epidemiology Team Leader, DEPI-II, OSE **(retired as of 8/31/15)**
Subject:	Lack of concurrence with reviewer recommendations with regard to azithromycin and fluoroquinolone labeling
Drug Name(s):	Azithromycin (Zithromax and generics)
OSE RCM #:	2012-1106
	TSI 1321

The purpose of this memo is to document a difference of opinion between DEPI-II management (Judy Staffa and Elizabeth Maloney) and one of DEPI-II's senior reviewers (Andrew Mosholder) on his recommendations for labeling changes for azithromycin and fluoroquinolone antibiotics regarding risk of serious cardiac arrhythmias and mortality.

Dr. Mosholder has recently reviewed two published observational studies[1,2] that examined the risk for serious cardiac arrhythmias and mortality in relation to use of azithromycin. Both studies stated in their objectives that they intended to examine risk not just in users of azithromycin, but also in users of levofloxacin (Rao study) and in users of levofloxacin, moxifloxacin, clarithromycin and ciprofloxacin (Chou study). The Rao study employed users of amoxicillin as the referent group; the Chou study referenced users of amoxicillin/clavulanate. Both studies were retrospective and used administrative claims data; the Rao study used data from the Veterans' Administration (VA) and the Chou study used data from the Taiwan National Health Insurance Program.

Both of these studies reported increased risk of arrhythmia and death in users of azithromycin and levofloxacin in comparison to the reference group; the Chou study additionally reported increased risk associated with moxifloxacin. Dr. Mosholder thoroughly reviewed both studies, as he had previously been the primary reviewer for a paper published in 2012[3] that was the first epidemiologic study in the medical literature to find an increased risk for cardiovascular death associated with azithromycin. Dr. Mosholder found substantial limitations in each study, which he documented in his review; Dr. Maloney and I agree with those limitations which include not validating or adjudicating outcomes, focusing on all-cause mortality rather than cardiovascular mortality (Rao study) and likely inadequate strategies for controlling for potential

confounding by indication, particularly non-pneumonia indications (Rao study), and uncertain success of propensity-score adjustment for all indications (Chou study).

Despite these shortcomings, Dr. Mosholder has made 5 recommendations based on these 2 published studies. Dr. Maloney and I agree with 4 of his 5 recommendations, but disagree with the final recommendation which reads as follows:

Enhancements to the existing labeling regarding arrhythmogenic effects for both macrolides and fluoroquinolones would be appropriate. For fluoroquinolones, it would be appropriate to add the current warning regarding QT prolongation to the existing boxed warning. For azithromycin and other macrolides, it would similarly be appropriate to box the existing labeling regarding QT prolongation. (This reviewer previously recommended this for azithromycin, based on the findings from the Vanderbilt study (Ray et al, NEJM 2012), which on balance may be viewed as providing the strongest evidence from among these studies.)

Although we share Dr. Mosholder's concerns that serious cardiac arrhythmias are an important safety issue relating to the use of these products, we are not yet comfortable with recommending boxed warnings for either azithromycin or fluoroquinolones. For both azithromycin and fluoroquinolones, risk for serious cardiac arrhythmias is currently a labeled event, and we don't agree with strengthening this warning to the level of a boxed warning at this time.

For azithromycin, our rationale is outlined in Dr. Maloney's CDTL memo (TSI 1321, 11/16/2012). We agree that Dr. Ray's study has provided the strongest evidence to date; the current studies provided results consistent with Dr. Ray's study, however, these studies suffered from limitations that, as Dr. Mosholder pointed out, will be addressed via the postmarketing required studies that Pfizer is currently undertaking (b) (4) Given the potentially significant shifts in prescribing and utilization that a boxed warning might trigger, we would prefer to have more than one well-designed study supporting this important finding prior to recommending a boxed warning.

With regard to fluoroquinolones, we agree with Dr. Mosholder's recommendation that a thorough review of all the literature relating to fluoroquinolones and risk for arrhythmias and cardiac death be conducted; Dr. Natasha Chen is currently conducting such a review, which includes follow up with the investigators of the Chou study to gather additional information. In light of the limitations of this study, as described briefly above and more in detail in Dr. Mosholder's review, we believe it crucial to understand this association better before changing labels. For example, the current studies suggest that risks may differ across agents within the class, with levofloxacin and moxifloxacin carrying greater risk than ciprofloxacin. Since it remains unclear at this time whether there are indeed differential risks, or whether these differences result from differences in indications for use, we are hesitant to place a box on the entire class at this time. Additionally, some of the findings from the Chou study are not intuitive and require further investigation. For example, the observed odds ratios were higher in patients WITHOUT evidence of prior cardiovascular disease than in those WITH such evidence. This is not consistent with the findings from the Ray paper, and could reflect some kind of flaw in study design, or in definition of covariates or outcomes. We look forward to Dr. Chen's review for further investigation of these findings to inform labeling recommendations.

In summary, at this time, we agree with Dr. Mosholder's scientific review of these studies, but respectfully disagree with one of his recommendations that relates to adding boxed warnings for azithromycin and fluoroquinolones (class) for arrhythmias and cardiac death. We will continue to study this issue, and have asked that the data from Dr. Chen's review be shared at the upcoming advisory committee on November 5, 2015 and included in the discussion of risks and benefits of fluoroquinolones in relation to less serious indications.

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JUDY A STAFFA
09/22/2015

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology Review (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Literature Review of Peripheral Neuropathy

Date:	September 23, 2015
Reviewer:	Veronica Sansing, Ph.D., M.S., Epidemiologist Division of Epidemiology II
Team Leader	Tamra E Meyer, Ph.D. Division of Epidemiology II
Division Director	Judy Staffa, Ph.D., R.Ph. Division of Epidemiology II
Drug Name(s):	Fluoroquinolones
Subject	Literature Review of Fluoroquinolone Exposure and Peripheral Neuropathy
OSE RCM #:	2014-0896

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1 EXECUTIVE SUMMARY

The Division of Anti-infective Products (DAIP) consulted the Division of Epidemiology II (DEPI-II), requesting a literature review of fluoroquinolone-associated adverse events that are currently labeled. DEPI-II engaged in three parallel reviews. This review focuses on fluoroquinolone (FQ) exposure and the risk of peripheral neuropathy (PN). On May 15, 2015, we conducted a search of articles retrieved from the National Library of Medicine's PubMed database, which resulted in one qualifying article. Etminan et al. (2014) conducted a claims based, case-control study to quantify the risk of PN with oral FQ using data from IMS Lifelink commercial health claims database. [11] This study assessed PN cases identified by ICD-9-CM codes among a cohort of men age 45-80 years. After adjusting for comorbid conditions, compared to non-users, any oral FQ use in the past year was associated with a higher risk of developing PN (rate ratio [RR]=1.30, 95% confidence interval [CI] 1.21–1.40); current new users had the highest risk of PN (RR=2.07, 95% CI 1.56–2.74). The risk of PN remained similar across the most frequent FQ types: ciprofloxacin (RR=1.93, 95% CI 1.32–2.82, levofloxacin (RR=2.06, 95% CI 1.24–3.40), and moxifloxacin (RR=2.61, 95% CI 1.12–6.07). The negative control, finasteride, showed a modest non-significant elevation in risk that was lower than the risks seen with FQ's.

The study contains numerous limitations, primarily the lack of adjustment for additional confounders, the lack of validation of the outcome and exposure algorithms, and the lack of justification of the sample size. Despite the weak evidence of the association from this case-control study, case reports of the link between FQs and PN were compelling and described severe PN shortly after starting the FQ treatment. Therefore, it is still possible that a true association does exist. Based solely on the data from the case-control study presented, we do not recommend labeling changes regarding FQ and PN.

2 INTRODUCTION

The Division of Anti-infective Products (DAIP) consulted the Division of Epidemiology II (DEPI-II), requesting a literature review of fluoroquinolone-associated adverse events that are currently labeled. DEPI-II engaged in three parallel reviews. This review focuses on fluoroquinolone (FQ) exposure and the risk of peripheral neuropathy (PN). In 2001, the Division of Drug Risk Evaluation (DDRE) within the Office of Drug Safety (ODS) uncovered 35 reports of quinolone-associated PN and 46 cases of potentially prolonged paresthesia collected by the Adverse Event Reporting System (AERS) across the quinolone class (including reports for ciprofloxacin, ofloxacin, and levofloxacin). [a, 1] Twenty eight of these cases lasted over one month which prompted concerns regarding the severity of the condition, so an additional analysis of prolonged PN was conducted in 2003.[2] The median age of patients affected with PN ranged from 43 to 50 years, the gender distribution was fairly equal, and most patients had no other conditions

[a] The Division of Drug Risk Evaluation (DDRE) of the Office of Drug Safety (ODS) was the predecessor of the Divisions of Pharmacovigilance I and II (DPV) in the Office of Pharmacovigilance and Epidemiology (OPE) in the Office of Surveillance and Epidemiology (OSE). The Adverse Event Reporting System (AERS) was the predecessor to the FDA Adverse Event Reporting System (FAERS).

predisposing to PN. Onset of PN was acute (2.5-4 days post-treatment). This review prompted labeling changes among the three drugs warning of the risk of rapid onset and the potential for rapid progression and irreversibility of the FQ-induced neuropathy, especially if therapy continues after symptom onset. In 2013, FDA required similar labeling changes for all FQ's (oral and injected).

2.1 Background

2.1.1 Epidemiology of Peripheral Neuropathy

PN is damage to or disease of the peripheral nervous system which may impair sensation in the hands or feet, movement, gland or organ function, and more. Risk factors for PN include diabetes mellitus, alcohol abuse, vitamin deficiencies (particularly B), infections, such as Lyme disease, shingles, Epstein-Barr virus, hepatitis C and HIV, autoimmune diseases, such as rheumatoid arthritis and lupus, kidney, liver or thyroid disorders, exposure to toxins, repetitive motions or compressive trauma, and family history of neuropathy.[3]

An estimated 20 million people in the United States have some form of PN.[4] PN disorders are relatively common conditions that affect 2.4% of the population. Even higher prevalence rates have been reported with increasing age and with various forms of criteria used to diagnose PN. About a third of people with diabetes suffer from some form of diabetic peripheral neuropathy.[5]

2.1.2 Fluoroqinolones and Peripheral Neuropathy

FQs are fluorinated quinolones with the capability of crossing the blood–brain barrier and achieving central nervous system penetration.[6] However, there are no well documented studies which describe a mechanism of action between FQ and the peripheral nervous system. There is pathological evidence of axonal degeneration with secondary breakdown of the myelin sheath (demyelination) that has been noted in patients with FQ induced PN.[7]

A 2001 study found that 80% of study participants with PN reported severe events with symptom onset as early as 24 hours after beginning FQ's; 58% of these cases had symptoms which lasted beyond one year.[8] In 2013, the Food and Drug Administration (FDA) issued a communiqué requiring a label change that specifically addressed the risk of PN for all oral FQs.[9] The new label warnings are based on a recent review of the FDA's Adverse Event Reporting System (FAERS) database that showed a link between systemic exposure to FQ and PN, including more severe forms of nerve damage such as Guillain-Barré Syndrome.[10] The highest reporting frequencies were found for ciprofloxacin and levofloxacin as they are widely used in the US.[10]

FQ labels carry information warning physicians and patients of the risks and measures to take regarding PN, similar to the information listed in the ciprofloxacin label (2/2015) below:

Warnings and Precautions

"Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including CIPRO IV. Symptoms may occur soon after initiation of CIPRO and may be irreversible. Discontinue CIPRO immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness, or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation, and/or motor strength in order to minimize the development of an irreversible condition."

Information for Patients

"Inform patients that peripheral neuropathies have been associated with ciprofloxacin use, symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, immediately discontinue CIPRO IV and contact their physician."

3 REVIEW METHODS AND MATERIALS

3.1 Document to be Reviewed

- Etminan M, Brophy JM, Samii A. Oral fluoroquinolone use and risk of peripheral neuropathy: a pharmacoepidemiologic study. Neurology 2014;83:1261-1263.

3.2 Methods

Conducted on May 15, 2015, a search of the National Library of Medicine's PubMed database used the following search string: (fluoroquinolone[MeSH]) AND (((“acute kidney injury”[MeSH] OR “anaphylaxis”[MeSH] OR “hypersensitivity”[MeSH] OR “tendinopathy”[MeSH] OR "peripheral nervous system diseases"[MeSH] OR "retinal detachment"[MeSH] OR "arrhythmias, cardiac"[MeSH] OR "death"[MeSH] or "Drug-Related Side Effects and Adverse Reactions"[MeSH]))). The literature search included 722 publications written in English, dealing with humans, and published anytime from January 1, 1986, to the date of the search. The literature search excluded:

- publications that did not mention fluoroquinolones
- case reports and case series
- commentaries and reviews
- methods development studies and studies based on adverse event reports
- QT prolongation studies
- studies with no safety data
- studies where fluoroquinolones were only used by ophthalmic, otic, or topical routes of administration, among pediatric populations, or in the inpatient setting

This literature review was restricted further to studies of FQ and PN outcomes. Additional studies were identified from the selected studies' citations. Two articles which pertained to FQ and PN were reviewed. One was excluded due to the use of data from a passive surveillance system.[10] One article remained for in-depth review.[11]

4 REVIEW RESULTS

One study by Etminan et al. (2014) examined the association between oral FQ use and PN (Appendix). [11] This study assessed PN cases identified by ICD-9-CM codes among a cohort of older men. It is of note that the results are not generalizable to women or younger populations.

Etminan et al. (2014) conducted a claims based, case-control study to quantify the risk of PN with oral FQ using data from IMS Lifelink commercial health claims database. The IMS Lifelink database contains paid claims from over 102 US healthcare plans and includes fully adjudicated medical and pharmacy claims for over 68 million patients.[12] Within this study, 1 million patients were randomly selected and patients with diabetes were excluded using an undefined algorithm for diabetes. The final sample size included 31,130 male patients between the ages of 45-80 years enrolled between the years 2001 to 2011. There were 6,226 cases (ICD-9-CM codes for idiopathic or drug-induced PN at first physician visit: 356.4, 356.8, or 357.6) and 24,904 controls matched 1:4 respectively by age, follow-up duration, and calendar time using density-based sampling (each time a case is diagnosed controls are selected from the available cohort at the time).

FQ exposure was assessed in multiple ways accounting for window of usage and frequency of use. Any use of a FQ was defined as having received at least one prescription of FQ in the year before the index date (first visit for PN), current users were those with a FQ prescription within 14 days of the index date, current new users only received one prescription, and prevalent users received more than one prescription.

The study adjusted for the following confounding variables in the conditional logistic regression model: chronic renal failure, chronic liver disease, hypothyroidism, postherpetic neuralgia, and the use of nitrofurantoin and metronidazole, with each variable being more prevalent in the cases (Table 1). Although logistic regression outputs odds ratios, the authors considered them equivalent to rate ratios (herein referred to as RR) because of the density-based sampling

Compared to non-users, any oral FQ use in the past year was associated with a higher risk of developing PN (RR=1.30, 95% confidence interval [CI] 1.21–1.40; Table 2); current new users with only one FQ prescription had the highest risk (RR=2.07, 95% CI 1.56–2.74). The risk of PN remained similar across the most frequent FQ types: ciprofloxacin (RR=1.93, 95% CI 1.32–2.82, levofloxacin (RR=2.06, 95% CI 1.24–3.40), and moxifloxacin (RR=2.61, 95% CI 1.12–6.07). The study does not state the length of the PN symptoms, nor the time to onset. As a negative control, current use of finasteride (RR=1.21, 95% CI 0.97–1.51) showed a modest non-significant elevation in risk, but the magnitude of the association was lower than with FQ use.

Table 1. Characteristics of cases with peripheral neuropathy and their matched controls (Etminan et al. [11])

	Cases	*Controls*
No. of subjects	6,226	24,904
Age, y, mean ± SD	68.7 ± 12.9	68.7 ± 12.9
Follow-up, y, mean ± SD	2.6 ± 2.1	2.6 ± 2.1
Comorbidities the year before index, %		
Chronic renal failure	6.5	3.7
Chronic liver failure	4.1	2.2
Hypothyroidism	7.7	4.9
Postherpetic neuralgia	1.5	0.9
Metronidazole, %	2.7	1.9
Nitrofurantoin, %	1.6	1.1

Table 2. Rate ratios for FQ and peripheral neuropathy

				Adjusted	
	Cases	*Controls*	*Crude rate ratio*	*Rate ratio*	*95% CI*
No. of subjects	6,226	24,904	—	—	—
No use of FQ in the past year, %	76.9	81.7	1.00	1.00	—
Any oral FQ in the past year, %	23.1	18.3	1.35	1.30	1.21–1.40
Current use	2.2	1.2	1.88	1.83	1.49–2.27
Current new use	1.2	0.6	2.08	2.07	1.56–2.74
Current prevalent use	1.0	0.6	1.70	1.61	1.19–2.18
Any use of finasteride in the past year, %	7.0	7.2	0.96	0.95	0.85-1.07
Current use of finasteride	1.8	1.5	1.20	1.21	0.97-1.51

5 DISCUSSION

5.1 General

This paper lacks critical details to support the validity of the authors' conclusions. Among many elements, the paper most notably is missing:

- a description of the original objective and patients in the cohort study (since this was a nested-case control study)
- a Baseline Clinical Demographic Table comparing the cases to controls with respect to other potential confounders such as healthcare utilization frequency, other comorbidities, etc.
- results from the univariate analyses examining the candidate variables to the study outcome (see Section 5.4)
- the number of cases and controls with exposure to each fluoroquinolone type
- detailed validation methods of their algorithms used to identify exposure groups (Section 5.2), outcomes (Section 5.3) and important confounders (e.g., diabetes, renal/liver failure, hypothyroidism, postherpetic neuralgia; Section 5.4)
- a detailed statistical section including a sample size justification including magnitude of difference, alpha level, 1- or 2-sided, and minimum sample size – the article simply states that it can test a difference with a 5% significance level.

5.2 Exposure

The study's exposure groups are prone to misclassification bias. The data source, Lifelink, is a commercial database of administrative claims from mostly employer-based plans. Patients with employer-based healthcare are prone to switching between insurance plans. Each time a patient switches plans they will enter as a new patient. Therefore, a patient may be included multiple times as a different subject.

The authors also stated that exposures were measured in the one year of data prior to the index date - first date of initial visit for cases, but unspecified for controls. Users of FQ had a FQ prescription within one year of the index date. The authors could have additionally conducted a cohort study in which time to event analysis could be used to examine the temporal relationship between the FQ and PN. Given they used a case-control study, they examined current new and current prevalent users (use within 14 days) to assess the recency of use. In fact, there was an increase in RR from Any Use of FQ within a year (RR=1.30, 95% CI 1.21-1.40) to Current New Use within 14 days (RR=2.08, 95% CI 1.18-2.18) which is consistent with the case reports that noted a short onset time between FQ exposure and development of PN. However, given the large sample size, and lengthy study duration, the authors potentially had the power to provide stronger evidence of an association between FQ and PN using a cohort study with time-to-event analysis and accounting for duration of use.

5.3 Outcome

The authors provided no validation of the algorithm used to assess the outcome of PN. Instead, the authors provided what they termed a "sensitivity analysis" by using their algorithm to assess two drugs that are not associated with PN. Per communication with the authors, both azithromycin (RR=0.74, 95% CI: 0.44-1.23) and current use of finasteride (RR=1.21, 95% CI 0.97–1.51) showed no risk. They stated that they did not find any validation of PN codes in large claims databases in the literature, and evidently had no access to medical charts to conduct their own validation. It is noted that in order to exclude hereditary neuropathy, the authors examined only idiopathic or drug induced polyneuropathy (ICD-9 356.4, 356.8, 357.6, respectively) as advised to them by their neurologist, Dr. Samii. The reviewer found no further publications to support the validity of the algorithm. The lack of outcome validation could contribute to misclassification bias of the outcome in which actual cases are classified as controls or vice versa. For example, studies that use a single ICD-9-CM code to identify outcomes in administrative healthcare claims data are at risk of classifying a "rule out code" for PN as a case, even though later evaluation may find that the patient was not a true case. Therefore, claims-based algorithms often require 1) more than one outcome code for the condition within a certain amount of time, 2) an outcome code from a specialist visit, 3) a diagnostic plus procedure code, 4) a combination of diagnostic/procedure codes and prescriptions, and 5) validation of coding algorithms using medical chart review.[13]

The study also does not indicate how many of the patients were diagnosed with conditions such as Guillain-Barré syndrome, an illness in which the body's immune system attacks the peripheral nervous system, initially causing symptoms similar to that of PN. In such instances, Guilliain-Barré would be the diagnosis rather than PN. Further, the study does not report how many patients crossed over from controls to cases.

Given the complexity of the possible misclassification biases in this study, it is difficult to say whether the true number of cases is overestimated or underestimated. However, due to the common occurrence of rule-out codes in studies using administrative claims data and the large number of differential diagnoses, such as Guilliain-Barré, in the work-up of PN, the true number of cases are likely to be overestimated by not validating the coding algorithms.

5.4 Confounders

This study does not adjust for the indication for use of FQ and may therefore suffer from confounding by indication. This is very important as the case group had significantly more claims for concomitant conditions compared to the control group, indicating that there may be differences in the indications for use between cases and controls.

The text notes that concomitant conditions such as chronic renal failure, chronic liver disease, and hypothyroidism were included in the adjusted model, but does not provide a univariate table or a clinical baseline table providing evidence that these are in fact confounders. In addition, although

all of the subjects were male and matched by age, adjusted models do not account for *any other* demographic variables (should there have been evidence of any demographic variable as potential confounders).

5.5 Results

The authors noted an almost doubling of risk of PN in FQ users compared to non-users. Due to the aforementioned limitations, it is likely that the Rate Ratios are overestimated or underestimated.

This is a case-control study nested within a cohort study, which would be able to provide the required incidence rate. Within the current article, the incidence of PN was not stated, nor was the number of subjects (N) with PN. The authors were asked for the incidence rates via email and did not provide them.

6 CONCLUSION

The study shows an approximate two-fold risk of PN with current use of FQ in older males. The amount of evidence to support the positive association between FQ and peripheral neuropathy noted in current FQ labeling is weak due to the missing information in the article regarding additional possible confounders, the lack of validation of the outcome and exposure algorithms, and the lack of justification of the sample size. Due to the limitations it is likely that the magnitude of the results is inaccurate. Despite the weak evidence of the association from this case control study, case reports of the link between FQs and PN were compelling and described severe PN shortly after starting the FQ treatment. Therefore, it is still possible that a true association does exist.

7 RECOMMENDATIONS

Based solely on the data from the case-control study presented, we do not recommend labeling changes regarding FQ and PN.

8 APPENDIX: SUMMARY OF CASE-CONTROL STUDY OF FLUOROQUINOLONES AND PERIPHERAL NEUROPATHY

Selection Criteria	Exposure Definition	Outcome Definition	Sample Size & Analytical Approach	Findings
Etminan (2014), nested case-control study [11]				
Study Period: 2001-2011 Data Source: IMS Lifelink-1 million randomly selected men ages 45-80 years Inclusion Criteria: Cases: First claim for non-hereditary PN. Prevalent cases were excluded, but the criteria for exclusion were not described. Controls: Incidence density sampling from a pool of all subjects who had (1) not received a PN code (ICD-9-CM 356), (2) were the same age as the case (±1 year), and (3) had the same follow-up as the case. 4 controls selected per case. Exclusion Criteria: diabetes (no definition provided)	Any use of a FQ: At least one prescription of FQ in the year before the index date Current users: A FQ prescription within 14 days of the index date Current new users: Current users with only 1 prescription Prevalent users: >1 prescription Non-users: N prescriptions Negative Control: Any prescription for finasteride	Incident cases of idiopathic or drug-induced PN - first physician visit with ICD-9-CM diagnosis code 356.4, 356.8, 357.6.	Sample Size: N=31,130 (n=6,226 cases, n=24,904 controls) Ho: FQ users are not at a higher risk of PN than non-FQ users at a 5% significance level. Statistical analysis: conditional logistic regression (matched on age, calendar time, and follow-up year) model between users and non-users adjusting for chronic renal failure, chronic liver disease, hypothyroidism, postherpetic neuralgia, and the use of nitrofurantoin and metronidazole	Current users, especially new users of FQs, were at a higher risk of developing PN. Any oral FQ use in the past year adjusted rate ratio (aRR)=1.30 (95% CI 1.21–1.40) - Current use aRR=1.83 (1.49-2.27) -- Current new use aRR=2.07 (1.56–2.74) -- Current prevalent use aRR=1.61 (1.19-2.18) Ciprofloxacin aRR=1.93 (1.32–2.82) Levofloxacin aRR=2.06 (1.24–3.40)

				Moxifloxacin aRR=2.61 (1.12–6.07) Negative Control (Finasteride): Any use in past year aRR=0.95 (0.85-1.07) -Current use aRR=1.21 (0.97-1.51) --Current new use aRR=1.04 (0.57-1.91)

KEY: FQ- fluoroquinolones; H_0 - null hypothesis; PN - peripheral neuropathy, aRR – adjusted rate ratio

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(13) U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER.

Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005.

APPENDIX G: FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012 and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

APPENDIX H: DRUG UTILIXATION DATABASE DESCRIPTIONS AND LIMITATIONS

APPENDIX H: DRUG UTILIXATION DATABASE DESCRIPTIONS AND LIMITATIONS

The findings from this review should be interpreted in the context of the known limitations of the databases used. Based on IMS National Sales Perspectives™ sales data for 2014, approximately 82% of oral levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, and ciprofloxacin bottles were distributed to outpatient retail pharmacy settings in the U.S., followed by 17% to non-retail pharmacy settings, and 1% to mail-order/specialty pharmacies. As this drug use analysis was focused only on the U.S. outpatient retail pharmacy setting, these estimates may not apply to other settings of care in which these products are used, such as mail-order/specialty and non-retail pharmacy care settings. The estimates provided in this review are national estimates, but no statistical tests were performed to determine any statistically significant changes over time or between products; therefore, all changes over time or between products should be considered approximate and may be due to random error.

1. IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

2. IMS, National Prescription Audit

The National Prescription Audit™ (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

3. IMS, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

4. *Encuity Research, LLC., TreatmentAnswers™*

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

APPENDIX I: Top diagnoses Associated with the Selected Fluoroquinolones

APPENDIX I: Top diagnoses associated with the selected fluoroquinolones (oral systemic forms only) as reported by U.S. office-based physician surveys, stratified by molecule and ICD9 code, for years 2010 and 2014

2010	Uses (000)	*Share %*	95% C.I. (000)
Total	**28,271**	***100.0%***	**27,478 - 29,065**
ciprofloxacin	**16,215**	***57.4%***	**15,614 - 16,816**
5990 URIN TRACT INFECTION NOS	6,977	*43.0%*	6,583 - 7,372
5959 CYSTITIS NOS	820	*5.1%*	685 - 955
6019 PROSTATITIS NOS	696	*4.3%*	571 - 820
5621 DIVERTICULA OF COLON	583	*3.6%*	469 - 697
7909 ABN BLOOD FINDINGS NEC	383	*2.4%*	291 - 476
All Others	6,756	*41.7%*	6,368 - 7,144
levofloxacin	**8,159**	***28.9%***	**7,733 - 8,585**
4860 PNEUMONIA, ORGANISM NOS	1,362	*16.7%*	1,188 - 1,536
5990 URIN TRACT INFECTION NOS	1,109	*13.6%*	951 - 1,266
4900 BRONCHITIS NOS	991	*12.2%*	843 - 1,140
4739 CHRONIC SINUSITIS NOS	813	*10.0%*	678 - 947
4660 ACUTE BRONCHITIS	382	*4.7%*	290 - 475
All Others	3,502	*42.9%*	3,223 - 3,781
moxifloxacin	**3,574**	***12.6%***	**3,291 - 3,856**
4739 CHRONIC SINUSITIS NOS	737	*20.6%*	609 - 866
4860 PNEUMONIA, ORGANISM NOS	620	*17.3%*	502 - 737
4900 BRONCHITIS NOS	564	*15.8%*	452 - 676
4660 ACUTE BRONCHITIS	302	*8.5%*	220 - 384
4619 ACUTE SINUSITIS NOS	231	*6.5%*	160 - 303
All Others	1,119	*31.3%*	961 - 1,277
gemifloxacin	**225**	***0.8%***	**155 - 296**
4900 BRONCHITIS NOS	110	*49.0%*	61 - 160
4860 PNEUMONIA, ORGANISM NOS	37	*16.5%*	8 - 66
4619 ACUTE SINUSITIS NOS	30	*13.1%*	4 - 55
4660 ACUTE BRONCHITIS	29	*13.0%*	4 - 55
4739 CHRONIC SINUSITIS NOS	19	*8.5%*	< 0 5 - 40
ofloxacin	**98**	***0.4%***	**51 - 145**
5990 URIN TRACT INFECTION NOS	44	*45.0%*	13 - 76
6149 FEM PELV INFLAM DIS NOS	18	*18.4%*	< 0 5 - 38
7881 DYSURIA	12	*12.2%*	< 0 5 - 28
4739 CHRONIC SINUSITIS NOS	9	*9.6%*	< 0 5 - 24
4860 PNEUMONIA, ORGANISM NOS	6	*6.6%*	< 0.5 - 18
All Others	8	*8.2%*	< 0.5 - 21

2014	Uses (000)	*Share %*	95% C.I. (000)
Total	**29,373**	***100.0%***	**28,516 - 30,231**
ciprofloxacin	**17,867**	***60.8%***	**17,198 - 18,536**
5990 URIN TRACT INFECTION NOS	7,629	*42.7%*	7,192 - 8,066
6019 PROSTATITIS NOS	771	*4.3%*	632 - 910
5621 DIVERTICULA OF COLON	688	*3.9%*	557 - 820
5959 CYSTITIS NOS	571	*3.2%*	451 - 691
5999 URINARY TRACT DIS NOS	527	*3.0%*	412 - 642
All Others	7,681	*43.0%*	7,242 - 8,120
levofloxacin	**9,493**	***32.3%***	**9,005 - 9,981**
4860 PNEUMONIA, ORGANISM NOS	2,058	*21.7%*	1,830 - 2,285
5990 URIN TRACT INFECTION NOS	1,260	*13.3%*	1,082 - 1,438
4900 BRONCHITIS NOS	1,065	*11.2%*	902 - 1,228
4660 ACUTE BRONCHITIS	1,046	*11.0%*	884 - 1,208
4739 CHRONIC SINUSITIS NOS	652	*6.9%*	524 - 779
All Others	3,413	*36.0%*	3,120 - 3,705
moxifloxacin	**1,791**	***6.1%***	**1,580 - 2,003**
4900 BRONCHITIS NOS	392	*21.9%*	293 - 491
4860 PNEUMONIA, ORGANISM NOS	341	*19.0%*	248 - 433
4739 CHRONIC SINUSITIS NOS	327	*18.3%*	237 - 418
4619 ACUTE SINUSITIS NOS	224	*12.5%*	149 - 299
6829 CELLULITIS NOS	122	*6.8%*	67 - 178
All Others	385	*21.5%*	287 - 483
gemifloxacin	**132**	***0.5%***	**75 - 190**
4660 ACUTE BRONCHITIS	119	*89.9%*	64 - 173
4900 BRONCHITIS NOS	13	*10.1%*	< 0.5 - 32
ofloxacin	90	*0.3%*	42 - 137
5990 URIN TRACT INFECTION NOS	69	*76.6%*	27 - 110
V670 SURGERY FOLLOW-UP	11	*11.9%*	27 - 27
3669 CATARACT NOS	**6**	***6.9%***	**27 - 19**
3829 OTITIS MEDIA NOS	4	*4.7%*	27 - 14

Source: Encuity Treatment Answers™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015

NOS: Not otherwise specified, NEC: Not elsewhere classified

APPENDIX J: FAERS Case Report Information

FDA Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Disclaimer: Submission of a safety report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.

Case Id(s):

5828854	6166079	6536107	6571148	6579895	6588484	6620284
6657012	6672101	6707623	7133559	7219290	7416727	7452557
7943437	8318839	8326901	8333778	8348625	8382160	8382187
8391445	8393838	8442603	8444899	8457908	8504039	8523536
8536164	8611507	8744529	8744551	8744592	8745000	8745367

Run by: STEPPERH

Date Run: 23-SEP-2015 13:36 PM

Total Cases: 35

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 5828854

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 020634 /

FDA Rcvd Date: 02-Sep-2005 **Mfr Rcvd Date:** 24-Aug-2005 **Mfr Control #:** US-JNJFOC-20050601449

Patient Information:

Age: 50 YR **Sex:** Female **Weight:** 49.9 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	750 MG/	Oral		BRONCHITIS		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN			U				

Event Information:

Preferred Term (MedDRA © Version: 17.0)	ReC
Alopecia	
Arthralgia	
Back injury	U
Back pain	
Carpal tunnel syndrome	U
Hypoaesthesia	
Migraine	U
Tendonitis	

Case ID: 5828854

Event/Problem Narrative:

Report received from a consumer (a nurse): 1-154210179. A 50 year old woman with a history of 3-6 drinks per week and 1/2 pack cigarettes daily was treated with levofloxacin 750mg tablets for 5 days in Dec-04 for pneumonia. Concomitant medication included salbutamol and a decongestant. In Dec-04 she experienced severe pain in neck, elbows, knees and low back. This pain continues. In Jan-05 she experienced migraines. In Jan-05 the right elbow pain became severe and her fingers in that hand became numb. She is now in a full arm cast and has been unable to work for 3 and one half months. This report is serious (medically significant). Additional information received from consumer 22-Jun-05: The woman has been unable to work due to tendinitis of elbow and wrist and in addition also reports that she had surgery in Feb-05 with no improvement (surgery unspecified). An MRI (magnetic resonance imaging) of her right elbow was done in Jun-05 and results are pending. She also had an MRI of her back which revealed "2 tears of L5 - S1". Although she had originally been diagnosed with pneumonia and treated with levofloxacin her physician now told her that the indication for levofloxacin was bronchitis. She also reports hair loss. Medical authorization received from this consumer. Followup information requested from physicians. Hair loss has been added as a non-serious event. Based upon information received 22-Jun-05 this case is now considered a 15 day alert. Additional information received from a physician, (orthopedist), on 3-Aug-05: A 50 year old woman, with a history of a hysterectomy in 1974 reported she developed right elbow discomfort after levofloxacin therapy, (750mg daily x 5 days). Subsequently the patient had multiple arthralgias and some numbness and tingling in her right upper extremity. In Jan-05 she had EMG (electromyograph), and nerve conduction velocities which were consistent with carpal tunnel syndrome. In Feb-05 the patient underwent a carpal tunnel release, which helped some of the discomfort in her hand, but the right elbow discomfort persisted. The patient has had injections to the right elbow by another physician on 3 occasions, (last received on 12-May-05), with only mild relief. Physical examination revealed the patient was point tender over her lateral epicondyle with pain at extremes of elbow extension or flexion. She has pain to extension of her wrist against resistance. She has a negative Tinel's overlying the ulnar nerve at her elbow. Xrays of the elbows are unremarkable. On 27-May-05 the patient was put into a long arm cast in slight supination and slight wrist extension. On 10-Jun-05 the long arm cast was removed. Elbow discomfort was somewhat improved, but not completely resolved. The patient was referred to therapy for fabrication of a long arm splint with a Heelbo pad to be worn as much as possible. An MRI (magnetic resonance imaging) scan of the elbow revealed no changes consistent with any problem that would be amenable to surgery and the patient was referred for pain management. In Jul-05 an MRI of the cervical and lumbar spine and left hip was performed, (ordered by pain management physician). Results: left hip unremarkable, lumbar spine MRI reportedly showed some changes at L5-S1 with disk changes and facet narrowing. Cervical MRI reportedly showed multiple level bulging disks with various levels of cord compression and some foraminal stenosis at C4-C5 and C5-C6. The final formal interpretation of these studies has been requested. The patient has been unable to work for months. Additional information received from a physician on 24-Aug-05: The patient, (110 pounds), reported diffuse neck, shoulder, low back and leg pain after taking levofloxacin in 2005 for bronchitis. She was seen for chronic pain treatment. At the time of this report, she has not recovered. 1-Sep-05: The event carpal tunnel syndrome added.

Case ID: 5828854

Relevant Medical History:

3-6 drinks per week

Disease/Surgical Procedure	Start Date	End Date	Continuing?
HYSTERECTOMY	1974		UNKNOWN
TOBACCO USER			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events
NSAIDS				

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
NUCLEAR MAGNETIC RESONANCE IMAGING	left hip-unremarkable				N
NUCLEAR MAGNETIC RESONANCE IMAGING	lumbar spine-changes at L5-S1				N
NUCLEAR MAGNETIC RESONANCE IMAGING	cervical-multiple level bulging disks.				N
X-RAY	e bow-unremarkable				N
NUCLEAR MAGNETIC RESONANCE IMAGING	e bow-negative changes.				N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ALBUTEROL		Nasal		BRONCHITIS			
2	DEXTROMETHORPHAN							
3	INTAB DM							
4	PHENYLEPHRINE HYDROCHLORIDE							

Case ID: 5828854

Reporter Source:

Study Report?: No

Sender Organization: JOHNSON AND JOHNSON

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6166079

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:** 020634 /

FDA Rcvd Date: 13-Nov-2006 **Mfr Rcvd Date:** 06-Nov-2006 **Mfr Control #:** US-JNJFOC-20061101670

Patient Information:

Age: 59 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	750 MG/	Oral		SINUSITIS		
2	LEVAQUIN	500 MG/	Oral				

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN			N				
2	LEVAQUIN			N				

Event Information:

Preferred Term (MedDRA Â© Version: 17.0)	ReC
Abasia	N
Arthralgia	N
Fatigue	N
Headache	N
Nausea	N

Case ID: 6166079

Event/Problem Narrative:

This spontaneous report from a consumer concerns a 59-year-old female from the United States: #1-303070196. The patient's past medical history/concurrent conditions included asthma. The patient's height and weight were not reported. Concomitant medications included Advil (ibuprofen) for pain. The patient was treated with two different regimens of LEVAQUIN (levofloxacin tablets, oral). The first was at 750/day, initiated in OCT-2006 for sinusitis and the second course was at 500 mg/day also initiated in OCT-2006 for sinusitis. In OCT-2006, on the second day of the second course, the patient developed joint pain (especially in both knees), headache, fatigue, nausea and an "inability to walk". Outcome: recovering/resolving. Action taken with levofloxacin: withdrawn/discontinued. This report was serious (permanent disability).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
ASTHMA			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ADVIL		Oral		PAIN			

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6166079

Reporter Source:

Study Report?: No

Sender Organization: JOHNSON AND JOHNSON

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6536107

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 019537 /

FDA Rcvd Date: 19-Nov-2008 **Mfr Rcvd Date:** 13-Nov-2008 **Mfr Control #:** US-BAYER-200715026NA

Patient Information:

Age: **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO	500 MG/		Total daily dose: 1 G Unit dose: 500 MG	URINARY TRACT INFECTION		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO			U				BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Arthralgia	U
Disability	U
Nerve injury	U
Unevaluable event	U

Case ID: 6536107

Event/Problem Narrative:

This spontaneous case was reported by a consumer, via E-mail, via Bayer MailDesk (in Germany), via West Haven Bayer Representative, in the United States and was received 28-Nov-2007. A male consumer, age unknown, treated with CIPRO (ciprofloxacin hydrochloride) for a urinary tract infection. Dosing/dates not provided. Concomitant conditions/history/concomitant medications not reported.The consumer reported experiencing CONSTANT PAIN IN ALL JOINTS and NERVE DAMAGE IN FEET. He reported being in great health before taking Cipro 17 months ago and "now I can't even walk 50 feet". He also reported that he can't work, my wife has left me and is about to lose my home. He wrote he, " is going to mail a letter to ALL the major new stations about what happened and the (b) (6) The problem is ongoing and is quoted as "ruined my life".FOLLOW UP RECEIVED 10-Dec-2007: BayerHealthcare Drug Safety attempted contact with consumer via email on 29-Nov and again on 03-Dec-2007 to request additional information regarding events. As of 10-Dec-2007, no response has been received.FOLLOW UP RECEIVED 16-Jan-2008: BayerHealthcare Drug Safety attempted to contact the consumer via telephone. A message was left requesting a call back for additional information regarding the events.FOLLOW UP RECEIVED 28-Jul-2008: Consumer sent another query via internet site providing a few additional details about his experience with Cipro. Consumer took Cipro for 10 days and has been "severely injured for over 2 years now". FOLLOW-UP RECEIVED 13-NOV-2008: The certified letter sent to the consumer was returned with additional information. Recieved Cipro 500 mg, 2 times per day (dates unspecified). He also experienced CRIPPLED for 27 months and N.D.I. (nos). No physician information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Case ID: 6536107

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6571148

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Outcomes:** DS,OT, **(A)NDA/BLA:** 021085 /

FDA Rcvd Date: 04-Sep-2015 **Mfr Rcvd Date:** 26-Aug-2015 **Mfr Control #:** US-BAYER-200815032NA

Patient Information:

Age: **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AVELOX	400 MG/QD	Oral		Sinusitis	25-Jan-2008	30-Jan-2008
2	Levaquin	500 MG/		500 mg, UNK	Sinusitis	12-Apr-2006	18-Apr-2006

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	AVELOX			A				BAYER
2	Levaquin			A				

Event Information:

Preferred Term (MedDRA Â© Version: 18.0)	ReC
Emotional distress	
Gait disturbance	
Injury	
Neuropathy peripheral	
Neuropathy peripheral	
Pain	
Pain	
Pain in extremity	
Paraesthesia	
Tendonitis	

Case ID: 6571148

Event/Problem Narrative:

This initial spontaneous report was received 26-Feb-2008 from a consumer via the Schering-Plough Call Center in the United States.

The female consumer, age unknown, took AVELOX (moxifloxacin hydrochloride) tablets in Jan-2008 for an unknown indication. Therapy dates and dosing details were not reported.

Medical history, concomitant conditions and concomitant medications were not reported.

She discontinued the Avelox after three days because she FEELS PINS AND NEEDLES IN HER LEGS, is WALKING DIFFERENTLY, AREAS OF HER BODY ARE SORE, she has TENDONITIS and NEUROPATHY, SHOOTING PAIN UP HER ARMS, and she FEELS LIKE PINS AND NEEDLES ARE SPREADING TO DIFFERENT PARTS OF HER BODY. The consumer was under treatment with a neurologist because the events were not subsiding.

Contact information for her physician was provided.

[Follow-up information received 01-Apr-2008] The patient's physician returned the MedWatch (case summary) confirming the events as reported. Additional information was provided as well.

Avelox start date was 25-Jan-2008 until its discontinuation on 30-Jan-2008. She was being treated for sinusitis she had for nine days. She had past therapy with Levaquin (levofloxacin) and has had similar symptoms in the past while not taking Avelox. It was not clear if she had the symptoms while taking the Levaquin.

[Addendum <26-SEP-2010>: This case was converted from the Clintrace database into Argus. The medical content of the case was not changed.]

**Follow-up (FU) received in the form of legal complaint on 26-Aug-2015: As per complaint co-suspect drug Levaquin was added.

Plaintiff was prescribed a 7 day course of Levaquin (500mg) on or about April 12, 2006 for sinusitis and took the medication as directed. Shortly thereafter, Plaintiff began experiencing SYMPTOMS RELATED TO PERIPHERAL NEUROPATHY IN HER EXTREMITIES. Then, on or about January 25, 2008, Plaintiff was prescribed a 10 day course of Avelox (400mg) for sinusitis and took the medication as directed. While using Avelox, Plaintiff's PERIPHERAL NEUROPATHY SYMPTOMS WORSENED. Plaintiff subsequently made an appointment with a neurologist, who diagnosed her with peripheral neuropathy on or about May 2008. Plaintiff continues to suffer from peripheral neuropathy today.

Case ID: 6571148

On an unspecified date, the plaintiff also experienced PERSONAL INJURIES/INJURIES/SEVERE AND PERMANENT PHYSICAL INJURIES, EMOTIONAL INJURIES and PAIN.

No causality was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**
Levaquin				

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Case ID: 6571148

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6579895

Case Information:

Case Type: NON-EXPEDITED **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:** 019537 /

FDA Rcvd Date: 21-Apr-2008 **Mfr Rcvd Date:** 09-Apr-2008 **Mfr Control #:** US-BAYER-200815464NA

Patient Information:

Age: 43 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO	250 MG/	Oral	Total daily dose: 500 MG Unit dose: 250 MG	URINARY TRACT INFECTION	01-Feb-2008	02-Feb-2008

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO			U				BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Arthralgia	U
Musculoskeletal pain	U
Neck pain	U
Pain in extremity	U
Tendon pain	U

Case ID: 6579895

Event/Problem Narrative:

This initial spontaneous report was received on 29-Feb-2008 from a consumer via the Schering-Plough Call Center in the United States.The 43 year-old female consumer received CIPRO (ciprofloxacin hydrochloride) 250 mg tablets for the treatment of a potential urinary tract infection. She took one 250 mg tablet in the morning, and one in the evening of 01-Feb-2008. Medical history and concomitant conditions included allergies to penicillin, cephalosporins, sulfonamides, Ultram (tramadol HCl), and other pain medications (nos). Concomitant medication was Aciphex (rabeprazole sodium) as needed (nos) and a course of steroids (nos) in Jan-2008. She reported herself to be in "good health".In Feb-2008, after taking the second dose of Cipro the evening of 01-Feb-2008, the consumer experienced PAIN AND TENDERNESS OF BOTH ACHILLES TENDONS, which spread to be PAIN IN BOTH KNEES, ELBOWS, HANDS, SHOULDERS and NECK. It is a BURNING PAIN that has increased in intensity over the course of one month. All tests are negative (nos). In addition to taking Motrin 800 mg 2-3 times per day, her physician has prescribed diazepam 2.5 mg several times per day. Her condition, described as "debilitating" by the consumer, has not improved. She reported that she could previously bicycle for 30-40 miles.[Follow-up information received 09-Apr-2008] The consumer's physician returned the MedWatch (case summary) confirming the events and annotated with additional information.Therapy dates for Cipro were 01-Feb to 02-Feb-2008. The course of steroids in Jan-2008 was specifically a Medrol Dose Pak (methylprednisolone) from 04-Jan-09-Jan-2008. The following laboratory tests performed 11-Feb-2008 were all normal: complete blood count, complete metabolic panel, urinalysis, thyroid stimulating hormone, Lyme enzyme immuno-assay. The patient was referred to an orthopedist and a neurologist.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
DRUG HYPERSENSITIVITY			UNKNOWN
DRUG HYPERSENSITIVITY			UNKNOWN
DRUG HYPERSENSITIVITY			UNKNOWN
DRUG HYPERSENSITIVITY			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6579895

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACIPHEX							
2	MEDROL		Oral			04-Jan-2008	09-Jan-2008	

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6588484

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS **(A)NDA/BLA:** 020634 /

FDA Rcvd Date: 13-May-2008 **Mfr Rcvd Date:** 06-May-2008 **Mfr Control #:** US-JNJFOC-20080303419

Patient Information:

Age: 45 YR **Sex:** Female **Weight:** 90.27 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	750 MG/	Oral		URINARY TRACT INFECTION		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN			N				

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Back pain	N
Blood immunoglobulin G increased	N
Burning sensation	N
Fatigue	N
Muscle twitching	N
Muscular weakness	N
Neuropathy peripheral	N
Pain	N
Pelvic pain	N
Sensory loss	N
Sexual dysfunction	N
Skin warm	N
Tendon disorder	N

Case ID: 6588484

Event/Problem Narrative:

This spontaneous report from a physician, who is also the patient, concerns a 45 year old female from the United States: #1-578947640. The patient's medical history and concurrent conditions included: hypothyroidism, constipation and pain. The patient's weight was 180 pounds. Other medical history included the patient had no know allergies, no history of drug abuse or illicit drug use, did not drink alcohol and did not smoke. The patient was treated with LEVAQUIN (levofloxacin, tablets, oral) at 750 mg once a day, initiated on 20-SEP-2007 to 22-SEP-2007 for a possible urinary tract infection. Concomitant medications included levothyroxine sodium for hypothyroidism, fish oil for nutritional support, cyanocobalamin for nutritional support, multivitamins for nutritional support and ibuprofen for pain. On 21-SEP-2007, the patient experienced generalised peripheral neuropathy and shooting electricity through the patient's back, legs, hands, feet and half of her face. As a result of these symptoms, the patient stopped taking levofloxacin on 22-SEP-2007. On an unknown date in SEP-2007, the patient experienced back pain that started as a lower thoracic pain that progressed to the entire back. The patient's skin also became hot to the touch, although there were no fever symptoms, and there was a loss of sensation in the genital area. In OCT-2007, the patient experienced fatigue, muscle twitching, tendon clicking, weak hand muscles, so that the patient could not hold anything heavy, and a loss of sensation in the hands, feet, back anal area and face. The patient underwent a series of test, and the only abnormal test results were that the patient's blood immunoglobulin G was elevated to a value of 1860 and her gamma globulin was slightly elevated. Laboratory data was provided as follows: Magnetic resonance imaging OCT-2007 brain: normal. OCT-2007 back and neck: normal. Lumbar puncture JAN-2008: normal. Copper blood level Unknown date: normal. Lyme test OCT-2007: normal. Other blood work OCT-2007: normal. The patient had slightly improved from peripheral neuropathy general, shooting electricity through the patient's back, legs, hands, feet and half of her face, back pain, loss of sensation in genital area, loss of sensation in hands, feet, back, anal area and face, tendon clicking, weak hand muscles, skin becoming hot to the touch and fatigue. The patient had recovered from muscle twitching in FEB-2008 and the outcome was unknown for elevated immunoglobulin G. Treatment with levofloxacin was withdrawn. This report was serious (permanent disability). Additional non-medically relevant information received on 07-APR-2008. Signed Authorisation for Disclosure of Medical Information form received giving contact details of 2 physicians. Additional information received from a physician on 06-MAY-2008 processed with information received from another physician received on 06-MAY-2008. Patient demographics were updated. The patient's medical history and concurrent conditions included hypothyroidism beginning 2007, menstrual migraine, and vitamin b12 deficiency. The patient's weight was 199 pounds. In SEP-2007, the patient developed bilateral hand numbness after taking levofloxacin for a urinary tract infection. The patient experienced numbness in low torso and in NOV burning in pelvic area and burning in legs. The patient had nerve conduction studies, the results of which are unknown. Magnetic resonance imaging was performed for brain and cervical thoracic spine- all negative for degenerative changes. Lyme, anti-nuclear antibody, renal function, C-reactive protein, eythrocyte sedimentation rate were all normal. The patient had a neurological exam which, showed no abnormal findings. At the time of this report, the patient had partially recovered from the events.

Case ID: 6588484

Relevant Medical History:

the patient had no know allergies, no history of drug abuse or illicit drug use, did not drink alcohol and did not smoke

Disease/Surgical Procedure	Start Date	End Date	Continuing?
HYPOTHYROIDISM	2007		YES
CONSTIPATION	04-Sep-2007		YES
MIGRAINE			UNKNOWN
PAIN			YES
VITAMIN B12 DEFICIENCY			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
NUCLEAR MAGNETIC RESONANCE IMAGING	back and neck: normal				N
NUCLEAR MAGNETIC RESONANCE IMAGING	brain: normal				N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ADVIL		Oral		PAIN			
2	FISH OIL		Oral		NUTRITIONAL SUPPORT			
3	MULTIVITAMINS		Oral		NUTRITIONAL SUPPORT			
4	SYNTHROID		Oral		HYPOTHYROIDISM			
5	VITAMIN B12		Oral		NUTRITIONAL SUPPORT			

Case ID: 6588484

Reporter Source:

Study Report?: No **Sender Organization:** ORTHO

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6620284

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 019537 /

FDA Rcvd Date: 02-May-2008 **Mfr Rcvd Date:** 23-Apr-2008 **Mfr Control #:** US-BAYER-200819763NA

Patient Information:

Age: **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO	500 MG/	Oral	Total daily dose: 500 MG Unit dose: 500 MG	URINARY TRACT INFECTION	01-Sep-2007	05-Sep-2007

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO	2 Hour		U				BAYER

Event Information:

Preferred Term (MedDRA © Version: 17.0)	ReC
Fatigue	
Joint swelling	
Lymphadenopathy	U
Muscular weakness	
Myalgia	
Neuropathy peripheral	U
Pyrexia	U
Tremor	

Case ID: 6620284

Event/Problem Narrative:

This initial spontaneous report was received 10-Apr-2008 from a consumer's mother via the Schering-Plough Call Center Representative in the United States.A female consumer, age unknown, received Cipro (ciprofloxacin hydrochloride) 500 mg for a 5 day course beginning on 01-Sep-2007. The indication, lot number and expiration date were not provided. Relevant medical history and concomitant conditions were not reported. She had taken one dose of Diflucan (fluconazole) the day before starting Cipro therapy.The consumer experienced painful and diffuse muscle symptoms-described as muscle tremors, muscle weakness and joint swelling after her first dose of Cipro on 01-Sep-2007. A skin biopsy was done and "toxic involvement was observed" as FIBER NEUROPATHY. She also experienced LARGE LYMPH NODES, FEVER of 100.3 and such extreme fatigue her mother said her daughter "cannot even walk a city block". Again, according to her mother, her symptoms are worsening even now 6 months after finishing Cipro therapy and she had to take a medical leave of absence from school. Her daughter has been tested for "everything" and is clear of all viruses and diseases. No further information was provided concerning treatment, action taken or outcomes.[Follow-up information received 22-Apr-2008] Drug Safety contacted the reporter who provided additional information.Indication for Cipro therapy was urinary tract infection. There was no relevant medical history and no concomitant conditions. The events began two hous after the initial dose of Cipro and remained ongoing. No treatment had been provided as the physicians do not have a diagnosis. The consumer has had multiple tests including being tested for "1000 viruses" and bloodwork, all of which were within normal limits.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**
DIFLUCAN	31-Aug-2007		PRODUCT USED FOR UNKNOWN INDICATION	

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Case ID: 6620284

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6657012

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 020634 /

FDA Rcvd Date: 04-Jun-2008 **Mfr Rcvd Date:** 09-May-2008 **Mfr Control #:** US-JNJFOC-20070401077

Patient Information:

Age: 41 YR **Sex:** Female **Weight:** 54.43 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	500 MG/	Oral		SINUSITIS		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN			U				

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Muscle spasms	U
Myalgia	U
Neurological symptom	U
Sensory disturbance	U
Tendon pain	U

Case ID: 6657012

Event/Problem Narrative:

This spontaneous report from a patient concerns a 41 year old female from United States: 1-427413989. The patient's medical history was not reported. The patient's weight was 120 pounds. Other medical history included the patient has allergies to "some things" does not abuse drugs and does not smoke cigarettes or consume alcohol. The patient was treated with LEVAQUIN levofloxacin (tablets, oral) 500 mg once a day, initiated on 09-MAR-2007 to 03-APR-2007 for sinus infection. On 03-APR-2007, the patient experienced muscle pain in legs. Concomitant medications were not reported. The patient had not recovered from muscle pain in legs. Treatment with levofloxacin was withdrawn. This report was not serious. Case upgraded based on additional information received from a patient on 09-MAY-2008. The patient reported that she was previously a healthly mother who had taken two, 10 day courses of fluoroquinolones with no apparent problems. In MAR-2007, the patient was prescribed a 28 day course of fluoroquinolone and a nasal corticosteriod spray (concomitant medication) for a sinus infection. Within a couple of weeks, on a unknoen date the patient developed vibration sensations in her legs. On an unknown date, 25 days after starting levofloxacin the patient experienced cramping in legs, and was advised to discontinue treatment by an ENT nurse. On the following day, 26 days after starting levofloxacin, the patient developed severe cramping, tendon pain and several neurological symptoms (unspecified). The patient was seen by four internal medicine physicians, a neurologist, gynecologist, rheumatologist, infectious disease physician, physical therapist, allergist and a ENT. According to the patient all the health care professionals stated that the fluoroquinolones had no side effects, except the rheumatologist, who stated that they definitely could cause tendon issues. The patient outcome was unknown for cramping in legs, tendon pain, neurological symptoms and vibration sensations in her legs. The patient stated she had a "casade of debilitating symptoms", some of which were continuing at the time of reporting. This report was serious (permanent disability, medically significant).

Relevant Medical History:

the patient has allergies to "some things" does not abuse drugs and does not smoke cigarettes or consume alcohol

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Case ID: 6657012

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CORTICOSTERIOD		Nasal		SINUSITIS			

Reporter Source:

Study Report?: No **Sender Organization:** ORTHO

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6672101

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS **(A)NDA/BLA:** 019537 /

FDA Rcvd Date: 19-Jun-2008 **Mfr Rcvd Date:** 10-Jun-2008 **Mfr Control #:** US-BAYER-200825404NA

Patient Information:

Age: 36 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO		Oral		URINARY TRACT INFECTION		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO			U				BAYER

Event Information:

Preferred Term (MedDRA © Version: 17.0)	ReC
Arrhythmia	U
Arthralgia	U
Carpal tunnel syndrome	U
Fatigue	U
Fibromyalgia	U
Gastrointestinal disorder	U
Multifocal motor neuropathy	U
Pain	U

Case ID: 6672101

Event/Problem Narrative:

This spontaneous case was received on 10-Jun-2008 in the United States by an internet website via Ortho-McNeil Janssen Pharmaceutical Safety Operations via Schering-Plough Call Center Representative. This is case 1 of 7 by this reporter. Please refer to associated cases 200825406NA, 200825407NA, 200825409NA, 200825411NA, 200825412NA and 200825415NA.A 36-year-old male consumer received Cipro (ciprofloxacin hydrochloride) for a "possible " urinary tract infection on an unspecified date. Concomitant diseases, relevant medical history, and concomitant medications were not reported. On an unspecified date, consumer developed chronic debilitating MULTIFOCAL NEUROPATHY, FIBROMYALGIA, CHRONIC FATIGUE, GASTROINTESTINAL PROBLEMS, HEART ARRHYTHMIA requiring pacemaker, CARPAL TUNNEL SYNDROME, CHRONIC MULTIPLE JOINT PAINS and CHRONIC PAIN. Duration for these events indicated as 5 years (nos). Consumer is disabled. The details concerning onset dates/times, actions taken, treatments and the outcomes were not provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Case ID: 6672101

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6707623

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 019537 /

FDA Rcvd Date: 23-Jul-2008 **Mfr Rcvd Date:** 15-Jul-2008 **Mfr Control #:** US-BAYER-200211737BWH

Patient Information:

Age: 76 YR **Sex:** Female **Weight:** 86 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO	250 MG/	Oral	Total daily dose: 500 MG Unit dose: 250 MG	URINARY TRACT INFECTION	03-Mar-2001	Mar-2001

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO	3 Day		U				BAYER

Event Information:

Preferred Term (MedDRA © Version: 17.1)	ReC
Activities of daily living impaired	U
Adverse event	U
Arthralgia	
Arthropathy	U
Bladder discomfort	U
Bone pain	U
Burning sensation	
Depression	U
Discomfort	
Erythema	
Feeling abnormal	
Formication	
Gait disturbance	

Case ID: 6707623

Preferred Term (MedDRA Â Version:	17.0	ReC
Hypoaesthesia		
Joint dislocation		
Joint injury		U
Limb discomfort		U
Neuropathy peripheral		U
Oedema peripheral		U
Pain in extremity		
Skin odour abnormal		
Tremor		U
Varicose vein		U
Vein discolouration		

Event/Problem Narrative:

This initial spontaneous report was provided by a consumer in the United States, and was received on 05-MAR-2002. Additional information was received from the physician on 06-MAR-2002.A 76-year-old Caucasian female was treated with CIPRO (ciprofloxacin hydrochloride) for the indication urinary tract infection at a dose of 1000 mg daily for 5 days during MAR-2002. The consumer has a history of occasional urinary tract infections. Concomitant medications include LEVOTHROID (levothyroxine sodium) which the consumer has been taking for 15 years.Sometime after the third day of CIPRO (ciprofloxacin hydrochloride) use, the consumer developed LEGS SNAPPING, CRACKLING AND POPPING, KNEES FIRE RED, SWELLING ABOVE KNEES, and SENSATION OF SKIN CRAWLING ON LEGS. The consumer reported the events to her physician who found nothing on examination. She completed the course of CIPRO. An MRI of her legs and knees showed degenerative and arthritic changes. She has been evaluated by a neurologist and an orthopedic physicians. No further diagnoses were given by any of the physician. The reporting physician feels the events are totally unrelated to use of CIPRO (ciprofloxacin hydrochloride). The consumer reports the symptoms of LEGS SNAPPING have subsided. The events KNEES FIRE RED, SWELLING ABOVE KNEES are ongoing at the time of report. The outcome of the event SENSATION OF SKIN CRAWLING ON LEGS was not reported.F/U 22-APR-2002 and 25-APR-2002: Event onset date and dates of therapy were previously inaccurately reported as MAR-2002. The patient received CIPRO and the previously reported events began in MAR-2001.Since MAR-2001, the consumer has been evaluated by several physicians, including an orthopedist, an emergency room visit and a neurologist. About 2 months after her symptoms began, she reports her legs smell so she went to an orthopedist. The doctor felt the symptoms were not an orthopedic problem. An emergency room physician who evaluated her, felt she had INJURY TOTHE KNEE

Case ID: 6707623

JOINT. She was given an injection for pain and released. She has been treated with amitriptyline for pain, but it caused blurry vision so the medication was stopped. She has been treated with VIOXX (rofecoxib), which did not alleviate the symptoms. She reports that she also is experiencing LEGS RED. The symptoms were ongoing at the time of report.The consumer reports she has recently been diagnosed with NEUROPATHY. The symptoms began in MAR-2001 when she reported experiencing a sensation of skin crawling on legs and feet hot and cold. Additional symptoms include burning sensation from hips to toes and legs feel heavy like lead (onset dates unknown).The consumer reports the she has a thyroid condition (nos).[This consumer also reports two additional cases: see cases 200214114BWH and 200213911BWH.]F/U 06-MAY-2002: Additional symptoms SWELLING (FEET AND LEGS) and HIP PAIN, both of which began recently. She has DIFFICULTY WALKING due to the pain in her hips. The patient feels DEPRESSED over symptoms. The patient again reports a burning sensation from her legs to feet. She reported this to her physician who attributes the symptoms to her neuropathy. She is being treated with NEURONTIN (gabepentin) for the neuropathy.[This consumer reported another additional case: see case 200214229BWH]F/U 20-MAY-2002: Her symptoms have worsened. She also reported symptoms of numbness in her legs down to her feet and pain in back. She was evaluated by her physician about 2 weeks ago. Her physician is aware of the symptoms. She takes prednisone as needed for her symptoms and she is still depressed regarding the chronic nature of her discomfort.F/U 31-MAY-2002: Her neuropathy symptoms are ongoing and worsening. She is unable to participate in activities that she did previous to the onset of her symptoms. The consumer reports CIPRO was prescribed for a bladder infection. No other new information.[This consumer reported an additional case: see 200215531BWH]F/U 19-JUN-2002: Her symptoms are ongoing and she is using cortisone intermittently as needed. She reports PAIN IN BONES OF HER REAR END. The patient was encouraged to follow-up with her physician. No other new information was provided.F/U 09-JUL-2003: New events: SHAKING SO VIOLENTLY, BURNING IN THE BLADDER, NOT ENJOYING LIFE ANYMORE, COULD NO LONGER DRIVE; an additional symptom of NEUROPATHY reported: legs very painfulThe consumer sent another handwritten letter detailing the previously reported events. Newly reported information included names of orthopedic physician, neurologist and hospital emergency room physician. The CIPRO start date was reported as 03-MAR-2001 and the dosage was changed from 500mg twice daily to 250mg twice daily. The consumer stated that the previously reported event INJURY TO KNEE JOINT resulted in a "long term disability" according to the emergency room physician. It was not clear from the consumer's letter if she was admitted to the hospital or treated and released. Diagnostic tests included x-rays and MRI, but the results of these tests were not reported. Treatment was described by the consumer as "ice packs, a needle in my arm for pain and medicine that made me worse and affected my eyes". In addition, the consumer also experienced SHAKING SO VIOLENTLY, BURNING IN THE BLADDER, NOT ENJOYING LIFE ANYMORE and COULD NO LONGER DRIVE. The onset date of these events were not reported; outcome of these events was reported as ongoing. F/U 04-AUG-2003: Consumer returned the signed patient consent form with permission to contact the primary physician along with another handwritten letter detailing previously reported events and treatments. She denied having back pain, and also mentioned that she had previously being treated with sulfamethoxazole for bladder infection. Symptoms of burning in right knee and knee

Case ID: 6707623

joint feels like going out of place were added to the previously reported INJURY TO KNEE JOINT. SHAKING SO VIOLENTLY that the she previouslyreported had nothing to do with CIPRO, it was due to the medications (nos) given to her in the emergency room. In a follow-up phone call later the same day, the consumer reported that the NEURONTIN has not helped her condition and the amitriptyline caused blurry vision in one eye.F/U 09-JUL-2003: New events; SHAKING SO VIOLENTLY, BURNING IN THE BLADDER, NOT ENJOYING LIFE ANYMORE, COULD NO LONGER DRIVE; an additional symptom of NEUROPATHY reported: legs very painful.F/U 04-AUG-2003: "Pain in back" was deleted as a symptom of NEUROPATHY; "burning in right knee" and "knee joint feels like going out of place" were added as symptoms of INJURY TO KNEE JOINT.F/U 25-AUG-2003: Physician confirmed the adverse events as reported without adding any additional information. F/U 25-Apr-2005: New event: LEGS LOOK LIKE VEINS ARE BULGING OUT; she developed disease of the joints (previously reported as legs snapping, crackling and popping; knees fire red; swelling above knees; injury to knee joint) and disease of the central nervous system (previously reported as neuropathy; depressed; shaking so violently). She also stated that now her LEGS LOOK LIKE the VEINS ARE BULGING OUT; the onset date and action taken were not reported. She stated that the back of her leg was burning at the time of the report, and that she will probably need a cortisone shot.The consumer reported having being treated by an orthopedic physician for 2 1/2 months. She stated that her (primary care) physician of 25 years prescribed the Cipro tablets. She would not provide any further consent to contact her physicians.F/U 15-JUL-2008: Consumer took Cipro for 3 days (prev reported as 5 days). New sx: "veins turning pink and blue and all different colors". New event BODY GOES OUT OF JOINT (whole body is horrible/nos)._____BAYER Comment;All events considered non-serious. FEET HOT AND COLD unlisted, other events listed. Causal relationship between reported events and ciprofloxacin cannot beexcluded due to temporal association; alternative explanation unknown. F/U 22-Apr-2002 and 25-Apr-2002: Additional AEs: INJURY TO KNEE JOINT; NEUROPATHY. INJURY TO KNEE JOINT and NEUROPATHY (symptoms [sx] burning from hips to toes, feet hot and cold, sensation of skin crawling on legs, legs felt heavy like lead, legs smell, and legs red) are considered serious (important medical events). INJURY TO KNEE JOINT and NEUROPATHY are not listed for Cipro (ciprofloxacin hydrochloride). However, report lacks information on temporal relationship of event NEUROPATHY; therefore cannot be assessed for causal association with cipro. It's conceivable thyroid condition could lead to neuropathy. This cannot, however, be proven on evidence available. Based on information received, proven alternative explanation for LEGS SNAPPING, CRACKLING AND POPPING, KNEES FIRE RED, SWELLING ABOVE KNEES, and INJURY TO KNEE JOINT; evidence suggests events should not be attributed to cipro; alternative explanation of pre-existing condition (arthrosis/arthritis of knee joint) more likely.F/U 06-May-2002: Additional sx (neuropathy): swelling (feet and legs), hip pain, difficulty walking, depressed; no further change.F/U 20-May-2002: Additional sx (neuropathy); no further change. Correction: "depressed" listed as separate diagnosis, not sx of neuropathy. DEPRESSED non-serious/listed/excluded (no temporal association); alternative explanation of concomitant disease (neuropathy).

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 6707623

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
THYROID DISORDER			UNKNOWN
URINARY TRACT INFECTION			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	LEVOTHROID							
2	NEURONTIN							
3	PREDNISONE							
4	VIOXX							

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 7133559

Case Information:

Case Type: NON-EXPEDITED **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 021085 /

FDA Rcvd Date: 29-Sep-2009 **Mfr Rcvd Date:** 23-Sep-2009 **Mfr Control #:** US-BAYER-200933887NA

Patient Information:

Age: **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AVELOX	400 MG/			BRONCHITIS	Apr-2009	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	AVELOX	1 Month		U				BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Arthralgia	U
Gait disturbance	
Oedema peripheral	U
Pain in extremity	
Scab	U
Skin erosion	U
Tendon rupture	U
Wheelchair user	

Case ID: 7133559

Event/Problem Narrative:

This web based a report from Lawyers and Settlements.com website was received 23-Sep-2009 from Bayer Legal, referring to a male consumer.Starting in Apr-2009, a male consumer used AVELOX (moxifloxacin hydrochloride) for bronchitis.Relevant history/concomitant conditions/concomitant medications: not provided.He stated the Avelox got rid of the bronchitis but almost got rid of him; he stated now he had one foot on a banana peel and the other on Avelox. By 04-May-2009, his right foot was painful, he thought it was a cramp so he took some aspirin. He was limping around the next day and by bedtime his right foot was swollen almost to twice its size. He took a pain pill (nos) and went to bed. On 05-May-2009, he was limping around all day with a swollen foot; the following day, he could barely walk. This time he thought it was gout so he called his doctor. He had an x-ray which showed no broken bones and an angiogram which showed no blood clots. He then had a CAT scan which showed a RUPTURED TENDON; two weeks later, he was in a wheelchair. His lung doctor asked what he was doing in a wheelchair and asked which medications he was taking. When he mentioned the Avelox, he stated he was told that this was the problem. He was advised to stop taking the Avelox; he had one pill left which he discarded. He stated he was surprised and upset and he was not sure if he would ever walk again. He was in the wheelchair for another 3 weeks; eventually the swelling went down, but on 21-Jul-2009, his RIGHT FOOT was SWOLLEN again. It took 7 days for the swelling and pain to subside. He then had a SCAB ON his RIGHT LEG above the ankle. He stated when he had this problem, his SHIN BROKE OUT INTO one MASSIVE SKIN EROSION, like something was eating his skin. He started putting antibiotics (nos) on it and it took about a month to heal. He stated it looked ok but he still had PAIN IN his RIGHT ANKLE because of Avelox. He stated he checked online and saw that the only cure was an operation. He stated no one had told him about the FDA warning for Avelox and if he knew, he would not have taken it. He stated he signed a contract to go forward with a lawsuit and that Avelox kept him from doing a lot of things so he should be compensated for that and the medical costs.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Case ID: 7133559

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 7219290

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 020634 /

FDA Rcvd Date: 05-Mar-2010 **Mfr Rcvd Date:** 15-Jan-2010 **Mfr Control #:** US-JNJFOC-20091101702

Patient Information:

Age: 38 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	250 MG/	Oral			07-Oct-2009	08-Oct-2009
2	LEVAQUIN	500 MG/	Oral		URINARY TRACT INFECTION	07-Oct-2009	08-Oct-2009

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN			U	CP11702			
2	LEVAQUIN			U	CP11702			

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Arthralgia	U
Dry eye	U
Eosinophilia	U
Fatigue	U
Insomnia	U
Monocytosis	U
Myalgia	U
Photosensitivity reaction	U
Tendonitis	U
Vitamin D decreased	U

Case ID: 7219290

Event/Problem Narrative:

This spontaneous report from a physician (patient's father) via company representative concerns a female patient of unknown age from the United States: 1-887907530. The patient's height, weight and medical history were unknown. The patient was treated with levofloxacin (tablets, oral) 500 mg once a day, initiated in SEP-2009 for urinary tract infection. Concomitant medications were not reported. After a dose of levofloxacin, the patient experienced pain in both calves. The dose of levofloxacin was decreased from 500 mg to 250 mg and the patient experienced tendonitis of both ankles and knees. Treatment with levofloxacin was withdrawn on an unknown date. The patient had not recovered from tendonitis of both ankles and knees. This report was serious (medically significant). Additional information received on 07-DEC-2009. This report concerns a 38 year old healthy active athletic female. Patient demographics were updated. The patient was treated with levofloxacin (tablets, oral, batch NDC-00045-1525-50) (tablets, oral, batch CP11702) 500 mg once a day, initiated on 07-OCT-2009 and 250 mg once a day, initiated on 08-OCT-2009 for urinary tract infection. In OCT-2009, the patient experienced tendonitis of both ankles and knees (previously reported as SEP-2009) arthralgias, dry eyes, fatigue, insomnia, myalgia and increased photosensitivity and in an unknown date, the patient experienced monocytosis, eosinophilia and had a low vitamin D level (shortly after injection). The patient had not recovered from myalgia, arthralgias, increased photosensitivity, dry eyes, fatigue and insomnia and outcome was unknown for eosinophilia, low vitamin D level and monocytosis. This report was serious (disability, medically significant). Additional information received from a physician on 15-JAN-2010. The other identification number as: 2009SA007910. In OCT-2009, the patient experienced monocytosis, eosinophilia and low vitamin d level.

Relevant Medical History:

The patient had no allergies and no history of drug abuse.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Case ID: 7219290

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** ORTHO

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 7416727

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 020634 /

FDA Rcvd Date: 27-Sep-2011 **Mfr Rcvd Date:** 20-Sep-2011 **Mfr Control #:** US-JNJFOC-20100601517

Patient Information:

Age: 49 YR **Sex:** Female **Weight:** 74.84 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	500 MG/	Oral		BRONCHITIS	29-Dec-2009	05-Jan-2010
2	LEVAQUIN	500 MG/	Oral		SINUSITIS	29-Dec-2009	05-Jan-2010

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN			N				
2	LEVAQUIN			N				

Event Information:

Preferred Term (MedDRA Â© Version: 17.0)	ReC
Arthralgia	N
Mania	N
Oedema peripheral	N
Pain in extremity	N
Tendon injury	N
Tendon rupture	N
Tendonitis	N

Case ID: 7416727

Event/Problem Narrative:

This spontaneous report was received from a 49-year-old female patient reporting on herself from the United States: 1-1033787070. The patient's height was 64 inches and weight was 165 pounds. The patient's medical history and concurrent conditions included: alcohol use (very rare), anxiety, depression, high blood pressure, high cholesterol, smoking (10 per day), and thyroid replacement. The patient's history of allergies was not reported. The patient had no history of drug abuse or illicit drug use. After the first day of taking a tablet of levofloxacin (tablets, oral) 500 mg once a day, initiated on 29-DEC-2009 to 05-JAN-2010 for bronchitis, and on 30-DEC-2009 she developed a painful, swollen right hand. Her physician advised the patient to continue with the course of therapy. The (b) (6) completing the 7 tablet course, on (b) (6) she experienced sudden onset of excruciating pain in her left knee while at work. Later, that evening she was seen in the emergency department and given oral steroids to treat the event. She stated that she also felt "manic" in JAN-2010 and she attributed that to levofloxacin. She also had a continuous, dull, aching pain in both knees which made ambulation difficult. She stated that she was unable to work and was on disability. Concomitant medications included duloxetine hydrochloride for depression, atorvastatin calcium for high cholesterol, metoprolol succinate for high blood pressure, levothyroxine sodium for thyroid replacement, lorazepam for anxiety, and clonazepam for anxiety. The dose of levofloxacin was not changed. The patient had not recovered from difficulty ambulating and aching in knees, had recovered from right hand swollen and painful right arm in 2010 and outcome was unknown for left knee pain, tendinitis, leg and manic feeling. This report was serious (permanent disability, medically significant). This case, from the same reporter is linked to 20100601777. Additional case version opened on 10-JUL-2010. Information was received from levofloxacin line listing forwarded on to us by Daiichi Sankyo. This case version was created for the purpose of quality improvement. Upon review the following corrections were made: the local case identification number was updated. Additional information received from an attorney on 20-SEP-2011: Documents were received in the form of Legal Summons and Complaint: 2:11-cv-03289-VEH. The patient was treated with levofloxacin initiated in late 2009 for sinusitis. The patient experienced a tendon injury in her knee and hand and also experienced a tendon rupture. The patient underwent extensive physical therapy and treatment. The patient's outcome for tendon rupture and tendon injury was not reported. Reporter screen was updated.

Relevant Medical History:

the patient's history of allergies was unknown. The patient had no history of drug abuse or illicit drug use.

Disease/Surgical Procedure	Start Date	End Date	Continuing?
ALCOHOL USE			YES
ANXIETY			UNKNOWN
BLOOD CHOLESTEROL INCREASED			UNKNOWN

Case ID: 7416727

DEPRESSION	UNKNOWN
HYPERTENSION	UNKNOWN
THYROID HORMONE REPLACEMENT THERAPY	UNKNOWN
TOBACCO USER	YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CYMBALTA		Oral		DEPRESSION			
2	KLONOPIN		Oral		ANXIETY			
3	LEVOXYL		Oral		THYROID HORMONE REPLACEMENT THERAPY			
4	LIPITOR		Oral		BLOOD CHOLESTEROL INCREASED			
5	LORAZEPAM		Oral		ANXIETY			
6	TOPROL XL		Oral		HYPERTENSION			

Reporter Source:

Study Report?: No **Sender Organization:** ORTHO

Literature Text:

Case ID: 7416727

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 7452557

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 021085 /

FDA Rcvd Date: 04-Aug-2010 **Mfr Rcvd Date:** 28-Jul-2010 **Mfr Control #:** US-BAYER-201026131NA

Patient Information:

Age: 83 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AVELOX	400 MG/	Oral	Total daily dose: 400 MG Unit dose: 400 MG	SINUSITIS	23-Apr-2010	26-Apr-2010

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	AVELOX	1 Day		U				BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Asthenia	U
Dizziness	U
Hypoaesthesia	U
Mobility decreased	U
Myalgia	U
Pain	U
Pain in extremity	U
Tendon disorder	U
Tendon pain	U

Case ID: 7452557

Event/Problem Narrative:

Source of report and patient demography:This spontaneous case report was received on 22-Jun-2010 from a Merck in the United States, referring to an 83 year-old male consumer. Medical and drug history:Patient had concomitant condition of Hypertension. Concomitant drugs have been given. For details see section "Concomitant Drugs" at the end of this report.Suspect drug(s), timing and conditions surrounding the onset of the reaction(s):Patient received AVELOX (moxifloxacin hydrochloride) for sinus infection. Administration began on 23-Apr-2010, for a duration of 4 days at a total daily dose of 400 MG oral with lot UNK, expiration date unknown. The progression of the event(s) and its (their) outcome in the patient:Consumer only took 4 pills, because he started to feel EXTREMELY DIZZY, BAD MUSCLE PAIN, TENDON PAIN, EVERY OTHER PAIN IMAGINABLE and he COULD NOT WALK TO THE MAILBOX.He stated that he went to "multiple doctors including cardiologists, neurologists, etc and did many tests which came out fine but he did not recovere.AVELOX was withdrawn.The original reporter's clinical assessment:No assessment was given. *FU received from consumer on 28-Jul-2010:Concomitant drug included high blood pressure pill. On 23-Apr-2010, consumer also experienced NUMBNESS, WEAKNESS, and PAIN IN LEGS which started as soon as he started taking Avelox. He also experienced dizziness, and his TENDONS WERE POPPING AND SNAPPING ALL OVER BODY. Consumer stated he was in perfect health and walked 2 miles a day prior to taking Avelox. His physician order 7 different tests, but was unable to determine what was wrong with him. Consumer sought medical attention but he had not recovered at time of report.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
HYPERTENSION			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 7452557

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ASPIRIN							
2	HIGH BLOOD PRESSURE PILL		Oral		HYPERTENSION			

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 7943437

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:** 019537 /

FDA Rcvd Date: 04-Oct-2011 **Mfr Rcvd Date:** 18-Aug-2011 **Mfr Control #:** US-BAYER-2011-038047

Patient Information:

Age: **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO		Oral	UNK	URINARY TRACT INFECTION		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO							BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Aphagia
Arthralgia
Asthenia
Burning sensation
Dizziness
Fatigue
Gait disturbance
Malaise
Muscle tightness
Muscular weakness
Musculoskeletal discomfort
Musculoskeletal pain
Myalgia

Case ID: 7943437

Rotator cuff syndrome

Tendonitis

Vision blurred

Event/Problem Narrative:

Serious, listed and related case. This spontaneous case report was received on 03-May-2011 from a registered nurse in the United States via Merck call center in the United States (ref# US11-025277). The report refers to the reporter's (father) 28 year-old daughter who received Cipro (ciprofloxacin) and experienced severe tendonitis, severe weakness(severe fatigue, can barely walk or get out of bed) and dizziness The patient’s has no relevant medical history. The patient's relevant concomitant medications and relevant past drug history is unknown. On an unspecified date, patient started to take oral Cipro (ciprofloxacin) for urinary tract infection. It was not reported whether Cipro (ciprofloxacin) was used previously in this patient. On an unspecified date, after seven out of ten day course of Cipro (ciprofloxacin), patient was admitted to the ER (emergency room) for severe tendonitis, severe weakness(severe fatigue, can barely walk or get out of bed) and dizziness Relevant laboratory data are unknown. As of 03-May-2011 (day of report), she no longer takes Cipro (ciprofloxacin) . However, events are ongoing. No further details were reported. ***Follow-up received on 18-AUG-2011*** The consumer called the company on 18-AUG-2011. She provided her date of birth and the name of her physician. She stated that her father called in an adverse event (AE) for her 6 months ago, because she took Cipro for 3 days ' and it totally ruined every aspect of her life'. Contact information was obtained. The consumer wanted someone in the Legal Department to contact her because her father was receiving letters from Bayer asking for her medical records and she wanted the requests to stop. Caller then hung up. The consumer called back a second time on 18-AUG-2011. She wanted to make sure that her safety report had been documented. She provided additional information about the adverse events she experienced. She started using Cipro for a bladder infection. After taking about 7 pills, she FELT SICK, her MUSCLES WERE WEAK, she had pain and weird burning sensations. Besides, she experienced DIZZINESS and was unable to focus her eyes. She also had tightness in calfs and achilles tendons of both legs. After she stopped taking CIPRO, the symptoms got ten times worse. She had to drop out of school and cancel her wedding. She still could not walk right or ride a bike. It felt like her shoulders would disconnect from her body and her rotator cuff tendons hurt. She was diagnosed with TOTAL TENDONITITS. The MUSCLES IN her JAW HURT and she could not eat right. She was on crutches and used a cane. Consumer also stated that she still had hip, knee and shoulder pain, muscle weakness and extreme fatigue. The consumer was never admitted to the hospital. Consumer was on Tramadol and other natural supplements.

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 7943437

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	NATURAL SUPPLEMENTS							
2	TRAMADOL HYDROCHLORIDE							
3	VICODIN							

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8318839

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 03-Jan-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8018732

Patient Information:

Age: 53 YR **Sex:** Female **Weight:** 62.6 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	500 MG/QD	Oral	1 tablet	SINUSITIS	11-Feb-2011	15-Feb-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN				092550TP515			
2	LEVAQUIN				0925-50 TP515			

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Arthralgia
Dizziness
Eye irritation
Eye swelling
Hypoaesthesia oral
Ocular hyperaemia
Pain in extremity
Paraesthesia
Plantar fasciitis
Visual impairment
Vitreous floaters

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8318839

Event/Problem Narrative:

I had a sinus infection with 101.8 fever. I am allergic to penicillin and mycin drugs so the doctor gave me Levaquin 500mg tablet. In 4 days I stopped medication because I had pains in my foot, burning bloodshot eyes, tingling fingers, felt dizzy and my tongue felt numb. I reported it to the doctor and she gave me Avalox. I stopped that medication in 2 days due to pain in my hands and knees. Since this time, I have been to the doctor for redness, swelling, burning and "floaters" in my eyes as well as drastic vision change. He gave me Padaday -7/30/2011-and told me it was allergies and I now need progressive lenses as my vision has changed. I went to the podiatrist who told me I had plantar faciitis and I purchased inserts, new shoes and when that did not help he wanted to use shock wave therapy or a cortisone shot or more medicine -which I refused-In fact the exercises and treatments made my pain unbearable. I researched foot pain and was directed to the list of side effects from Levaquin and realized this fit my symptoms. At this point I am waiting for an MRI to see if I have torn Achilles tendons or Achilles tendinitis.
WILSONJ: |*********| 2012-01-03-09.55.16 |*********| USFDAMWVOLUNTARY_198828_11810_20120102.xml
Route To: AERS : Electronic

Relevant Medical History:

Allergies: Penicillin, Ace Inhibitors, TAO, Mycin Drugs Race: Caucasian Not pregnant but have 4 children Never smoked, drink alcohol 2 times a month No preexisting foot problems, no preexisting eye problems -used magnifying/reading glasses from drug store- No known kidney, liver, joint problems. High cholesterol treated with diet and -Until recently- exercise

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
VISION TEST					
FOOT XRAYS					

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AVELOX	QD	Oral	1 tablet	REFUSAL OF TREATMENT BY PATIENT	16-Feb-2011	17-Feb-2011	

Case ID: 8318839

Reporter Source:

Study Report?: No

Sender Organization:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8326901

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 09-Jan-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8030396

Patient Information:

Age: 58 YR **Sex:** Male **Weight:** 88.45 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO		Oral	standard	SINUSITIS	26-Nov-2006	05-Dec-2006
2	LEVAQUIN				PROSTATE INFECTION		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO		N					
2	LEVAQUIN		N					

Event Information:

Preferred Term (MedDRA Â© Version: 17.0) **ReC**

Cardiac fibrillation
Meniere's disease
Neuropathy peripheral
Paraesthesia
Sensory disturbance
Sudden hearing loss

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8326901

Event/Problem Narrative:

After multiple prescriptions of Cipro, Levaquin and Floxin, I began to have several neurological problems, including but not limited to, peripheral neuropathy, nerve pulsation sensations, sudden hearing loss and other "Meniere's disease" symptoms, tingling sensations all over my body, and heart fibrillations. My primary care physician and a neurologist both thought I might have ALS, but subsequent tests ruled that out. While some of these have subsided, I still have persistent peripheral neuropathy, heart fibrillations -less often than before-, and some of the neuro-sensory aberrations described above. WILSONJ: |*********| 2012-01-09-09.29.36 |*********| USFDAMWVOLUNTARY_199134_12073_20120107.xml Route To: AERS : Electronic

Relevant Medical History:

Light alcohol consumption. Allergic to Ceclor, amoxycillin, and erythromycin. Poss bly not able to tolerate Vicadin now as I had an adverse reaction to it after a surgery some years ago.

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
ELECTROMYOGRAM NERVE CONDUCTION TEST					

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8326901

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8333778

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 12-Jan-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8041883

Patient Information:

Age: 44 YR **Sex:** Female **Weight:** 68.04 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN 500MG UNKNOWN	500 MG/1X	Oral	500 MG	SINUSITIS	09-Sep-2009	19-Sep-2009

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN 500MG UNKNOWN		A					

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Anxiety

Depression

Movement disorder

Muscle rupture

Psychotic disorder

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8333778

Event/Problem Narrative:

Ruptured piriformus and tore hamstring very sudden and without warning with a mild leaning over. Periodically I cannot move my left arm. The other and even worse issues have been the periodic depression, anxiety, sense of impending doom, and psychosis. Can't believe doctors aren't connecting the dots with these drugs and are still prescribing them. The "black box warning" isn't doing any good if it doesn't reveal that these side effects can show up MONTHS LATER AND WITHOUT WARNING! WILSONJ: |*********| 2012-01-12-07.34.20 |*********| USFDAMWVOLUNTARY_199376_12284_20120111.xml Route To: AERS : Electronic

Relevant Medical History:

Never had any other tendon or muscle issues. Only back pain previously which was treated with RFA successfully. No other psychological issues other than stress at various times of my life.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8333778

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8348625

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 23-Jan-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8062950

Patient Information:

Age: 53 YR **Sex:** Male **Weight:** 79.38 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AVELOX	400 MG/QD	Oral	400mg tablet one per day	SINUSITIS	09-May-2010	10-May-2010

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	AVELOX							

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Activities of daily living impaired
Anxiety
Disturbance in attention
Feeling abnormal
Feeling cold
Gait disturbance
Insomnia
Malaise
Muscle spasms
Palpitations
Paraesthesia
Peripheral coldness
Tendonitis

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8348625

Event/Problem Narrative:

I took two of the prescribed doses of Avelox that was provided to me for a sinus infection. On the evening of the second day, I had a sudden pain and tightness in my right achilles. It was stiff and difficult to walk on. About 40 minutes later, I felt the same sudden onset of tendinitis in my left achilles. I went to bed at about 10:00 and was not feeling well. I was woken at about 11:30 with pain in my right wrist and forearm and my muscles were in spasm in that arm. I ran it under cold water in an attempt to calm the arm. i went back to bed and felt anxious, my heart was racing and I could not sleep. I called the Dr and he was "puzzled". I asked if it might be a reaction to the Avelx and he said no. I stopped taking the drug immediately, having taken just the two days worth. Since then, I have had to undergo extensive and long term physical therapy for tendonitis on both legs. I have had difficulty with concentration, and a feeling of being in a fog. This situation persists today. I have tingling in my hands that comes and goes. My tendons are still sore in my left achilles, now my left elbow, with other periodic flareups in other locations like right elbow. I seem to be cold much easier, particularly my hands. I still have difficulty sleeping. I have fewer issues with anxiety, but have become much more risk averse, and have modified my activities - my life has been changed by this adverse reaction. wilsonj: |*********| 2012-01-23-10.58.36 |*********| USFDAMWVOLUNTARY_200014_12883_20120123.xml Route To: AERS : Electronic

Relevant Medical History:

I am allergic to penicillin. I was extremely fit prior to taking avelox. I studied martial arts and practiced daily prior May 4th, 2010. I have yet to rejoin that class. My life has changed, I have aged significantly since taking just two pills. This is unacceptable and this drug should only be prescr bed for specific cased where a last resort situation exists. From my research, I have found that a significant number of people have been seriously and permanently injured and damaged by this class of drugs. Please do the right thing.

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
BLOOD TESTS	"NORMAL"				

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Case ID: 8348625

Reporter Source:

Study Report?: No

Sender Organization:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8382160

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 01-Feb-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8103009

Patient Information:

Age: 34 YR **Sex:** Female **Weight:** 55.34 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	500 MG/QD	Oral	500 mg	SINUSITIS	07-Apr-2011	15-Apr-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN		N				50458-0925-50	JANSSEN

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Arthralgia
Burning sensation
Gait disturbance
Magnesium deficiency
Musculoskeletal pain
Nerve injury
Pain
Tendon disorder
Tendon pain
Tendonitis

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8382160

Event/Problem Narrative:

I was prescribed Levaquin for a sinus infection in March and April 2011. I suffered damage to ALL of my tendons, right down to the tiny tendons that run into your fingers and toes. I have had severe pain, especially in both achilles, both knees, both hands and wrists and my right shoulder. All other areas are painful, but not severe. For 6-8 weeks following the reaction had had tremendous difficulty walking. I have had continual inflammation in both achilles, both knees and shoulders. I also suffered nerve damage issues in my face, which consists of tinging and burning sensations across my cheeks and chin and especially in my eyes. I have had severe burning sensations in both hands and arms. I have also learned through test results that my gut no longer makes any good flora, and as a result I am dealing with a yeast overgrowth. I also am deficiently in magnesium and B5, and I am having difficulty absorbing them from supplements and food. To try to get my numbers up, I have to receive the in weekly IV. I am 10 months out from this adverse event and am STILL dealing with the damage. wilsonj: |*********| 2012-02-01-07.29.02 |*********| USFDAMWVOLUNTARY_200531_13326_20120131.xml Route To: AERS : Electronic

Relevant Medical History:

The only preexisting medical condition I have are seasonal allergies.

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8382160

Literature Text:

Case ID: 8382187

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 01-Feb-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8103036

Patient Information:

Age: 32 YR **Sex:** Female **Weight:** 61.69 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO				URINARY TRACT INFECTION		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO							

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Amnesia
Anxiety
Asthenia
Balance disorder
Decreased appetite
Disturbance in attention
Dry mouth
Muscular weakness
Pain in extremity
Plantar fasciitis
Tendon disorder
Tendon pain
Urticaria

Case ID: 8382187

Visual field defect

Waxy flex bility

Weight decreased

Event/Problem Narrative:

I took Ciprofloxacin -Cipro- from ~ November 17-20, 2011. On December 2, 2011 the following occurred: 1. Hives all over my body 2. Plantar Fasciitis 3. Weakness in my legs 4. Tightness of the tendons in my legs 5. Loss of memory 6. Loss of peripheral vision 7. Loss of appetite and weight 8. Loss of flexibility 9. Loss of balance 10. Loss of energy 11. Dry mouth 12. Anxiety 13. Pain in my feet All of the above symptoms started suddenly. The starting of my symptoms coincided with the beginning of my menstrual cycle and taking ibuprofen. Over the last 2 months, my symptoms have improved but there is some lasting damage. My tendons are tight and sometimes painful. I cannot run. My general physical ability is greatly diminished. My memory is worse and my attention span is shorter than it was before having an adverse reaction to Cipro. wilsonj: |*********| 2012-02-01-08.29.51 |*********| USFDAMWVOLUNTARY_200575_13370_20120131.xml Route To: AERS : Electronic

Relevant Medical History:

Non-smoker Occasional drinker -5 drinks per week- White Female Healthy weight Healthy lifestyle - exercised 5 times per week College Educated Never Pregnant Not on any sort of medication at the time of sickness

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
LYME DISEASE	HEALTHY				

Case ID: 8382187

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8391445

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,HO,LT,OT **(A)NDA/BLA:**

FDA Rcvd Date: 06-Feb-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8115390

Patient Information:

Age: 28 YR **Sex:** Male **Weight:** 61.23 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVOFLOXACIN	750 MG/	Oral	1 tablet	SINUSITIS	11-Oct-2011	24-Oct-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVOFLOXACIN		N	A				

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Abasia
Activities of daily living impaired
Asthenia
Balance disorder
Dizziness
Eating disorder
Family stress
Feeling abnormal
Hyperacusis
Hypoaesthesia
Impaired work ability
Insomnia
Malaise

Case ID: 8391445

Muscle spasms

Pain

Paraesthesia

Quality of life decreased

Speech disorder

Thinking abnormal

Toxicity to various agents

Vertigo

Event/Problem Narrative:

I was a healthy 28 year old in September 2011. I was prescribed Levaquin -750mg for 14 days- for an upper respritory infection in October of 2011. I was very weak right after finishing the treatment. About t (b) (6) after completing the treatment I began to get severe attacks of vertigo that sent me to the hospital many times. I was constantly sick and dizzy. As time went on, I became sicker and sicker. I have lost my balance. I am unable to walk and function. I get spasims through out my body. I get pain all over my body. I get tingling and numbness everywhere. Normal sounds are so loud and powerful they vibrate my entire brain. It is very difficult to eat, sleep, think and talk. I have constant brain fog. I get worse everday. My life is ruined. I am unable to go back to work and I am probably going to lose my job. I was just engaged in September when I was perfectly healthly. My family is being torn apart and destroyed over this Levaquin poisoning. I might lose my fiance. I am dieing from this drug. My doctors have no idea what is going on because they are not educated about the horrible adverse reactions to this drug. This drug should only be used in life threating situations. My life and family had beeen destroyed by this Levaquin. Please do not let it destroy and more families. There are thousands of people on the internet with have been destroyed by this class of drugs -Cipro, Levaquin and others-. Please help. (b) (6) |*********| 2012-02-06-09.40.27 |*********| USFDAMWVOLUNTARY_200873_13619_20120205.xml Route To: AERS : Electronic

Relevant Medical History:

Allergies and sinus infections were my only medical conditions prior to Levaquin.

Disease/Surgical Procedure	Start Date	End Date	Continuing?

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8391445

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8393838

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:**

FDA Rcvd Date: 07-Feb-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8119133

Patient Information:

Age: 43 YR **Sex:** Female **Weight:** 69.85 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPROFLOXACIN	500 MG/BID	Oral		URINARY TRACT INFECTION	09-Oct-2009	12-Oct-2009

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPROFLOXACIN		N					BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Amnesia
Arthralgia
Brain injury
Ear discomfort
Eye irritation
Movement disorder
Quality of life decreased
Sleep disorder
Tendon pain
Trigeminal neuralgia

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8393838

Event/Problem Narrative:

I was prescribed cipro 500mg. I took four pills. Now its 2 and a half years later. I suffer from short memory loss. A doctor said I developed triglemial nueralgia.I also have limited motion to all my extremeties. I have pain on my achilles heals,elbows,wrists, rotator cuffs, knees, hips. If there's a tendon!!! it hurts thats really the bottom line. The worst is the brain damage that no doctor can find. I have little electrical movements in my head. I also have fullness in my ears burning in my eyes and sleep disorder. THIS ANTIBIOTIC CIPRO has ruined my life. What is bayer going to do. NOTHING probably!!!! To much income coming in from this poison. I need relief and not just me many others have been damaged and even lost their lives!!!! (b) (6) |*********| 2012-02-07-08.23.32 |*********| USFDAMWVOLUNTARY_200907_13652_20120206.xml Route To: AERS : Electronic

Relevant Medical History:

I was a healthy long distant runner no im nothing but mush.

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8393838

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8442603

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 06-Mar-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8186762

Patient Information:

Age: 75 YR **Sex:** Male **Weight:** 105.68 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVOFLOXACIN	750 MG/QD	Oral		SINUSITIS	30-Jan-2012	04-Feb-2012

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVOFLOXACIN		N	A	TEVA 7293			

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Diarrhoea

Dysgeusia

Joint swelling

Oedema peripheral

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8442603

Event/Problem Narrative:

Started taking Levofloxacin four days prior to feet and ankles swelling up and experiencing diarrhea. Both symptoms continue at this writing. I have not gone for medical treatment yet as conditions seem to lesson on occasion. I also seem to have a very bad after-taste in my mouth whenever I eat anything. (b) (6) |*********| 2012-03-06-08.03.43 |*********| USFDAMWVOLUNTARY_202584_15184_20120305.xml Route To: AERS : Electronic

Relevant Medical History:

none

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	**Start Date**	**End Date**	**Indications** **Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8442603

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8444899

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:**

FDA Rcvd Date: 07-Mar-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8190089

Patient Information:

Age: 48 YR **Sex:** Female **Weight:** 54.43 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVOFLOXACIN	500 MG/	Oral		SINUSITIS	30-Dec-2011	05-Jan-2012

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVOFLOXACIN							

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Feeling abnormal
Influenza l ke illness
Memory impairment
Muscle tightness
Musculoskeletal stiffness
Pain
Polyarthritis
Tendonitis

Case ID: 8444899

Event/Problem Narrative:

Levofloxin Took Levofloxin and had serious side effects. Tendonitis, both legs but right threatening to sever. Inflamation in all joints and tendons, -shoulder, elbo knee etc.- Fatue and general feeling of being "sick" Like having arthritis and the flu at the same time. Tightening of muscles. I think that these drugs should be allowed, but only under extremem circumstances. I am now two months out and still only at about 65% of normal. I have stiffness and pain every day. My head is a bit forgetful and I feel generally yucky. Please, please educate the doctors so they don't perscribe these drugs with Advil. Educate the patient so they know what to look for in side effects and understand that the risk is high and possibliy permanent. If another drug will work, the doctors should be perscribing something else. This drug is way overused, and I suspect the side effects are way under reported and recognized. WILSONJ: |*********| 2012-03-07-08.47.22 |*********| USFDAMWVOLUNTARY_202666_15247_20120306.xml Route To: AERS : Electronic

Relevant Medical History:

I have had cipro and levoflocin before. Have had some of side effects before, but never put two and two together. This time the reaction was severe and fast. No question that the levoflocin caused the trouble. I was also told by two nurse practitioners to take high doses of Advil while on the floxin. Understand that this probably intensified the bad effects. I am allergic to Penecillin, don't smoke or drink. Was running over two miles a day- 6 days a week before the levofloxin. Now I am lucky if I can walk 3/4 a mile 3 times a week, and this I have had to really really work at. It has been very difficult.

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8444899

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8457908

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 14-Mar-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8207641

Patient Information:

Age: 47 YR **Sex:** Female **Weight:** 99.79 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVOFLOXACIN	500 MG/QD		500 MG tablet	BRONCHITIS	06-Dec-2011	13-Dec-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVOFLOXACIN		A	A				

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Asthenia
Dizziness
Gait disturbance
Pain
Pharyngeal oedema
Product substitution issue
Speech disorder
Stupor
Swelling
Swollen tongue
Tremor

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8457908

Event/Problem Narrative:

12/5/2011, Prescribed Levofloxacin 500 MG for bronchitus. Was given a shot of steriod 12/5/2011 and prescribed Prednisone Pack. Name brand Levaquin has been prescribed over the years. I had experienced dizziness while taking this before. However, thought this was associated with illness and did not realize this could be a reaction. 12/5/11 was the first time I took the generic Levofloxacin, manufactered by DR REDDY'S LAB. On 12/14/2011, while taking medication I became light headed, tongue and throat swollen, and felt as if I was in a stuper. My physician advise me to stop taking the Levofloxacin. By 12/16/2011, I could not speak I could only get partial words out. My arms and limbs were affected, I could barely walk or move due to severe pain. The achilles could not bear weight. I continue to have chronic pain, tremors, swelling, and weakness and have been disabled since 12/14/2011. WILSONJ: |*********| 2012-03-14-08.25.13 |*********| USFDAMWVOLUNTARY_203148_15656_20120313.xml Route To: AERS : Electronic Route To: DQRS : : Paper

Relevant Medical History:

Penicillin allergy High Blood Pressure Thyroid No Smoking Use alcohol rarely on social occasaion

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8457908

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8504039

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,HO **(A)NDA/BLA:**

FDA Rcvd Date: 11-Apr-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8274273

Patient Information:

Age: 57 YR **Sex:** Female **Weight:** 41.28 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPROFLOXACIN HYDROCHLORIDE	250 MG/	Oral	250mg	URINARY TRACT INFECTION	01-Aug-2011	05-Aug-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPROFLOXACIN HYDROCHLORIDE		A	A			76125-0900-10	

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Alopecia
Back pain
Burning sensation
Chills
Fatigue
Headache
Hypoaesthesia
Musculoskeletal pain
Pain in extremity
Palpitations
Panic reaction
Peripheral coldness
Weight decreased

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8504039

Event/Problem Narrative:

Was prescribed ciprofloxacin hcl 250 /2times per day for 5 days for a suspected uti. Started taking the cipro on 8/1/2011 and finished on 8/5/2011 within [redacted] (b) (6) developed a severe headache took 2 Aleave next day my scalp stated to burn. It felt like someone had poured kerosine on my head and lit it on fire. Started to lose hair. This lasted approximately 5 weeks then the burning and severe stinging started on my back then within a week moved to my feet, legs, thighs, buttocks. My feet would be freezing one minute -feeling like I was walking on blocks of ice- and then the next be back to burning and stinging. I can not get dressed or even wear shoes due to severe burning and stinging.I also experience severe fatigue, panic,numbness, heart palpitations, chills, loss of approx 18 lbs and continued hair loss. severely disabled symptoms persisting still after 8 months.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
SMALL FIBER NERVE BIOPSY EMG					

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8504039

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8523536

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT,RI **(A)NDA/BLA:**

FDA Rcvd Date: 20-Apr-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8301201

Patient Information:

Age: 49 YR **Sex:** Female **Weight:** 90.72 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPROFLOXACIN	500 MG/BID	Oral	1 tablet; 2x day	URINARY TRACT INFECTION	16-Jun-2011	16-Jun-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPROFLOXACIN		N	A				

Event Information:

Preferred Term (MedDRA Â© Version: 17.0) **ReC**

Fatigue

Neuralgia

Tendon rupture

Urinary tract infection

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8523536

Event/Problem Narrative:

I was diagnosed with a simple UTI and prescribed the fluoroquinolone antibiotic, Ciproflaxacin. Thankfully I only took one dose. A couple hours later while on a walking path, I felt a pulling in my foot, then a snaping, accompanied by the most excutiating pain. My foot swelled and bruised, and I couldn't walk on it. Ciproflaxin caused a tendon tear. I suffered with this for months, and it still is not completely healed. The RX paper said tendon tear extremely rare, and with people over the age of 60. This was not enough of a warning! After researching,I have found that there are many injuries and health complications from these drugs. I also believe I've sustained nerve pain, and fatigue issues from a prior precription of Cipro. The danger of these drugs are published in many medical sources, as well as numerous individual accounts of long lasting, permanent injury. There are many safer antibiotic choices for Physicians to choose. Please pull the fluoroquinolone drugs, such as Ciprofloxacin from the market. Other Concomitant Medical Product Description: Arch supports and exercise therapy recommended Triage Quality Control: WILSONJ: |*********| 2012-04-20-07.33.55 |*********| USFDAMWVOLUNTARY_205353_17542_20120419.xml Route To: AERS : Electronic

Relevant Medical History:

No preexisting medical conditions.

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
EXRAYS	DIAGNOSIS OF TENDON RUPTURE				

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Case ID: 8523536

Reporter Source:

Study Report?: No

Sender Organization:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8536164

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 30-Apr-2012 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-8321486

Patient Information:

Age: 29 YR **Sex:** Male **Weight:** 83.91 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AVELOX		Oral	1	SINUSITIS	07-Mar-2012	08-Mar-2012

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	AVELOX		N	A	N/A			BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Anxiety
Dizziness
Fatigue
Feeling abnormal
Formication
Insomnia
Joint crepitation
Muscle spasms
Muscle tightness
Nausea
Night sweats
Pain
Palpitations

Case ID: 8536164

Peripheral coldness

Photophobia

Presyncope

Tendon pain

Tremor

Visual acuity reduced

Vitreous floaters

Event/Problem Narrative:

I was prescribed Avelox -400mg for 10 days- for a possible sinus infection. I was not told of any of the side effects. I took only two 400 MG Avelox pills due to the side effects I was experiencing. The first dose was taken on 3/7/2012 at 5:00pm and the second on 3/8/2012 at 5:30pm. My side effects included: popping joints, tight and sore tendons -all over-, muscle tightness -all over-, muscle spasms -particularly bad in calves where is felt like something was crawling under my skin-, random isolated dull aches/pains, racing heart, heart palpitations, anxiety, insomnia, vision acuity loss -with light sensitivity-, increase in visual floaters, nausea/dizziness/spacy feeling/lightheaded, fatigue/feeling faint, achy body, feeling shaky, cold hands and feet and night sweats. As of today 4/27/2012 my symptoms include: popping joints, tight and sore tendons -mainly in arms, hands, legs-, muscle spasms -calves and arms mostly but occur all over-, visual floaters, decreased vision in right eye. Triage Quality Control: (b) (6): |*********| 2012-04-30-09.27.33 |*********| USFDAMWVOLUNTARY_205877_17986_20120428.xml
Route To: AERS : Electronic

Relevant Medical History:

I had no preexisting medical conditions. I only would drink alcohol socially on weekends. I was very healthy.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Case ID: 8536164

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
COMPREHENSIVE BLOOD PANEL	WITHIN NORMAL RANGE				
GLUCOSE	ONE POINT OVER THE NORMAL RANGE				
FULL EYE EXAM	SLIGHT LOSS IN ACUITY				

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8611507

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,HO,OT **(A)NDA/BLA:** 021085 /

FDA Rcvd Date: 13-Jun-2012 **Mfr Rcvd Date:** 02-Jun-2012 **Mfr Control #:** US-BAYER-2012-055846

Patient Information:

Age: **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AVELOX	1		1 pill	SINUSITIS	2010	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	AVELOX							BAYER

Event Information:

Preferred Term (MedDRA © Version: 17.0)	ReC
Amnesia	
Arthralgia	
Arthropathy	
Contusion	
Coordination abnormal	
Disorientation	
Drug hypersensitivity	
Excessive eye blinking	
Facial pain	
Fatigue	
Feeling cold	
Headache	
Hyperacusis	

Case ID: 8611507

Hyperhidrosis

Hypoaesthesia

Insomnia

Limb discomfort

Loss of employment

Migraine

Muscle twitching

Muscular weakness

Pain

Pain in extremity

Paraesthesia

Photophobia

Speech disorder

Tenderness

Vertigo

Event/Problem Narrative:

serious, related, unlisted This spontaneous case report was received on 02-Jun-2012 from a female consumer of unspecified age from UNITED STATES. She was referring to herself and describing the use of AVELOX (moxifloxacin). No information about medical history or concurrent conditions was provided. Consumer’s drug history included steroid and Z pack for sinus infection, and steroid was used as concomitant medication. On an unspecified date on 2010, consumer used AVELOX (moxifloxacin) at 1 pill, for sinus infection. It was not reported whether AVELOX was used previously. Lot number, expiration date and bottle count were not provided. Consumer reported that she had a sinus infection, and she used Zpack and steroids, on an unspecified date in 2010. Nurse practitioner prescribed AVELOX (moxifloxacin) for her ongoing sinus infection. She bought steroids and AVELOX. Consumer report that , on an unspecified date in 2010, she took one pill of AVELOX and within a half hour the following events started: UNCONTROLLED BLINKING and FACIAL TWITCHING. Her boyfriend contacted Poison Control to see what they have to do, and they told him to take her to the nearest ER. Then she started to experience SEVERE SENSITIVITY TO LIGHT AND SOUND, which was making her DISORIENTED; she COULD NO LONGER GET MOST OF HER WORDS OUT; FACIAL TWITCHING continued and she BEGAN TO LOSE CONTROL OF HER HEAD, and she felt EXTREME PAIN IN HER HEAD. She was hospitalized for 3 weeks and

Case ID: 8611507

tested for everything, and she reported that she CAN’T REMEMBER ANYTHING that happened and during hospitalization she felt NUMBNESS and PAIN IN HER FACE and she was NOT ABLE TO SIT UP. Consumer reported that none of the doctors could identify what was wrong with her, and they said that she had to inform any doctor that will treat her that she is ALLERGIC TO AVELOX. Consumer considered all those events related to the use of AVELOX. She stated that, to this day, it has been 2 years 5 months and 2 days that she had to deal with ongoing symptoms and she went to see multiple neurologist/doctors. Consumer reported that she suffer from COMPLEX MIGRAINES, VERTIGO, TWITCHING OF HER RIGHT ARM and the TWITCHING STAYS IN HER HAND, PAIN IN LEFT HIP, her LEFT KNEE SOUNDS LIKE CRACKLING AND POPPING, she can’t GO FOR LONG WALKS BECAUSE SHE TIRE EASILY, PAIN IN LEGS, EXHAUSTED, INSOMNIA, her BODY HURTS TO TOUCH, she feels like HER WHOLE BODY HAS BEEN USED AS A PUNCHING BAG and she has BRUISING ALL OVER, she fells PIN AND NEEDLES IN RIGHT FOOT. She also feels AS AN ELECTRIC SHOCK GOES THRU HER BODY CAUSING HER BODY TO JUMP OFF THE BED and an ELECTRIC FEELING IN HER LEGS, NIGHT FREEZING COLD, she GET SOAKING WET FROM SWEATING and she LOST HER JOB DUE TO NOT BEING ABLE TO PERFORM HER JOB. The causality assessment of those events was not reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**
STEROID			SINUSITIS	
Z PACK			SINUSITIS	

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	STEROID ANTIBACTERIALS							

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8611507

Reporter Source:

Study Report?: No **Sender Organization:** BAYER

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8744529

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 06-Sep-2011 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-7731063

Patient Information:

Age: 42 YR **Sex:** Female **Weight:** 46.27 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN		Oral	AS PRESCRIBED PO	URINARY TRACT INFECTION		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN		N					

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Arthralgia
Asthenia
Back pain
Bone pain
Dyspnoea
Dysstasia
Impaired work ability
Memory impairment
Tendonitis
Weight decreased

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8744529

Event/Problem Narrative:

I am reporting in order to help track this issue and the drugs affects. Will have to check that date to confirm when Levaquin was originally began. Had more than 1 prescription. Thought what I was feeling was transient synptoms that would go away after stopping the medicines. No one told me any different. No warnings. Approximately 9 years ago I began taking Levaquin for a while before it eventually on Jan 25th it took its toll on me. Doctor prescribed Levaquin for an UTI. Began having elbow pain and severe weakness and breathlessness. A burning pain in my back on the right side between my scapula and ribs that to this day remains to a degree.Could hardly stand to sit up. Lost down to 79 pounds and was begging for help to hospitals and doctors with nothing more than a "It's in your head reply". My memory, ability to recall and have all been affected. I tried to got o work in 2005 and worked for several months before having to quit and have not been able to work since. Physician said the elbow pain was probably tendonitis. Soon I was hurting from head to tail bone and in my hips as well. Over time I begin having ringing in my head which continues to date. Over time was diagnosed vaguely for many pains throughout my body particularly with my neck, jaws, back, shoulder blade area, shoulder and hips. I knew at once this was from Levaquin and reported it to my pharmacists who told me to never take Levaquin again because it could cause tendon ruptures and other side affects. WHen I told doctors this they quickly brushed it aside, doctor after doctor. They stated this was all in my head. Because doctors refused to admit my symptoms were from Levaquin I have undergone several surgeries believing the doctors knew what they were talking about and had some answers to some of the pain. They really are hiding facts, and are ill prepared to handle this issue. The problem is now out of the closet and meeds to be addressed PUBLICLY before more people are harmed. [redacted] (b) (6) |*********| 2011-09-06-10.32.03 |*********| USFDAMWVOLUNTARY_191865_5937_20110902.xml Route To: AERS : Electronic

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Case ID: 8744529

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8744551

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** Y **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 26-Sep-2011 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-7777034

Patient Information:

Age: 48 YR **Sex:** Female **Weight:** 54.43 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CIPRO	500 MG/BID	Oral	500MG BID	URINARY TRACT INFECTION	16-Jul-2011	20-Jul-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	CIPRO		N	A		16-Jul-2012		BAYER

Event Information:

Preferred Term (MedDRA Version: 17.0) **ReC**

Arthralgia

Hypoaesthesia

Neuropathy peripheral

Paraesthesia

Tendonitis

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8744551

Event/Problem Narrative:

I was prescribed cipro -500mg bid x5 days- for a UTI. On day 4 of the cipro, I noticed that my right elbow began aching and both foremarms had some tingling and numbness. I finished the cipro, believing that these side affects would go away once the meds were finished. They persisted. I have now been diagnosed with tendonitis in my right elbow and the neuropathy remains 2 months after completing the course of meds. I have never experienced similar problems in my entire life. My primary physician has advised me to never take any quinolone antibiotics again wilsonj: |*********| 2011-09-26-08.52.34 |*********| USFDAMWVOLUNTARY_193146_7035_20110924.xml
Route To: AERS : Electronic

Relevant Medical History:

no pre-existing medical conditions

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Case ID: 8744551

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8744592

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS,OT **(A)NDA/BLA:**

FDA Rcvd Date: 26-Sep-2011 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-7777047

Patient Information:

Age: 58 YR **Sex:** Female **Weight:** 58.97 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	QD	Oral	1 TABLET DAILY FOR 5 DAYS	SINUSITIS	03-Jan-2011	07-Jan-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN		N	A			50458-0930-20	ORTHO

Event Information:

Preferred Term (MedDRA Version: 17.0)	ReC
Abasia	
Acne	
Activities of daily living impaired	
Arthralgia	
Asthenia	
Burning sensation	
Grip strength decreased	
Immune system disorder	
Irritable bowel syndrome	
Muscular weakness	
Pain in extremity	
Tendon pain	
Tinnitus	

Case ID: 8744592

Event/Problem Narrative:

On the day following my 5 days of taking Levaquin 750 mg tablets -one each day- I awoke with moderate to severe pain in my left achilles tendon. In the months since then I have experienced continuing pain in that tendon. In addition, I have also experienced increasing pain in the tendons in my right ankle, all of my toes, both knees, both hips, both shoulders, both elbows, both wrists, and all of my fingers. In all of these areas I have pain, weakness, and reduction in function which varies in intensity, but is always present. At times. it keeps me from being able to perform activities of daily living such as home care and the requirements of my job. In the same areas of my body I also have burning pain sensation at times. On the palms of my hands and the soles of my feet I have extreme sensitivity to pressure which sometimes makes it impossible for me to grip things or walk barefoot across a hard surface. Since taking Levaquin I have also experienced skin acne issues which I have never had previously. This includes breakouts on my face, chest and back area. Previous problems, which had been occasional, have increased so as to be life-altering. While I had in the past had irritable bowel syndrome symptoms every so often, they have increased dramatically since January. I have begun experiencing loose bowel issues daily. At least one night per week I am up all night with diarrhea and stomach cramps. I have had to resort to taking multiple doses of Immodium to relieve the symptoms. I have also noticed an increase in tinnitus, which was occasional before, and is constant now. My immune system seems to be affected as I have had 4 head colds in the past 9 months each lasting 10 to 16 days. This is a higher frequency than normal for me. I have also noticed that my vision is blurry at times and this is another symptom I never experienced prior to the use of this drug. wilsonj: |*********| 2011-09-26-09.16.49 |*********| USFDAMWVOLUNTARY_193162_7051_20110925.xml Route To: AERS : Electronic

Relevant Medical History:

Pre-existing conditions: Inner ear disorder causing some dizzyness which had been under control for about 3 years. No other long term pre-existing conditions. No smoking ever. Minimal alcohol use.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
MRI OF LEFT ANKLE	FOUND TO SHOW EVIDENCE OF TENDONITIS				
ANTI-NUCLEAR AB	NORMAL				
SED RATE-ESR-	NORMAL				
BLOOD TESTS TO CHECK CK	NORMAL				

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8744592

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
RA -RHEUMATOID FACTOR-	NORMAL				

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8745000

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 26-Sep-2011 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-7777057

Patient Information:

Age: 46 YR **Sex:** Female **Weight:** 59.87 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LEVAQUIN	500 MG/	Oral	750MG 5 DAYS 500MG 14 DAYS	SINUSITIS	11-Jan-2011	16-Jan-2011
2	LEVAQUIN	750 MG/	Oral	750MG 5 DAYS 500MG 14 DAYS	SINUSITIS	05-Jan-2011	10-Jan-2011

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LEVAQUIN		A	A				JOHNSON AND JOHNSON

Event Information:

Preferred Term (MedDRA Â© Version: 17.0) **ReC**

Burning sensation
Hyperhidrosis
Hypoaesthesia
Neuralgia
Palpitations
Sinusitis
Tendon pain

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8745000

Event/Problem Narrative:

I was prescribed Levaquin by my family doctor for a possible sinus infection. Symptoms were not going away, so doctor prescibed 2 more rounds of Levaquin. Family doctor sent me to a Pulmanologist to try to figure out why I was still sick. Pulmanologist warned me about taking so much Levaquin, he was puzzled why the Family Doctor was prescribing so many rounds of a very powerful drug. By March I was feeling some pain in my rotator cuff. The pain and stiffness slowly increased each month. By April I was experiencing increasing pain in my Achillies tendon. I saw an Othopaedist who put me into Physical Therapy. After 4 weeks of PT, I began to get intense nerve pain in my left arm, the one that the rotator cuff was stiff and painful. My skin started to feel like it was buring, my heart started to palpitate. I was sweating profusley. It has been several months and I have a partially atrophied shoulder with nerve pain and numbness along my left arm. I have intermitten pain that comes and goes throughout my body.
wilsonj: |*********| 2011-09-26-09.31.00 |*********| USFDAMWVOLUNTARY_193172_7061_20110925.xml Route To: AERS : Electronic

Relevant Medical History:

I am a 46 yr. old Caucasion women, non-smoking and little alcohol use. I was in very good health with no existing problems before taking the Levaquin.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
MRI OF THE SHOULDER	ADHESIVE CAPSULITIS IMPINGEMENT				

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Case ID: 8745000

Reporter Source:

Study Report?: No

Sender Organization:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8745367

Case Information:

Case Type: DIRECT **eSub:** Y **HP:** N **Country:** USA **Outcomes:** DS **(A)NDA/BLA:**

FDA Rcvd Date: 08-Sep-2011 **Mfr Rcvd Date:** **Mfr Control #:** US-FDA-7736840

Patient Information:

Age: 73 YR **Sex:** Male **Weight:** 77.11 KG

Suspect Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	DECADRON	1 MG/	Intramuscular	1 MG, INJECTION, IM	EAR INFECTION	24-May-2011	24-May-2011
2	LEVAQUIN	500 MG/	Oral	500 MG, 1 PER DAY, PO	SINUSITIS		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	DECADRON		A	A				
2	LEVAQUIN		A	A				

Event Information:

Preferred Term (MedDRA Â Version: 17.0) **ReC**

Hypoaesthesia
Joint swelling
Oedema peripheral
Paraesthesia
Respiratory disorder

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8745367

Event/Problem Narrative:

I live in [redacted]. In march of 2011, I drove to [redacted] to visit with my son. During my visit,I went to [redacted] in [redacted] for congestion in my chest. I was given a prescription of Levaquin/500 mg. From [redacted] I traveled to [redacted] to visit with family there. On April 29, 2011 I had to go back to a medical facility [redacted] Medical Center-in [redacted] On that date I was given a Decadron injection -1 mg-, 250 mg Rocephin injection and 40 mg. of Depo-Medrol. On May 24, 2011, I returned to [redacted] Medical [redacted] and received another Decadron injection. I'm not sure what the amount was. The bill from the Medical Center states it was 1 mg but I have a report stating the amount administered was 4 mg. 5 hours after that injection, I experienced numbness and tingling in the right side of my face. I called the medical clinic and was told to come back the following week if the numbness was still there. On [redacted] I went to the Emergency Room at [redacted] Medical Center in [redacted] The ER doctor order a catscan of the head to rule out a stroke and a stroke was ruled out. He, then, prescribed another Levaquin round of 500 mg. I returned to [redacted] Medical center complaining about the numbness and a MRI of the brain was ordered. I was given a CD. My grandson was getting married in [redacted] so I returned there for the wedding and saw a Neurologist there to intrepret the MRI. After that, I returned to [redacted]. I saw my primary care physician, an ENT specialist, my eye doctor and finally, a Neurologist. I have had 2 MRIs, 3 catscans, over 200 blood tests and a lumbar puncture and still no diagnosis. The numbness and tingling now includes the left side of my face, as well. This nightmare started on May 24, 2011 when I was given a Decadron injection -1 mg or 4 mg-. I feel as though this medication is at the crux of my condition. In addition to the numbness and tingling in my face, I have swelling in my ankles, feet, knees, shoulders, elbows and wrists. Also, my ability to eat is in question as well as my breathing has suffered. Again, I have been miserable since May 24, 2011 and my condition has progressively gotten worse. I believe Decadron and, perhaps, Levaquin in combination with the Decadron administered in a short time period has created my current condition. I don't have any good days. They are all bad days. I have to question my will to live under the present circumstances. Can you help me find a doctor that is experienced with these medications to help me? Please!

Relevant Medical History:

Diagagnosed with COPD, High Blood Pressure. Allergic to Codeine and Myacin drugs. White male, 73 years of age. Was a smoker in the past.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Case ID: 8745367

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
LUMBAR PUNCTURE					
CT SCAN					
NEUROLOGICAL TESTING					
X-RAYS OF MOUTH					
MRI/MRA -HEAD/NECK-					
CT SCAN					
MRI-NECK SPINE W/0 DYE					
NEUROLOGICAL TESTING					

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization:

Literature Text:

Printer: CDPEDQ5
User: STEPPERH
Total Number of Pages: 285
Print Job Number: 10512

*Disclaimer: Submission of a safety report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.

Processed Case Id's for Images:

3160558 3169872 3215066 3255203 3403298 3417437 3445256 3449435
3456871 3472347 3571163 3578488 3640803 3741011 3757438 3779284
3784204 3795918 3813786 3862315 3905502 3915097 3925907 3948419
3952082 3999816 4000632 4007439 4046409 4053411 4065917 4075577
5657219 5691052 5699626 5732453 5735951 5744746 5762113 5780149
5804380 5817946 5834125 5840679 5852274 5866927 5882021 5891511
5946604 5947771 5947790 5985044 6014328 6027683 6031267 6123363
6135374 6223592 6256009 6261029 6294839 6326779 6437033 6610484
6617669 6709766 6733832 6946431 6955136 7029352 7111554 7173279
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7800646 7804996 7918609 7942111 7987954 8022885 8135973 8269115
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8896483 8901852 8925114 9004685 9145237 9193328 9264824 9292906
9470480 9486543 9496893 9517815 9563865 9586187 9625932 9631942
9639830 9648927 9690626 9695879 9723049 9725540 9782749 9803231
9870433 9908057 9924828 9971310 10029666 10061618 10061762 10101517
10101699 10264214 10264284 10395791 10449524 10466297 10472523 10524464
10589537 10637351 10637469 10693032 10694998 10732080 10936278
10997224 11047971

Failed Case Id's for Images:

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY repo
by health professionals of ad
events and product proble

Page ____ of ____ CDER

Individual Safety Report

3124027-5-00-01

A. Patient information

1. Patient identifier	2. Age at time of event: 56 or Date of birth: (b) (6)	3. Sex	4. Weight
in confidence		☒ female ☐ male	140 lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☒ disability Permanent
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
3/25/96	8/18/98

5. Describe event or problem

Severe Stomache pain, Rise in blood Pressure up to 160/120, Anxiety, Severe pain in JAW Neck and Shoulder, Dizziness, blurred vision, Headache, Tremors, Rash Joint + muscle pain, Severe weight loss 30 LBS, thirst, insomnia - cognitive Change, have trouble Keeping in Keeping a line of thought - Vasculitis, Pelvis Pain. ~~Visual~~ disturbance Visual disturbance - Has made me a non functionale Person Was given the cipro, after going to urgent care for rise in blood pressure, Blood Pressure has gone down. Still have Severe Pain in Jaw, neck Shoulder blades, After the cipro I felt a small explosion on the left Side of my head at the base of my Spine

6. Relevant tests/laboratory data, including dates

MRI of ~~Brain~~ BRAIN. 1996 - negative
MRI of Neck 96
98 Ruptured disc
~~Blood test for AIDS~~
AIDS Blood test 96 - negative
Autoimmune test 96 - negative

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

White, Smoker

REC'D.

AUG 27 1998

MEDWATCH CTU

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 FLOXIN
#2 Cipro

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) (mm/dd/yy or best estimate)
#1 400 mg	#1 3/24/96 - 7 days
#2 750 mg - 1 dose	#2 ~~3/25~~ 4/18/96 - 1 dose

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 Suspected Bladder infection	#1 ☐ yes ☒ no ☐ doesn't apply
#2 Bladder infection	#2 ☐ yes ☒ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1	#1	#1 ☐ yes ☐ no ☐ doesn't apply
#2	#2	#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for procuct problems only) – –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other:

5. Expiration date (mo/day/yr)

6.
- model #
- catalog #
- serial #
- lot #
- other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #
(b) (6) (b) (6)

2. Health professional?	3. Occupation N/A Permanent disabled	4. Also reported to
☐ yes ☒ no		☐ manufacturer ☐ user facility ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3169872

MEDWATCH
Individual Safety Report
3160979-5-00-01

For VOLUNTARY reporting
ealth professionals of adverse
ents and product problems

CDER

Page ___ of ___

Form Approved: OMB No. 0910-0291 Expires:12/31/94
See OMB statement on reverse

FDA Use Only
Triage unit sequence # 92995

A. Patient information

1. Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
In confidence	44 or (b) (6)	☑ female ☐ male	108 lbs or ___ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ___ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☑ disability
- ☐ congenital anomaly
- ☑ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: may 98'
4. Date of this report: Nov 98

5. Describe event or problem

Prescibed Cipro over the phone for mild bronchitis. 5days later went to ER with breathing problems, hyper feeling. Chest X-ray done sent to follow up with Pulmonary Dr. Pulmonary Dr. did no culture but prescribed 14 days of Levaquin his notes said (may be allergy, asthma, bronchitis, sinus) did no tests Drug Rash & burning sensation to body (face, chest, neck, back, arms.) later stomach feet, hands. Scalp. Treated with steroids (Medrol & Allegra) to counteract reaction. Rash came at end of Levaquin use. Diagnosed with Polysensory Neuropathy following use of Quinolones. Developed hair loss, still have skin rash, hair loss & Polysensory Neuropathy to entire body. in 9/98 put on Neurontin - had hysteria from it. 10/98 given Ultram for pain and had slurred Speech. couldn't move, hallucinated, after 1 pill. Put on clavl 3 days in 9/98 taken off after vision & dizzy problems.

6. Relevant tests/laboratory data, including dates

2 Emg Studies 8/98 10/98
MRI 7/98
B12 9/98
Toxic Screens 9/98
Lupus 7/98
Rheumatoid 7/98
Porphyria 9/98
Anti-mag 10/98
Siorgens 10/98
Cortisol 7/98
all tests negative except emg studies showing Polysensory Neuropathy
CBC 7/98
Diabetis 7/98
immunology panel 7/98
ANA panel 7/98
Oncology tests 9/98
Antibody tests 9/98
24 hour urine 9/98
Heavy metals 8/98
Thallium Screen 8/98
Demyliating test 8/98
Conn. Tissue tests 8/98
MS 9/98
others.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) None

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Cipro 500 mg 10 days
#2 Levaquin 500 mg 14 days

2. Dose, frequency & route used
#1 Cipro (oral)
#2 Levaquin (oral)

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 10 500 mg (May 2 98) 5/2/98
#2 14 days 500 mg (May 13 98) 5/13/98

4. Diagnosis for use (indication)
#1 Cipro prescibed by phone (no diagnosis)
#2 Levaquin - doctor wrote poss. allergy - asthma. bronchitis

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☑ no ☐ doesn't apply
#2 ☐ yes ☑ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)
none

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

REC'D
NOV 19 1998
MEDWATCH/CTU

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other:

5. Expiration date (mo/day/yr)

6.
model #
catalog #
serial #
lot #
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

2. Health professional? ☐ yes ☒ no

3. Occupation

4. Also reported to
- ☒ manufacturer
- ☐ user facility
- ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☒

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CTU92995

CaseID::3215066

MedWatch — Individual Safety Report

3204759-0-00-01

For VOLUNTARY reporting th professionals of adverse ts and product problems

Page CDER of CDER

Form Approved: OMB No. 0910-0291 Expires: 8/31/9 See OMB statement on reverse

FDA Use Only

Triage unit sequence # 98041

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: or 44 — Date of birth: (b) (6)
3. Sex: ☑ female ☐ male
4. Weight: 165 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☑ required intervention to prevent permanent impairment/damage
   - ☐ other: ongoing reaction 9 months so far.
3. Date of event (mo/day/yr): 5/15/98
4. Date of this report (mo/day/yr): 8/26/98 Ortho; 2/14/99 Patient
5. Describe event or problem

5/2/98 Prescribed Cipro for 10 days (for bronchitis?)
5/13/98 Prescribed Levaquin 500 mg 14 days. The N
Developed rash (acne-like) to face, neck, upper body + with burning sensations.
Given Medrol & Allegra to Counteract reaction.
Had constant burning of face, neck, back chest at onset of rash. Spread to entire body. Diagnosed by two Neurologists with Polysensory Neuropathy (axonal damage). Had Joint, Bone, Muscle Pain & cramping, gastro problems, hair loss and acute burning. Tics & pulsations in body. Burning escalates when excited. Symptoms have persisted without any relief, unable to work & housebound. Feb 99 Condition Continues. Still have all the same symptoms. Going for further evaluations to Dermatologists, Orthopedic & Neurologists. Continuing internal burning, joint pain, tics, cramping rash, gastro problems, muscle pain/stiffness/cramping & Polysensory Neuropathy.
(Also have arthritic like stiffness to entire body)

6. Relevant tests/laboratory data, including dates

2 Nerve Conduction Studies, Quantitative Sensory Testing. MRI's, Immunology Panels, CBC's, urine tests, toxic screens, Antibody tests, Ana Panels, B12 Screens, E Screens, Sed rates, cortisol levels. Hematology tests, Oncology tests. Endless Tests. Seen by Pulmonary, Dermatology, Internists, Pain Clinic, Neurologist, Neuromuscular Specialty Clinic, Allergist, Hematology/Oncology Specialties. To go to Orthopedist / Dermatology & Neuro Specialties again.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

No allergies. No Previous exposure to Fluroquinolones. No pre-existing medical conditions or relevant history.

FEB

MEDWATCH CTU

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   - #1 Levaquin 500 MG 14 days - started 5/13/98
   - #2 Cipro 500 MG 10 days started 5/2/98
2. Dose, frequency & route used
   - #1 500 mg oral
   - #2 500 mg oral
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   - #1 Cipro 5/2/98 10 days
   - #2 Levaquin 5/13/98 14 days
4. Diagnosis for use (indication)
   - #1 bronchitis
   - #2 bronchitis / sinusitis ?
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☒ no ☐ doesn't apply
   - #2 ☐ yes ☒ no ☐ doesn't apply
6. Lot # (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☒ doesn't apply
   - #2 ☐ yes ☐ no ☒ doesn't apply
9. NDC # (for product problems only) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device NOTE:
3. Manufacturer name & address

Reported to Ortho McNeil July 98' and 8/17/98. Manufacturer issued letter to my neurologist Nov 98. In Jan 98' FDA said I was NOT in their database.

4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. As of Jan 98 Neurologist had
   - model # not returned Ortho McNeil/
   - catalog # R.W. Johnsons request for
   - serial # further information. Since I
   - lot # was not in your database as
   - other # of Feb 99 am submitting this Report to you.
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   - ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address (b) (6)
   phone # (b) (6)
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Also reported to
   - ☒ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 CTU-98041 — submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event

Individual Safety Report
3204759-0-00-02

98041

February 14, 1999

Medwatch
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

To whom it may concern:

I reported the attached Medwatch report to the Manufacturer in July and August 98. I have also informed the Manufacturer several times since then that my symptoms are ongoing and have not abated. I had tried to obtain information from both the manufacturer and FDA if they had other reports of ongoing symptoms of this nature, in an attempt to learn how others were being treated or what the prognosis might be for these reactions. The Manufacturer and FDA informed me they had no follow up information in this regard.
A letter was issued in Nov. 98 by R.W. Johnson to my Neurologist requesting further information. In January 98, my Neurologist had not yet returned the requested information.
In February 99 when I contacted the FDA, I was told I was not in their database and no report had been received on my case. I thought the Manufacturer was required to file a Medwatch report with the FDA when the incident was reported. I have submitted this report because I was told by the FDA that I did not appear in their Medwatch database as of February 99. In November 98 I requested all summarized reports on Levaquin be sent to me through the Freedom of information act. I was sent ONLY 8 months worth of reports from 1997.
I made a second request for the remaining adverse reactions reported to the FDA on Levaquin.. To date, I have not received the reports. I was informed do to a new computer program being instituted that there was a delay in sending the remaining reports, and that they would be sent when the computer problems were resolved. To date I have not received those reports.
I wondered if anyone at the FDA or the Manufacturer has done any safety follow up to determine just how many people are experiencing disabling adverse reactions that have not abated since taking this drug. If there is any information in this regard I would appreciate anything you could tell me.
Sincerely,

(b) (6)

98041

CaseID::3255203

Individual Safety Report

3241311-5-00-01

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

CDER

For VOLUNTARY reporting by health professionals of adverse events and product problems

CDER

Page ___ of ___

Form Approved: OMB No. 0910-0291 Expires: 4/30 See OMB statement on reve

FDA Use Only

Triage unit sequence # 101269

A. Patient information

1. Patient Identifier (b) (6) In confidence

2. Age at time of event: 44 or Date of birth: (b) (6)

3. Sex: ☒ female ☐ male

4. Weight: 120 lbs or ___ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization – initial or prolonged
- ☒ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 2-2-99

4. Date of this report (mo/day/yr): 4-10-99

5. Describe event or problem

TOOK 12 days Levaquin 500 mg qd for sinusitis on 4th day developed joint pains, tendonitis foot, 11th-12th day chest pain 10 days after med. developed numbness tingling, weakness all 4 extremities, mylagia, muscle spasms & twitching which remain to this day. Dr. diagnosed as drug reaction to Levaquin

6. Relevant tests/laboratory data, including dates

MRI spine Feb 9th (NEC)

DSS

APR 19 1999

ADVERSE EVENT REPORTING SYSTEM

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

White american Non-smoker

MEDWATCH THE FDA MEDICAL PRODUCTS REPORTING PROGRAM HF-2

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Levaquin 500 mg

#2

2. Dose, frequency & route used

#1 500 mg

#2 qd po

3. Therapy dates (if unknown, give duration) from/to (or best estimate)

#1 JAN 7th – JAN 19th

#2

4. Diagnosis for use (indication)

#1 sinusitis

#2

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☒ no ☐ doesn't apply

#2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)

#1

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # (for product problems only)

- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device

- ☐ health professional
- ☐ lay user/patient
- ☐ other:

5. Expiration date (mo/day/yr)

6. REC'D.

model #

catalog # APR 19 1999

serial #

lot # MEDWATCH CTU

other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)

☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address

phone # (b) (6)

(b) (6)

2. Health professional? ☒ yes ☐ no

3. Occupation: RN.

4. Also reported to

- ☐ manufacturer
- ☒ user facility
- ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500 1/96

Submission of a report does not constitute an admission

CTU 101269

NO. 635

APR. 19. 1999 4:10AM MEMBER SERVICE CENTER

CaseID::3403298

DEC-16-99 THU 10:35 AM FAX: PAGE 1

3423149-9-00-01

VOLUNTARY reporting ealth professionals of adverse ents and product problems

CDER

CDER

Page 1 of 1

Form Approved: OMB No. 0910-0291 Expires: 11/00
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 114269

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 41 or Date of birth: (b) (6)
3. Sex: ☒ female ☐ male
4. Weight: 125 lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☒ life-threatening
   - ☒ hospitalization – initial or prolonged
   - ☒ disability
   - ☐ congenital anomaly
   - ☒ required intervention to prevent permanent impairment/damage
   - ☐ other: ____
3. Date of event (mo/day/yr): 07/27/99
4. Date of this report (mo/day/yr): 12/15/99
5. Describe event or problem

TACHYCARDIA, FOLLOWED BY (AND PRECEDED BY) SEVERE DISORIENTATION, NIGHTMARES, COGNITON PROBLEMS, MEMORY IMPAIRMENT, MUSCLE TWITCHES, PERIPHERAL NEUROPATHY, SEVERE HEADACHE, RASHES DIZZINESS, DISEQUILIBRIUM

PROBLEMS WITH CENTRAL NERVOUS SYSTEM CONTINUE - SUSPECT NEUROTOXIC EFFECT, perhaps permanent

6. Relevant tests/laboratory data, including dates

ABNORMAL EKG, ABNORMAL POTASSIUM IN BLOOD (LOW)

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

NONE

5'2"

125 lb woman

in prior excellent health

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   - #1 LEVAQUIN (500 mg)
   - #2
2. Dose, frequency & route used
   - #1 ORAL, 1 DAILY x 17 DAYS
   - #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   - #1 7/10/99 - 7/27/99
   - #2
4. Diagnosis for use (indication)
   - #1 SINUSITIS
   - #2
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☒ no ☐ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   - #1
   - #2
7. Exp. date (if known)
   - #1
   - #2
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☐ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only) - -
10. Concomitant medical products and therapy dates (exclude treatment of event)

FLONASE NASAL SPRAY

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____
5. Expiration date (mo/day/yr)
6. model # ____ catalog # ____ serial # ____ lot # ____ other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   - ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

DSS
DEC 17 1999
REC'D.
ADVERSE EVENT REPORTING SYSTEM
DEC 16 1999
MEDWATCH CTU

E. Reporter (see confidentiality section on back)

1. Name & address: (b) (6)
   phone #: (b) (6)
2. Health professional? ☐ yes ☒ no
3. Occupation: ANALYST
4. Also reported to
   - ☒ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☒

FDA Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to 1-800-FDA-0178

RECEIVED
DEC 16'99 AM 10:10
CTU 114269

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM
HF-2

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3417437

Individual Safety Report

3443683-5-00-01

VOLUNTARY reporting
alth professionals of adverse
nts and product problems

Page ___ of ___

CDER

CDER

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 115366

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 18 years or Date of birth: (b) (6)
3. Sex: [X] female [ ] male
4. Weight: 169 lbs or ___ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death (mo/day/yr)
   - [ ] life-threatening
   - [ ] hospitalization – initial or prolonged
   - [X] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event (mo/day/yr): 8/1/99
4. Date of this report (mo/day/yr): 12/29/99
5. Describe event or problem

On Floxin x 2 weeks, began with stiff neck, swollen knee, painful, reddened knuckle, blood work showed slightly Reactive R.A. Factor - elevated Sed Rate - Abnormal elevated Calcium level in Blood/urine - progressed to migratory joint pain, swelling, muscle tenderness, swelling - swollen calf muscle - difficulty walking, ↓ appetite - weight loss - cardiac palpitations - swelling in hands - knees - tendon swelling lasting 5 months going on six -

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

White Race

DSS

JAN 14 2000

CTU 115366

ADVERSE EVENT REPORTING SYSTEM

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 FLOXIN
   #2
2. Dose, frequency & route used
   #1 300 mg BID P.O.
   #2
3. Therapy dates (if unknown, give duration) from to (or best estimate)
   #1 7/5/99 – 7/18/99
   #2
4. Diagnosis for use (indication)
   #1 BLADDER INFECTION
   #2
5. Event abated after use stopped or dose reduced
   #1 [ ] yes [ ] no [X] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 [ ] yes [ ] no [X] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
9. NDC # (for product problems only)
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

REC'D.
JAN 14 2000
MEDWATCH CTU

4. Operator of device
   - [ ] health professional
   - [ ] lay user/patient
   - [ ] other:
5. Expiration date (mo/day/yr)
6. model #
   catalog #
   serial #
   lot #
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   [ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone
   (b) (6)
2. Health professional? [ ] yes [ ] no
3. Occupation: NA
4. Also reported to
   - [X] manufacturer
   - [ ] user facility
   - [ ] distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

Report Status: PARTIAL

3443683-5-00-02

115366

Test			Reference Range	Site Code
SED RATE BY MODIFIED WESTERGREN	73 H		MM/HR	< OR = 20 KP
CBC (INCLUDES DIFF/PLT)				KP
WHITE BLOOD CELL COUNT	5.6		THOUS/MCL	4.5-13.0
RED BLOOD CELL COUNT	3.97 L		MILL/MCL	4.10-5.30
HEMOGLOBIN	10.3 L		G/DL	12.0-16.0
HEMATOCRIT	31.6 L		%	36.0-49.0
MCV	79.5		FL	78.0-102.0
MCH	26.0		PG	25.0-35.0
MCHC	32.7		G/DL	31.0-37.0
RDW	16.5 H		%	9.0-15.0
PLATELET COUNT	228		THOUS/MCL	130-400
ABSOLUTE NEUTROPHILS	3360		CELLS/MCL	1800-8000
NEUTROPHILS	60		%	
ABSOLUTE LYMPHOCYTES	1736		CELLS/MCL	1200-5200
LYMPHOCYTES	31		%	
ABSOLUTE MONOCYTES	336		CELLS/MCL	200-1100
MONOCYTES	6		%	
ABSOLUTE EOSINOPHILS	112		CELLS/MCL	50-500
EOSINOPHILS	2		%	
ABSOLUTE BASOPHILS	56		CELLS/MCL	0-200
BASOPHILS	1		%	
Comprehensive Metabolic Panel without CO2				KP
GLUCOSE	87		MG/DL	70-115
UREA NITROGEN (BUN)	15		MG/DL	7-25
CREATININE	0.8		MG/DL	0.5-1.4
BUN/CREATININE RATIO	19		(CALC)	6-25
SODIUM	137		MEQ/L	135-146
POTASSIUM	4.9		MEQ/L	3.5-5.3
CHLORIDE	102		MEQ/L	95-108
CALCIUM	10.8 H		MG/DL	8.5-10.3
PROTEIN, TOTAL	8.0		G/DL	6.0-8.5
ALBUMIN	4.5		G/DL	3.2-5.0
GLOBULIN	3.5		G/DL (CALC)	2.2-4.2
ALBUMIN/GLOBULIN RATIO	1.3		(CALC)	0.8-2.0
BILIRUBIN, TOTAL	0.3		MG/DL	0.0-1.3
ALKALINE PHOSPHATASE	90		U/L	30-165
AST (SGOT)	23		U/L	0-42
URINALYSIS, COMPLETE				KP
COLOR	YELLOW			YELLOW
APPEARANCE	CLEAR			CLEAR
SPECIFIC GRAVITY	1.013			1.001-1.035
PH	6.5			4.6-8.0
GLUCOSE	NEGATIVE			NEGATIVE
BILIRUBIN	NEGATIVE			NEGATIVE
KETONES	NEGATIVE			NEGATIVE
OCCULT BLOOD	NEGATIVE			NEGATIVE
PROTEIN	NEGATIVE			NEGATIVE
NITRITE	NEGATIVE			NEGATIVE
LEUKOCYTE ESTERASE	NEGATIVE			NEGATIVE

DSS

JAN 14 2000

ADVERSE EVENT REPORTING SYSTEM

see note

CTU 115366

>> REPORT CONTINUED ON NEXT PAGE <<

8/26/99

(b) (6)

REPORT STATUS: FINAL	TEST	RESULT IN RANGE	RESULT OUT OF RANGE	UNITS	REFERENCE RANGE	SITE CODE
	Date of Birth: (b) (6)					115366
	PHOSPHORUS, INORGANIC	3.2		MG/DL	2.5-4.5	K
	COMPREHENSIVE METABOLIC PANEL WITHOUT CO2					K
	GLUCOSE	91		MG/DL	70-115	
	UREA NITROGEN (BUN)	14		MG/DL	7-25	
	CREATININE	0.8		MG/DL	0.5-1.4	
	BUN/CREATININE RATIO	18		(CALC)	6-25	
	SODIUM	142		MEQ/L	135-146	
	POTASSIUM	4.3		MEQ/L	3.5-5.3	
	CHLORIDE	101		MEQ/L	95-108	
	CALCIUM		11.4 H	MG/DL	8.5-10.3	
			VERIFIED BY REPEAT ANALYSIS			
	PROTEIN, TOTAL	7.7		G/DL	6.0-8.5	
	ALBUMIN	3.6		G/DL	3.2-5.0	
	GLOBULIN	4.1		G/DL (CALC)	2.2-4.2	
	ALBUMIN/GLOBULIN RATIO	0.9		(CALC)	0.8-2.0	
	BILIRUBIN, TOTAL	0.5		MG/DL	0.0-1.3	
	ALKALINE PHOSPHATASE	76		U/L	30-165	
	AST (SGOT)	18		U/L	0-42	
	SED RATE BY MODIFIED WESTERGREN		62 H	MM/HR	(OR = 20	K
	CBC (INCLUDES DIFF/PLT)					K
	WHITE BLOOD CELL COUNT	9.2		THOUS/MCL	4.5-13.0	
	RED BLOOD CELL COUNT	4.16		MILL/MCL	4.10-5.30	
	HEMOGLOBIN		10.2 L	G/DL	12.0-16.0	
	HEMATOCRIT		31.8 L	%	36.0-49.0	
	MCV		76.4 L	FL	78.0-102.0	
	MCH		24.6 L	PG	25.0-35.0	
	MCHC	32.1		G/DL	31.0-37.0	
	RDW		16.1 H	%	9.0-15.0	
	PLATELET COUNT	337		THOUS/MCL	130-400	
	ABSOLUTE NEUTROPHILS	6440		CELLS/MCL	1800-8000	
	NEUTROPHILS	70		%		
	ABSOLUTE LYMPHOCYTES	2208		CELLS/MCL	1200-5200	
	LYMPHOCYTES	24		%		
	ABSOLUTE MONOCYTES	460		CELLS/MCL	200-1100	
	MONOCYTES	5		%		
	ABSOLUTE EOSINOPHILS	184		CELLS/MCL	50-500	
	EOSINOPHILS	2		%		
	ABSOLUTE BASOPHILS	0		CELLS/MCL	0-200	

>> REPORT CONTINUED ON NEXT PAGE <<

(b) (6)

OSS
JAN 14 2000
ADVERSE EVENT REPORTING SYSTEM

Individual Safety Report

3443683-5-00-03

CTU 115366

1/10/99

CaseID::3445256

3474283-9-00-01

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

VOLUNTARY reporting [illegible] ealth professionals of adverse ents and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291 Expires: 8/31/00
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 118739

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: or Date of birth: (b) (6)
3. Sex: ☑ female ☐ male
4. Weight: 160 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☑ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply):
   - ☐ death ____ (mm/dd/yyyy)
   - ☑ life-threatening
   - ☑ hospitalization – initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☑ required intervention to prevent permanent impairment/damage
   - ☑ other: ____
3. Date of event: 02/19/1998 (mm/dd/yyyy)
4. Date of this report: 03/11/2000 (mm/dd/yyyy)
5. Describe event or problem:

Levaquin was prescribed to me, took one tab. Adverse reaction - Insomnia, emotional reaction and muscle/nerve discomfort that night in right extremities. Later burning face/eyes.Resulted in Pereipherial Neuropathy diagnosis in April, 1998. I still suffer PN discomfort.

DSS
MAR 1 4 2000

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

preexisting conditions: asthma, thyroid destroyed due to graves disease - thus on synthrcid rest of life. I am white. Iwas not smoking when the adverse reaction to levaquin occured, but did 4 months prior to the incident, and began again in July of 1998.

C. Suspect medication(s)

1. Name (Product Name) / (Labeled Strength) / (Mfr/Labeler)
   - #1 Levaquin
   - #2
2. Dose/Frequency/Route used
   - #1
   - #2
3. Therapy dates (if unknown, give duration) From / To (or best estimate)
   - #1 02/19/1998 - 02/20/1998
   - #2 -
4. Diagnosis for use (separate indications with commas)
   - #1 bronchitis/sinus infection
   - #2
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☑ no ☐ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   - #1
   - #2
7. Exp. date (if known)
   - #1
   - #2
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☐ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only) - -
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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MAR 1 3 2000
MEDWATCH CTU

4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____
5. Expiration date (mm/dd/yyyy)
6. model # ____ catalog # ____ serial # ____ lot # ____ other #
7. If implanted, give date (mm/dd/yyyy)
8. If explanted, give date (mm/dd/yyyy)
9. Device available for evaluation? (Do not send device to FDA)
   - ☑ yes ☐ no ☐ returned to manufacturer on ____ (mm/dd/yyyy)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name: phone # (b) (6)

(b) (6)

United States

2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   - ☑ manufacturer
   - ☑ user facility
   - ☑ distributor
5. If you do not want your identity disclosed to the manufacturer, place an "X" in this box. ☐

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

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MEDWATCH
MEDICAL PRODUCTS REPORTING

CTU 118739

HF-2

Individual Safety Report

3479296-9-00-01

yer

Mfr report M98-526 1

UF/Dist report

e 1 of 2

FDA Use Only

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 55 or Date of birth: (b) (6)
3. Sex: ☒ female ☐ male
4. Weight: 135 lb or 61 kg

B. Adverse event or product problem

1 ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2 Outcomes attributed to adverse event (check all that apply)

☐ death (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☒ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event (mo/day/yr): 19 Oct 1998
4. Date of this report (mo/day/yr): 3/22/00

5 Describe event or problem

[Please refer to next page for complete narrative]

6. Relevant tests/laboratory data, including dates

Patient states that ER physician told her that her sed. rate was elevated and "You have a major inflammation"

[From information received 1 Feb 99:] 14 Nov 98: ESR = 26, CBC = normal; ANA = neg. 21 Nov 98: MRI left ankle, left knee - normal. 23 Nov 98 ANA, CPK, ESR, C3, C4 CRP = normal

7 Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Pancreatitis summer 1998. Was given prednisone 7 yr ago for 5.5 months for "a sympathetic problem in my arm" but became unable to tolerate prednisone and was told she cannot take it again. No recent steroids. Pt was taking no other meds than Cipro and states she was not physically active. [From inf. rec'd 1 Feb 99:] Rheumatic & GI symptoms of uncertain etiology after exhaustive workup. Pancreatic enzymes - ? details.

FDA Form 3500A MC98.DTF

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event. (REV. 10/99)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Cipro tablet
#2 Floxin tablet

2. Dose, frequency & route used
#1 not PO
#2 not po

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 10/15/98 10/19/98
#2 1 day

4. Diagnosis for use (indication)
#1 UTI
#2 UTI

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☒ no ☐ doesn't apply
#2 ☐ yes ☒ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # – for product problems only (if known) _ –

10. Concomitant medical products and therapy dates (exclude treatment of event)
Pancreatic enzymes

G. All manufacturers

1. Contact office – name/address (& mfring site for devices)

Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

MAR 2 3 2000

2. Phone number: (888) 765-3203

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other

4. Date received by manufacturer (mo/day/yr): 20 Mar 2000

5. (A)NDA # 19-537
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
☐ 5-day ☒ 15-day
☐ 10-day ☐ periodic
☒ initial ☐ follow-up # _

8. Adverse event term(s)
ARTHRALGIA
MYALGIA
TENDONITIS
MYASTHENIA
NEURITIS PERIPH

DSS

MAR 2 4 2000

9. Mfr. report number: M98-526 (1)

E. Initial reporter

1. Name, address & phone # (b) (6)

(b) (6)

2. Health professional? ☐ yes ☒ no

3. Occupation: Consumer

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☒ unk

B 5. Describe event or problem

Patient stated she developed pain in her heels, knees, and fingers during therapy with Cipro. She d/c'd Cipro a week ago, but her discomfort remains. She could not identify her prescriber at the time of her report. UPDATE 21 Dec 1998: Patient states she had completed one course of Cipro (indication?) from local clinic, later had calf pain, and attended ER where physician was unable to identify cause of calf pain but determined she had a bladder infection and prescribed Cipro for it, unaware of first course. Stated she was switched to Floxin for last day of course. She stated that an MRI was done and showed nothing, but that her pain subsequently changed and foot got hot. Pt now in wheelchair in severe pain. Taking an anti-inflammatory which is not helping. Will see rheumatologist in a few days.

[From information received 1 Feb 99:] Per MD - 1 day afer beginning Cipro for UTI treated elsewhere, had onset muscle, joint and tendon pain. On 29 Oct 98, pt continued muscle, joint, tendon tenderness - mainly at tendon insertions. No significant objective findings.

[From information rec'd 20 Mar 2000:] Consumer found a follow-up letter, from Drug Safety dated 1998, which requested information about her adverse experience with Cipro. Consequently, she called and reported that she experienced weakness in legs and peripheral neuropathy after taking Cipro for approx. 7 days for a bladder infection. Subsequently, she was wheelchair bound for 4 months; she now has residual leg weakness. (No other details were provided.)

DSS
MAR 2 4 2000
MAR 2 3 2000

CaseID::3456871

3485173-X-00-01

CDER

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

FOR VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 1 of 1

Form Approved: OMB No. 0910-0291 Expires: 8/31/00
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 120219

CDER

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 41 Years or Date of birth: (b) (6)
3. Sex: ☑ female ☐ male
4. Weight: 160 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mm/dd/yyyy)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mm/dd/yyyy): 01/07/1999
4. Date of this report (mm/dd/yyyy): 04/06/2000
5. Describe event or problem

3 days after taking the first tablet of Ciprofloxin initial reactions were severe pain in legs along with onset of hearing loss right ear. Due to misdiagnosis of condition for 6 months paient has been diagnosed with bilateral profound hearing loss, tinnitus, inner ear damage which includes dizziness, non balance, nausea and vomiting. Also severe pains in both arm and legs joints, visual problems which include sensitivity to light and double vision, gastrointestinal problems which include gastritis and a hyatial hernia.

6. Relevant tests/laboratory data, including dates

blood panels 6/99 - 4/00, hearing tests 6/99-4/00. upper & lower endiscopy done 8/99, nuerological exams done 7/99-8/99. optonuerology exams done 7/99 - 2/00, ENT tests done 3/99-4/00

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

high blood pressure under control since 1994, smoked 6 cigarettes per day quit in November 1999.

ctu 20219

C. Suspect medication(s)

	1. Name (Product Name)	(Labeled Strength)	(Mfr/Labeler)
#1	Cipro	500 mg	Bayer
#2			

	2. Dose/Frequency/Route used	3. Therapy dates (if unknown, give duration) From	To (or best estimate)
#1	1/2x day / Pill / Oral	01/05/1999	01/11/1999
#2			

4. Diagnosis for use (separate indications with commas)
   #1 UTI
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☑ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 ukn
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☑ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
   ukn – –
10. Concomitant medical products and therapy dates (exclude treatment of event)
    1/13/99 - 4/5/00 ongoing

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

DSS

APR X 7 2000

REC'D.

4. Operator of device
   ☐ health professional
   ☐ lay user/patient
   ☐ other:
5. Expiration date (mm/dd/yyyy)
6. model #
   catalog # APR 07 2000
   serial #
   lot # MEDWATCH CTU
   other #
7. If implanted, give date (mm/dd/yyyy)
8. If explanted, give date (mm/dd/yyyy)
9. Device available for evaluation? (Do not send device to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on (mm/dd/yyyy)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name
   phone # (b) (6)
   (b) (6)
2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   ☑ manufacturer
   ☐ user facility
   ☐ distributor
5. If you do not want your identity disclosed to the manufacturer, place an "X" in this box. ☑

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787
or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3472347

Individual Safety Report
3498331-5-00-01

VOLUNTARY reporting
alth professionals of adverse
nts and product problems

Form Approved: OMB No. 0910-0291 Expires:12/31/94
See OMB statement on reverse

FDA Use Only
Triage unit sequence # 182083

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 2 CDER Clerk

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: or Date of birth: (b) (6)
3. Sex: [X] female [ ] male
4. Weight: 121 lbs or ___ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply):
   - [ ] death
   - [ ] life-threatening
   - [ ] hospitalization - initial or prolonged
   - [X] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event (mo/day/yr): 2-14-00
4. Date of this report (mo/day/yr): 5-2-00
5. Describe event or problem:

narrative attached —

DSS
MAY 10 2000

6. Relevant tests/laboratory data, including dates:

N/A

RECEIVED
MAY 10 2000
MEDWATCH-OTU

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.):

Fax - white
non pregnant
no cigs - no ETOH
no hx liver/kidney dysfunction

See narrative

RECEIVED
MEDWATCH-OTU
HF-2

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler if known)
   #1 Levaquin 500mg p.o.
   #2
2. Dose, frequency & route used
   #1 p.o. 500mg QD
   #2
3. Therapy dates (if unknown, give duration) (mo/day/yr)
   #1 2-14-00
   #2
4. Diagnosis for use (indication)
   #1 Sinusitis
   #2
5. Event abated after use stopped or dose reduced
   #1 [ ] yes [X] no [ ] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
6. Lot # (if known)
   #1 19N542
   #2
7. Exp. date (if known)
   #1 Oct 02
   #2
8. Event reappeared after reintroduction
   #1 [X] yes [ ] no [ ] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
9. NDC # (for product problems only)
   0045-1525-06
10. Concomitant medical products and therapy dates (exclude treatment of event)

N/A

see hx — med taken 7yr. ago

D. Suspect medical device

1. Brand name: N/A
2. Type of device: N/A
3. Manufacturer name & address: N/A
4. Operator of device
   - [ ] health professional
   - [ ] lay user/patient
   - [ ] other:
5. Expiration date (mo/day/yr)
6. model #
   catalog # N/A
   serial #
   lot #
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   [ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

N/A

E. Reporter (see confidentiality section on back)

1. (b) (6)
2. Health professional? [X] yes [ ] no
3. Occupation: M.D.
4. Also reported to
   - [ ] manufacturer
   - [ ] user facility
   - [ ] distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787
or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report
3498331-5-00-02

1.2 A 2 122083

RECEIVED
MAY 10 2000
MEDWATCH CTU

My Levaquin Story

March 1999

I went to the Doctor because of neck pain and ear pressure. The Dr. thought it could possibly be a sinus infection and so she prescribed Levaquin, 500 mg. for 7-10 days. After a day or two I was feeling very sick, trembling, shaky, weak, dizzy, no appetite and lights and noises bothered me. I had a difficult time getting through one hour of work, due to my symptoms. These symptoms lasted about a month and then pretty much went away. I didn't connect these symptoms to the Levaquin at that time.

In April of 1999 I noticed that my eyesight was not as good, so I went to the eye doctor for the first time in my life.

February 14, 2000

I went to the Doctor today for the same possible sinus infection. She again prescribed Levaquin, 500 mg. I took 1 Levaquin tablet at about 6:00PM.

At about 11:00PM I awoke with my heart racing, chest pain, fear, and I felt like I couldn't breathe. I basically sat up all night trying to ease the discomfort. I knew the Levaquin had caused this reaction and I thought it would go away soon. But it didn't go away-it got worse. I called the doctor and she told me not to take the Levaquin. On the (b) (6) the pain in my chest became more severe and I was trembling and felt shaky "inside." That evening I started worrying that maybe I was having a heart attack so I took a couple of aspirin. The pain and panic got worse until I went up to the Emergency Room at the hospital. They said the Levaquin would be out of my system in 72 hours and sent me home. I went home and had continuous panic attacks, severe chest pain, sweating, chills, trembling, dizziness, head pressure, pain in right eye and burning and numbness in right cheek and head. When I would try to sleep, just as I was about to doze off, I would feel a sudden sensation that felt like "an electric shock" that would make my chest feel like it was on fire and then radiate into my arms. I would also startle severely at the slightest noise. The flushing of a toilet seemed like a bomb went off right next to me. My symptoms continued for four weeks before I realized that I was experiencing severe panic attacks. I have never experienced anxiety or depression ever before. The attacks, startling, and all my symptoms were so difficult that I could hardly function, so my sisters took me to stay with family in Utah to try to recover.

DSS
MAY 10 2000

It has now been two months since I took the first dose of Levaquin. My life today is different from what it used to be. I've lost 20 pounds, I'm still trembling, I still startle at the slightest thing, and the other symptoms have improved only a little. I used to easily and happily cook and clean and do normal household chores and now even these tasks overwhelm me. I've always dearly loved spring and working out in my yard and flowers, but now I have to make myself go out. It is a chore instead of the fun and the love that it's always been. I have 2 grandchildren ages 3 and 4 years that I used to babysit eight hours a day for my daughter who was going to school. I can no longer help with my grandkids and it breaks my heart. It's just too hard on me.

The most difficult thing for me is to see how this has affected my family. They are so supportive and kind, but I see that it is taking its toll on them. The other night I asked my teenaged daughter how she was feeling about this whole thing. She paused, then through her tears said, "I just want my Mom back." She said it well. I just want my life back.

RECEIVED
MEDWATCH

CaseID::3571163

Individual Safety Report

3664798-2-00-01

MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

PHARM. RES. INST. USA
For use by user-facilities, distributors and manufacturers for
MANDATORY reporting

Page 1 of 2

Approved by FDA on 09/25/95

Mfr report #: PRIUSA200001217()
UF/Dist report #:
FDA Use Only

A. Patient information

1. Patient identifier: (b) (6) In confidence
2. Age at time of event: 84 yr or Date of birth: (b) (6)
3. Sex: [x] female [ ] male
4. Weight: 129 lbs or ____ kgs

B. Adverse event or product problem

1. [x] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____ (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization - initial or prolonged
- [x] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event (mo/day/yr): 02/10/00
4. Date of this report (mo/day/yr): 02/12/01

5. Describe event or problem

A woman reports that on 8-Feb-00 her mother (age unspecified) was prescribed a seven-day course of LEVAQUIN (levofloxacin) 500 mg (route unspecified) for a bladder infection. She states that two days later her mother developed severe pain in her heels with difficulty walking and was seen by a physician. LEVAQUIN was not discontinued. By 15-Feb-00 the pain was severe and "her heels had turned black". Her mother was prescribed celecoxib for inflammation. The pain and discoloration persisted. On 23-Feb-00 her mother was diagnosed with bilateral partially rupture Achilles tendons, confirmed with MRI. Her mother was unable to be treated surgically and has undergone extensive physical therapy. She states "this side effect causes my mother pain, suffering, limited mobility, and humiliation". She states that her mother "continues to suffer pain, little sense of balance, and great difficulty walking which has resulted in lots of falls resulting in cracked ribs, significant bruising, and large scrapes". She states that her mother "is presently recovering from a fall on 18-Sep-00 that resulted in an area of skin (Cont.)

6. Relevant tests/laboratory data, including dates

23-Feb-00: MRI confirmed bilateral, partially ruptured Achilles tendons

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Allergy
Additional information received 30-Jan-01: polymyalgia rheumatica, hypertension and allergy to penicillin

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 LEVAQUIN(unspecified)(LEVOFLOXACIN)
#2

2. Dose, frequency & route used
#1 500 mg, daily, oral
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 02/08/00 - 02/14/00
#2

4. Diagnosis for use (indication)
#1 CYSTITIS
#2

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [x] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [x] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
No Concomitant Products Reported

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
R.W. JOHNSON PHARM. RES. INST.
USA
DIV. OF ORTHO PHARMACEUTICAL CORP.
920 U.S. Route 202
P.O. Box 300
Raritan NJ 08869
USA
(Informing Unit)

2. Phone number: 908-704-4504

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [x] consumer
- [x] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer (mo/day/yr): 01/30/01

5. (A)NDA # 20-634
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
- [ ] 5-day
- [x] 15-day
- [ ] 10-day
- [ ] periodic
- [ ] Initial
- [x] follow-up # 1

8. Adverse event term(s)
1) TENDON DISORDER
2) ATAXIA
3) GAIT ABNORMAL
4) ACCIDENTAL INJURY

9. Mfr. report number
PRIUSA2000012170

E. Initial reporter

1. Name, address & phone #
Unidentified Physician
ID
USA

DSS
FEB 14 2001

2. Health professional? [x] yes [ ] no
3. Occupation: Physician
4. Initial reporter also sent report to FDA [ ] yes [ ] no [x] unk

3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

R.W. JOHNSON PHARM. RES. INST. USA
DIV. OF ORTHO PHARMACEUTICAL CORP.
920 U.S. Route 202
P.O. Box 300
Raritan NJ 08869
USA



Continuation Sheet for FDA-3500A Form Page 2 of 2

Mfr. report # : PRIUSA2000012170

Date of this report : 02/12/01

B. Adverse event or product problem

B.5 Describe event or problem (Cont...)

approximately 3" by 5" being torn open".

Additional information received 30-Jan-01 from physician: "Report as stated above is correct". Additional information provided: date of birth: (b) (6) patient weight: 129 lbs; history includes polymyalgia rheumatica, hypertension and allergy to penicillin. LEVAQUN formulation specified as tablets. Reporter states: "My diagnosis was confirmed by orthopedist".

DSS

FEB 1 4 2001

Individual Safety Report

#3626137-2-00-01#

;ON PHARM. RES. INST. USA

For use by user-facilities, distributors and manufacturers for **MANDATORY** reporting

Approved by FDA on 09/25/95

Mfr report # PRIUSA2000002337

UF/Dist report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient identifier: (b) (6) — In confidence
2. Age at time of event: or 46 yr — Date of birth: ??/???/??
3. Sex: [x] female [ ] male
4. Weight: 115 lbs or ____ kgs

B. Adverse event or product problem

1. [x] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ____ (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization - initial or prolonged
- [x] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other: ____

3. Date of event (mo/day/yr): ??/???/??

4. Date of this report (mo/day/yr): 09/12/00

5. Describe event or problem

A 46 year-old woman (weight 115 lb) was prescribed LEVAQUIN (levofloxacin) 500 mg PO on 7-Feb-00 for bronchitis. No concomitant medication was reported. After one or two days of LEVAQUIN therapy she developed a "funny feeling" (not sure if it was pain at this point) in her ankles, gas and nausea. Her physician decreased the LEVAQUIN dosage to 250 mg PO daily. On or about the fourth or fifth day, she experienced pain behind her knees (especially the left knee) which has persisted (three weeks at the time of this report) and prevents her from doing her normal activities. She is also experiencing "twinges" in her elbows and shoulders. Her eye muscles hurt and she was having trouble focusing but this has improved. No further information provided.

Additional information received 22-Jun-00 from physician: as of 9-Jun-00 the patient's "symptoms were all gone when at rest; she is 80% back to baseline when she exerts self; the aches are all over when they occur and improve with rest; she is able to do all her usual activities except run".

(Cont.)

6. Relevant tests/laboratory data, including dates

Additional information received 31-Aug-00: date unspecified: TSH (thyroid stimulating hormone): 0.3. CBC, FBS, BUN and urinalysis normal.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 LEVAQUIN(tablet)(LEVOFLOXACIN)
#2

(Cont.)

2. Dose, frequency & route used
#1 500 mg, daily, oral
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 02/07/00 - ??/???/??
#2

4. Diagnosis for use (indication)
#1 ACUTE BRONCHITIS
#2

5. Event abated after use stopped or dose reduced
#1 [ ] yes [x] no [ ] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [x] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
No Concomitant Products Reported

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
R.W. JOHNSON PHARM. RES. INST.
USA
DIV. OF ORTHO PHARMACEUTICAL CORP.
920 U.S. Route 202
P.O. Box 300
Raritan NJ 08869
USA
(Informing Unit)

2. Phone number: 908-704-4504

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [x] consumer
- [x] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other: ____

4. Date received by manufacturer (mo/day/yr): 03/06/00

5. (A)NDA # 20-634
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [x] periodic
- [x] Initial [ ] follow-up # ____

8. Adverse event term(s)
1) ARTHRALGIA
2) FLATULENCE
3) NAUSEA
4) MYALGIA
5) VISION ABNORMAL

9. Mfr. report number: PRIUSA2000002337

E. Initial reporter

1. Name, address & phone #: (b) (6)

NOV 30 2000

2. Health professional? [x] yes [ ] no

3. Occupation: Physician

4. Initial reporter also sent report to FDA: [ ] yes [x] no [x] unk

3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

R.W. JOHNSON PHARM. RES. INST. USA
DIV. OF ORTHO PHARMACEUTICAL CORP.
920 U.S. Route 202
P.O. Box 300
Raritan NJ 08869
USA

Individual Safety Report

3626137-2-00-02

Continuation Sheet for FDA-3500A Form Page 2 of 2

Mfr. report # : PRIUSA2000002337

Date of this report : 09/12/00

B. Adverse event or product problem

B.5 Describe event or problem (Cont...)

Additional information received 31-Aug-00 from physician: as of 26-Jul-00 most of her symptoms have resolved. Her aches only occur with heavy exertion. On last labs of 26-Jul-00, patient has new onset of hyperthyroidism. Unclear at this time if some of her symptoms may be related to this problem. Date unspecified: TSH (thyroid stimulating hormone): 0.3, CBC, FBS, BUN and urinalysis normal.

C. Suspect medication (Cont...)

Seq No. : 1
C.1 Suspect medication : LEVAQUIN(tablet)(LEVOFLOXACIN)
C.2 Dose, frequency & route used : 2) 250 mg, daily, oral

NOV 3 0 2000

CaseID::3640803

Individual Safety Report

3704768-9-00-01

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

OLUNTARY reporting
th professionals of adverse
~~ts and product~~ problems

Internet Submission - Page 1 CDER

Form Approved: OMB No. 0910-0291 Expires: 04/30/01
See OMB statement on reverse

FDA Use Only
Triage unit sequence # 141301

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 46 Years or Date of birth: (b) (6)
3. Sex: ☑ female ☐ male
4. Weight: 104 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mm/dd/yyyy)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ____
3. Date of event (mm/dd/yyyy): 02/09/2000
4. Date of this report (mm/dd/yyyy): 04/12/2001
5. Describe event or problem

I was treated in the emergency room for a UTI. The treating physician administered Floxin, 400 mg and prescribed a course of treatment for seven days, 2 x daily, thereafter. There was no mention of any possible side effects from taking this medication. Three days later I began having tremors, increased heart rate, anxiety, sleeplessness and extreme ringing in my ears. I was unable to reach the treating physician and had my medication changed by a nurse practitioner. I discontinued use of Floxin. I now have tinnitis, and permanent purpura. I had to undergo extensive testing and am now in therapy in an attempt to restore some semblance of normalcy to my life. I have lost my live savings and my job. I am unable to work and I now live with my mother.

6. Relevant tests/laboratory data, including dates

I have undergone extensive testing at (b) (6). I have had extensive blood work and AIDS testing (b) (6) and (b) (6) Hospital in (b) (6) audiology testing -Dr. (b) (6) (b) (6) ENT; (b) (6) Clinic; (b) (6) Clinic; , MRI (b) (6) Hospital in (b) (6)

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

I have no allergies. I am a white female. I am a smoker. I do not use alcohol. I have tested positive in the past for low grade hepatitis C. I had one kidney infection prior to the UTI event that I was given Floxin for.

CTV141301

C. Suspect medication(s)

1. Name (Product Name) / (Labeled Strength) / (Mfr/Labeler)
   - #1 Floxin / 400mg. / Ortho-McNeil
   - #2
2. Dose/Frequency/Route used
   - #1 400mg / 2 times / Oral
   - #2
3. Therapy dates (if unknown, give duration) From / To (or best estimate)
   - #1 02/09/2000 - 02/13/2000
   - #2
4. Diagnosis for use (separate indications with commas)
   - #1 Urinary Tract Infection
   - #2
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☐ no ☑ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   - #1
   - #2
7. Exp. date (if known)
   - #1
   - #2
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☑ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

I have extensive treatment to determine the problem and the extent of damage caused by the use of this medication

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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APR 16 2001

4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____
5. Expiration date (mm/dd/yyyy)
6. model # MEDWATCH CTU
   catalog # ____
   serial # ____
   lot # ____
   other # ____
7. If implanted, give date (mm/dd/yyyy)
8. If explanted, give date (mm/dd/yyyy)
9. Device available for evaluation? (Do not send device to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____ (mm/dd/yyyy)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name / phone # (b) (6)
   (b) (6)
2. Health professional? ☑ yes ☐ no
3. Occupation: Other Health Professional
4. Also reported to
   - ☑ manufacturer
   - ☑ user facility
   - ☐ distributor
5. If you do not want your identity disclosed to the manufacturer, place an "X" in this box. ☑

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

APR 13 2001

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3741011

U.S. Department of Health and Human Services

Individual Safety Report

3838510-8-00-01

For VOLUNTARY reporting of events and product problems

CDER

Page 1 of 1

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only
Triage unit sequence # 157040

A. Patient information

1. Patient identifier: In confidence
2. Age at time of event: or Date of birth: (b) (6)
3. Sex: ☒ female ☐ male
4. Weight: 143 lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☒ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ____
3. Date of event (mo/day/yr): June 2001
4. Date of this report (mo/day/yr): 11/28/2001
5. Describe event or problem

Contracted Sinus infection while on road trip from East Coast to (b) (6) state. Progressed to bronchitis with deep productive cough. Took Cipro, began to feel muscle aches within 24 hours, upper legs, upper arms. Took 10 day course of Cipro. Upon arrival home and increased activity, my condition worsened. Massage therapist pointed out that pain was associated with attachment points of connective tissues and joint pain. Contacted my physician. Am currently taking Ibuprofen to decrease inflammation and pain. Am unable to work sitting down for more than an hour at a time, cannot lift or carry more than about 10 pounds and must do stretching exercises daily to help maintain range of motion. Also experienced total loss of sense of smell. Connective tissues of upper back and neck are involved as well.

6. Relevant tests/laboratory data, including dates

7/26/2001 ESR = 33 mm/hr
8/8/2001 ESR = 23 mm/hr

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

CTVIS 7040

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 Cipro (500 mg) (Bayer)
   #2
2. Dose, frequency & route used
   #1 500 mg twice daily by mouth
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1 June 7, 2001 for 10 days
   #2
4. Diagnosis for use (indication)
   #1 Sinusitis → Bronchitis
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☒ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 unknown
   #2
7. Exp. date (if known)
   #1 unknown
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
   000 268 5135 1
10. Concomitant medical products and therapy dates (exclude treatment of event)

Premarin and Progesterone - have been taking these medications for 8 years.

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

RECEIVED
DEC 11 2001
MEDWATCH CTU

4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____
5. Expiration date (mo/day/yr)
6. model # ____ catalog # ____ serial # ____ lot # ____ other # ____
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address: (b) (6)
   phone # (b) (6)
2. Health professional? ☐ yes ☒ no
3. Occupation: Stay-at-home mom
4. Also reported to
   - ☒ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

PLEASE TYPE OR USE BLACK INK

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3757438

U.S. Department of Health and Human Services

Individual Safety Report

3858954-B-00-01

FDA VOLUNTARY reporting of events and product problems

Page 1 of 3 CDER

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only
Triage unit sequence # 160006

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 27 or Date of birth: (b) (6)
3. Sex: [X] female [ ] male
4. Weight: 150 lbs or kgs

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse even (check all that apply)
[ ] death (mo/day/yr)
[ ] life-threatening
[ ] hospitalization - initial or prolonged
[X] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[ ] other

3. Date of event (mo/day/yr): 11/25/01
4. Date of this report (mo/day/yr): 12/11/01

5. Describe event or problem

I took first dose of Avelox the morning of 11/23/01. Approx. 1 hr. later I felt a bit lightheaded and had itching of RIGHT ankle. This disappeared within 10 MIN My next symptom was on 11/25/01, I awoke in the morning with a severe stiff neck. The pain increased and spread down my back by the end of the day. ON 11/26/01, I took another dose of Avelox. Approx. 6 HRS later, the sensations in my muscles were severe. I had weakness in my arms, legs, wrists, ankles, knees, shoulders, neck, back, hands. My arms were too -CONTINUED-

6. Relevant tests/laboratory data, including dates

SEE ATTACHED

DSS
JAN 25 2002

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

WHITE, NONSMOKER, OCCASIONAL ALCOHOL USE, NO OTHER MEDICAL PROBLEMS

COV160006

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 MOXIFLOXACIN - AVELOX
#2 N/A

2. Dose, frequency & route used
#1 400 mg orally ONCE DAILY
#2 —

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 11/23/01 - 11/27/01
#2 —

4. Diagnosis for use (indication)
#1 Bronchitis
#2 —

5. Event abated after use stopped or dose reduced
#1 [ ] yes [X] no [ ] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
#1 UNK
#2 —

7. Exp. date (if known)
#1 UNK
#2 —

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [X] doesn't apply
#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # (for product problems only)
N/A

10. Concomitant medical products and therapy dates (exclude treatment of event)
N/A

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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4. Operator of device
[ ] health professional
[ ] lay user/patient
[ ] other:

5. Expiration date (mo/day/yr)

6. model # MEDWATCH CTU
catalog #
serial #
lot #
other #

7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address (b) (6)
phone # (b) (6)

2. Health professional? [ ] yes [X] no
3. Occupation
4. Also reported to
[ ] manufacturer
[ ] user facility
[ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787
or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3757438

(b) (6)

Patient Name: (b) (6) .3 Client: (b) (6) 9999

160006

Access#/ID: 16554611

Sex/DOB: F NON-FASTING

APT PHONE #: (b) (6)

(b) (6)

SS #: (b) (6)

Collected: 12/04/01 17:35
Received: 12/04/01 17:44
Reported: 12/06/01 13:00
Re-reported:
Report Status: FINAL

Page: 1

Test	In Range	Out of Range	Reference	Units	LOC
CBC/PLATELETS					
WHITE CELL COUNT	7.8		4.1-11.3	THOU/UL	
RED CELL COUNT	4.42		3.9-5.1	MILL/UL	
HEMOGLOBIN	14.2		12.0-16.0	G/DL	
HEMATOCRIT	42.5		36.0-48.2	%	
MCV	96		80-103	FL	
MCH	32.1		27.0-34.0	PG	
MCHC	33.3		31.0-36.0	GM/DL	
PLATELET COUNT	245		150-400	THOU/UL	
NEUTROPHILS	54		40-75	%	
LYMPHOCYTES	36		20-45	%	
MONOCYTES	7		0-12	%	
EOSINOPHILS	2		0-5	%	
BASOPHILS	0		0-3	%	
PLEASE NOTE NEW NORMAL RANGE(S)					
HEMATOLOGY					
ESR (WESTERGREN)	9		0-20	MM/HR	
IMMUNOLOGY					
ANTINUCLEAR ANTIBODY					
ANA		1.7 H POSITIVE	[illegible]	EXH UNITS	T2
COMPREHENSIVE METABOLIC PANEL/ COMPREHENSIVE METABOLIC PANEL					
GLUCOSE	88		60-120	MG/DL	
UREA NITROGEN	13		6-24	MG/DL	
CREATININE	0.7		0.5-1.5	MG/DL	
CALCIUM	9.4		8.5-10.4	MG/DL	
SODIUM	141		135-148	MEQ/L	
POTASSIUM	4.0		3.5-5.5	MEQ/L	
CO2	26		20-31	MEQ/L	
CHLORIDE	101		95-109	MEQ/L	
PROTEIN, TOTAL	7.6		6.0-8.2	G/DL	
ALBUMIN	5.0		3.5-5.0	G/DL	
GLOBULIN	2.6		2.0-3.5	G/DL	
A/G RATIO	1.9		1.0-2.5	RATIO	
BILIRUBIN, TOTAL	0.4		0.2-1.2	MG/DL	
ALKALINE PHOSPHATASE	93		30-130	IU/L	
AST (SGOT)	19		0-45	IU/L	
ALT (SGPT)	12		0-50	IU/L	
TROPONIN I					
TROPONIN I	0.20		(1.50)	NG/ML	T2
CHEMISTRY					
URIC ACID	2.6		2.0-6.5	MG/DL	
CREATINE KINASE TOTAL (CK)					
CPK	50		26-140	IU/L	
ENDOCRINOLOGY					
THYROID STIMULATING HORMONE (TSH)					
TSH	1.28		0.35-5.50	MIU/ML	

Individual Safety Report
3858954-8-00-02

DSS
JAN 25 2002

12/7/01

160006

LAST PAGE OF REPORT

MEDICAL DIRECTORS: (b) (6)

See side for Performin

Individual Safety Report

3858954-8-00-03

160006

B5

Weak to comfortably lift, carry anything, or write. My legs were weak and burning while walking or climbing stairs. I had a burning sensation throughout all muscles. I could not bend over to touch my toes without severe pulling/burning in back of knees, back, ankles, shins. My arms hurt/burned to hold a telephone to my ear. Over the next few days, the "PAIN" went away, but I am now left with an "exhausted" feeling in my bicepts, thighs, and forearm. Upon sitting my legs have a cold/wet sensation from my knees to my ankles, and my feet are extremley cold. I have minimal involvement in my back/neck. I experienced no numbness or pain on touch, only muscle weakness with burning and bouts of pain. The "coldness" feeling in my legs are unbarable at times while sitting. I am very concerned!!!

160006

CaseID::3779284

U.S. Department of Health and Human Services

Individual Safety Report

3893264-4-00-01

VOLUNTARY reporting of
se events and product problems

rnet Submission - Page 1 of 3

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 164696

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 65 Years or Date of birth:
3. Sex: [x] female [ ] male
4. Weight: 170 lbs or ____ kgs

B. Adverse event or product problem

1. [x] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - [ ] death (mo/day/yr)
   - [ ] life-threatening
   - [ ] hospitalization - initial or prolonged
   - [x] disability
   - [ ] congenital anomaly
   - [ ] required intervention to prevent permanent impairment/damage
   - [ ] other:
3. Date of event (mo/day/yr): 05/11/2001
4. Date of this report (mo/day/yr): 03/29/2002
5. Describe event or problem

Experienced extreme pain and weakness in my thighs, hips and knees within 1 hour after takin 1st dose. I could not get up from a sitting position without assistance. My walking gait became slow and halting, very painful. I have experienced extreme and constant ringing in my ears, a large protrusion, baseball size, came up on my wrist within 3 days which went away after 3 more days. I experienced nightly acid reflux for about 20 days. My left ankle began to swell to about 2x its size and another but slightly smaller protrusion came on my alkle. This lasted 1 day. I experienced rapid deterioriation of my eyesight with a new prescription required after only 1 year. The swelling now seems to be gone and the weakness and pain is much better but not gone. Sometimes, for no apparent reason, it gets worse again. The awkward gait is still evident. Vitamins, Calcium,

6. Relevant tests/laboratory data, including dates

The physician took blood tests to determine what was causing my problem but I never heard anything from him. I was afraid to call him and have him prescribe another medication for something I didn't have. I have been treating this problem with vitamins and minerals. I tried exercise but it just made the pain worse.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

I had gone to the doctor for my annual well woman's physical. People believe that I am in my 40s. I have had 4 children and was in excellent condition. I am happly married. I am alergic to sulfa drugs. I am caucasian, do not smoke or drink. I had hipatitus in 1960.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 Levofloxacin 500mg
   #2
2. Dose, frequency & route used
   #1 once day
   #2
3. Therapy dates (if unknown give duration) (from/to or best estimate)
   #1 05/11/2001 05/17/2001
   #2
4. Diagnosis for use (indication)
   #1 Urinary Tract Infection - misdiagnosed
   #2
5. Event abated after use stopped or dose reduced
   #1 [ ] yes [x] no [ ] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 [ ] yes [ ] no [ ] doesn't apply
   #2 [ ] yes [ ] no [ ] doesn't apply
9. NDC # (for product problems only)
10. Concomitant medical products and therapy dates (exclude treatment of event)

Previous diagnosis of UTI on April 17, 2001, Dr. perscribed unknown antibiotic. Adverse Drug Reaction caused ceasation of all

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - [ ] health professional
   - [ ] lay user/patient
   - [ ] other:
5. Expiration date (mo/day/yr)
6. model # catalog # serial # lot # other #

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APR 0 2 2002
MEDWATCH CTU

7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   [ ] yes [ ] no [ ] returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address: (b) (6)
   phone # (b) (6)
   (b) (6)
   APR 0 2 2002
   (b) (6)
   .com
2. Health professional? [ ] yes [x] no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   - [x] manufacturer
   - [x] user facility
   - [ ] distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

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CTU 164696

Received

Individual Safety Report

3893264-4-00-02

164698

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 2 of 3

B5. Describe event or problem continued

Magnesium and MSM seem to be helping. Walking is still halting and painful. I was a very energetic and physically fit person before. I am now tired a lot of the time. This was reported to the doctor and to the manufacturer at the time it happened-case # 219283. The doctor said it wasn't possible to be caused by the Levaquin tablets.

DSS

APR 0 2 2002

Individual Safety Report

3893264-4-00-03

MEDWATCH

164696

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page ~~5~~ 3 of 3

C10. Concomitant medical products and therapy dates continued

persperation. This antiobiotic was stopped immediately and replaced with a prescription for Macrobid 100mg. UTI went away.

D10. Concomitant medical products and therapy dates continued

DSS

APR 0 2 2002

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

164696

CaseID::3784204

U.S. Department of Health and Human Services

Individual Safety Report

3901189-0-00-01

For VOLUNTARY reporting of adverse events and product problems

CDER

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 165877

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 58 Years or Date of birth: (b) (6)
3. Sex: ☑ female ☐ male
4. Weight: 128 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr): 06/10/2001
4. Date of this report (mo/day/yr): 04/11/2002
5. Describe event or problem

I was perscribed Cipro for a UTI in June. After taking three pills I noticed joint pain in my knee- this lasted for 3 weeks-. I was told to continue and finish the Cipro anyway. Then about a month later during a massage, I noticed numbness from the left side of my neck down my left arm and from my left ankle up to my left knee. For the next several months this numbness came and went until it finally stayed fairly permanently - along with pain with any extended walking-. Vega machine used by Dr. Solomon revealed that yes, Cipro was responsible for my neuropathy symptoms. - Right arm also becamesensitive and intermittently numb and painful

6. Relevant tests/laboratory data, including dates

MRI of cervical spine was normal. B12 in blood was normal. Diabetes tests were normal.THat left the Cipro.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Yes I have allergies - mold/.pollen-and sensitivity to chemicals- paint, lysol etc-.

MEDWATCH

CTV165877 APR 16 2002

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   - #1 Cipro
   - #2
2. Dose, frequency & route used
   - #1 one tab/d 5 days
   - #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   - #1
   - #2
4. Diagnosis for use (indication)
   - #1 Cipro given for UTI
   - #2
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☑ no ☐ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   - #1
   - #2
7. Exp. date (if known)
   - #1
   - #2
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☑ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only) - -
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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APR 17 2002
MEDWATCH CTU

4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model # / catalog # / serial # / lot # / other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

DSS
APR 17 2002

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address: (b) (6)
   phone #: (b) (6)
2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

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FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3795918

05/13/2002 21:28 (b) (6) (b) (6) PAGE 04

Individual Safety Report

3918782-1-00-01

VOLUNTARY reporting
...lth professionals of adverse
...te and product problems

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB Statement on reverse.

FDA Use Only
Triage unit sequence # 168327

A. Patient Information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 13 or Date of birth: (b) (6)
3. Sex: ☒ female ☐ male
4. Weight: 120 lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g. defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
☒ disability
☐ death
☐ congenital anomaly
☐ life-threatening
☐ required intervention to prevent permanent impairment/damage
☐ hospitalization – initial or prolonged
☐ other:
3. Date of event: 5.13.98
4. Date of this report: 5.13.02
5. Describe event or problem: 13 y/o old female given Levaquin 500 mg 1/day for 10 days for sinusitis. Pt complained on the 6th day that wrists hurt. Mother could see nothing wrong Dr said continues (also stated that she felt funny). 3 days after cessation, pt sent home from school with severe pain + not "feeling right" with swollen wrists + ankles. Pt. taken to Dr. complained of pain around achilles tendon, neck into shoulders, wrists (swollen). Pt given wrist braces (see report). Pain cont - referred to Rheu at CHOC & arthritis or Immune problems (see report). This is the first time pt reported overall body pain in her life. Pt. now 17 continues to suffer from arthralgias, myalgias + neuropathic pain. Continues to see 2 Drs for pain management - does not function well.
6. Relevant tests/laboratory data, including dates

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MEDWATCH CTU

Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
Repetitive sinus infection
One head injury 1½ yr old E.R (not unconscious) & concussion

CTU168327

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer if known)
#1 Levaquin 500mg
#2
2. Dose, frequency & route used
#1 500 mg 1/day x 10 days p.o.
#2
3. Therapy dates (if unknown, give duration)
#1 4.30.98 - 5.10.98
#2
4. Diagnosis for use (indication)
#1 Sinusitis
#2
5. Event abated after use stopped or dose reduced
#1 ☐ yes ☒ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
#1
#2
7. Exp. date (if known)
#1
#2
8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
10. Concomitant medical products and therapy dates (exclude treatment of event)
Guaifenex 1200 mG 4.30.98 (pt. only took 2 doses)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device ☐ health professional

In phone con. w/ Reporter, Reporter indicates Report Made in 1998. I could not locate and Recommendation See Research

(b) (6)

Ph (b) (6)

(b) (6)

E. Reporter (see confidentiality section on back)

1. Name, address & phone # (b) (6)
2. Health professional? ☐ yes ☒ no
3. Occupation: Self
4. Also reported to ☐ manufacturer

Mail to: MEDWATCH or FAX to:

Received 5/13/02

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM
HF-2

5-4- D.

MAY 20 2002

05/03/2002 13:04 (b) (6) (b) (6) (b) (6) PAGE ~~13~~

D.O.B. female caucasian

P266

168327

4/30 98 given Levaquin 500 mg x10

13 yr old for sinus infection.
Pt complained on 6th day that
her wrists hurt. Mother could find
no signs of a problem. (wrists not
swollen). Complained that she didn't
"feel right." Reported to Dr. →
finish course (by phone). Took for
10 days. On the 13th day (3 days
after finishing course) pt sent home
from school with severe pain &
not "feeling right." Wrists were
swollen, reported pain down side
of neck into shoulder & achilles tendons.
(see Dr Duda). Pain con't. → (b) (6)
referred to (b) (6) (b) (6) Dr.
tests done & arthritis.
Pt now 17 continues to have
arthralgia, myalgias, neuropathic
pain + CNS symptoms.

Individual Safety Report
3918782-1-00-02

168327 13

DSS
MAY 20 2002

CaseID::3795918

05/03/2002 13:04 (b) (6) (b) (6) PAGE 16

OF BIRTH MOTHER'S NAME FATHER'S NAME FORM

DIAGNOSIS CPT CODE SUBJECTIVE OBJECTIVE ASSESSMENT PLANS ALLERGIES

Individual Safety Report

3918782-1-00-04

P 4586
168327

WEDNESDAY, MAY 13 1998

40 wrist pain x 1 wk
most dose swollen
L wrist sprain 2 days ago T-98.4
generic diclofenac (120 mg) ½ tab bid
- no known injury, does manage
ADL not affected. Is R-handed - uses a computer
<1% arthritis For 1 week has had pain
pseudarthrosis. (L) L 7 1
Transmission not being (R) x 2 d.
tendinitis + tendon rupture. Cont pain no A x time of day.
arthropathy in wrist + ROM → T pain - particularly (L)

CBC SR ANA Rheumatoid fact CRP

- wrist swelling noted x 2 wks. L>R. - began some time from school beg. swollen + 40 pain.
- shoulder hurt last sept - fell onto it playing ball, but it's been hurting - a month ago - o
knees hurt + swelling
No GI Sx (diarrhea, GI, nausea, reflux)
Conjunctivitis (Sinus) → better now after completing Zithromax
no rash

Ophth. - Tri -

(L) dc from (L) leg - seen x few days.
ROS: 40 adult female well.
- epigastric distress.
- HA
- rash

wrist splint

PE: Tall WM in pleasant Eyes T Chest -
(L) wrist - altho minimal sty it is visibly swollen I could see effusion if - pain + loss flexion (L). (R) less pain + swelling

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168327 16 DSS MAY 20 2002

05/03/2002 13:04 (b) (6) (b) (6) PAGE 1 546

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168327

Individual Safety Report
3918782-1-00-05

- no other pt involved.

Lip: arthralgia - knees
- just on Levaquin (prescribed by Dr Kaslow pt's metabolic specialist - treating Lyme for Tcoffee)

Plan - esc/SR/CRP/Rh factor/ANA.
to pedo ophth to r/o uveitis by slit lamp. w/ stop off of Levaquin. x 2 days.

5th PC - no answer

UR

5]

5,
(-

18

168327

DSS
MAY 20 2002

05/03/2002 13:04 (b) (6) (b) (6) PAGE 1

Individual Safety Report

3918782-1-00-06

pre-diagnosis + pre-op sinus surgery 168327

(b) (6)

June 11, 1998

This was undiagnosed hypoplasia of st many sinus. Cat scan done in July uncovered the abnormality & significant sinus disease

RE: (b) (6)
DOB: (b) (6)
Med Rec#:

Dear Doctors (b) (6)

Thank you for referring (b) (6) who was seen in Rheumatology Clinic on June 10. She is now a 13-year 9-month-old young lady with a history of Stevens-Johnson in May 1997. Evidently she had been on Cefzil at that time and had an emergency room visit which describes lesions and mucous membrane changes of Stevens-Johnson. She was started on a number of medications including steroids, high dose, which gave her hallucinations. Her mother said it looked as though she were on LSD. She was also treated with epinephrine and Atarax, and eventually this resolved. The parents tried to keep her off antibiotics; however, in March 1998 she had bronchitis and took Biaxin for 10 days. She again had problems with multiple lesions and mucous membrane swelling. She had sores throughout her mouth. She has subsequently had impetigo, ringworm, acne, and cellulitis, and because of this was treated with Levaquin. She had two to three doses and was much better, without any problems with diarrhea or upset stomach. However, about seven days after starting the Levaquin, she started having wrist pain, but there was no swelling. On the 12th day, the wrists blew up and she could not see the joints. She had pain throughout and complained of pain in her neck and shoulders. She also had CNS symptoms, including fairly significant insomnia and some behavior changes. The swelling has now decreased. They have tried Aleve, two tablets twice per day, but this did not help.

Recently, they have been concerned because she has had headaches. She gets the headaches in the back of her head, the sides and the middle, and it is a throbbing type of pain which is quite sharp. She has

168327

19 DSS

Cat scan 7.14 shows what caused this

MAY 20 2002

CaseID::3813786

Individual Safety Report
3945152-2-00-01

MEDWATCH CDER

The FDA Safety Information and Adverse Event Reporting Program

· VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only
Triage unit sequence # 171796

A. Patient information

1. Patient identifier (b) (6) — In confidence
2. Age at time of event: 30 Years or Date of birth:
3. Sex: ☑ female ☐ male
4. Weight: 125 lbs or kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr): 10/01/2001
4. Date of this report (mo/day/yr): 07/03/2002
5. Describe event or problem:

Severe vertigo and vision blurriness after taking one dose of Levaquin antibiotic for a sinus infection. Effects lasted on and off for approx. 4 months and caused much mental anxiety as well as about two weeks worth of missed work during which time I received only 60% of my salary. To this day, I am still dealing with anxiety problems, which first began after taking the drug.

6. Relevant tests/laboratory data, including dates:

MRI was normal -11/2001-. Thyroid hormone levels were normal -11/2001-. Neurological exam was normal -11/2001-

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

none

CTV171796

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 Levaquin not sure
   #2
2. Dose, frequency & route used
   #1 1 pill day Oral
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1 10/01/2001 10/02/2001
   #2
4. Diagnosis for use (indication)
   #1 sinus infection
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☑ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☑ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
10. Concomitant medical products and therapy dates (exclude treatment of event)

none

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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JUL 0 9 2002
MEDWATCH CTU

4. Operator of device
   ☐ health professional
   ☐ lay user/patient
   ☐ other:
5. Expiration date (mo/day/yr)
6. model #
   catalog #
   serial #
   lot #
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address
   phone # (b) (6)
   (b) (6)
   JUL 0 9 2002
   (b) (6)
2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   ☐ manufacturer
   ☐ user facility
   ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event

CaseID::3862315

U.S. Department of Health and Human Services

Individual Safety Report

4005806-9-00-01

VOLUNTARY reporting of e events and product problems

net Submission - CDER

cder

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 180563

A. Patient information

1. Patient identifier	2. Age at time of event: / or Date of birth:	3. Sex	4. Weight
Unspecified In confidence	67 Years	☑ female ☐ male	150 lbs or kgs

B. Adverse event or product problem

1. ☑ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)
- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☑ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
03/25/2002	11/06/2002

5. **Describe event or problem**

I was prescribed Cipro for a uninary tract infection, within 2 hours of taking the first tablet I experienced dizziness, nausea, exhaustion, within 8 hours of the second dose I suffered from muscle ache, anxiety, blurred vision, and other symptoms, which led me to stop taking the medication. Since that date I have had cycling of tendonitis, especially in my feet. I reported this adverse reaction to you before, but feel I must file another report, for after 7 months the symptoms still remain.

6. **Relevant tests/laboratory data,** including dates

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NOV 0 7 2002

7. **Other relevant history, including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

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NOV 0 7 2002

MEDWATCH CTU

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known)
#1 Cipro 500mg Bayer
#2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 500 mg 2 daily Oral	#1 03/25/2002 03/25/2002
#2	#2

4. **Diagnosis for use** (indication)
#1 Urinary tract infection
#2

5. **Event abated after use stopped or dose reduced**
#1 ☐ yes ☑ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1	#1
#2	#2

8. **Event reappeared after reintroduction**
#1 ☐ yes ☐ no ☑ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. **NDC #** (for product problems only)
- -

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

4. **Operator of device**
- ☐ health professional
- ☐ lay user/patient
- ☐ other:

6.
model #
catalog #
serial #
lot #
other #

5. **Expiration date** (mo/day/yr)

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address	phone #
(b) (6)	(b) (6)

2. Health professional?	3. Occupation	4. Also reported to
☐ yes ☑ no	Consumer/Non-Health Prof	☐ manufacturer ☐ user facility ☐ distributor

5. **If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box.** ☐

FDA

Mail to: **MEDWATCH** 5600 Fishers Lane Rockville, MD 20852-9787 *or* FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3905502

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Individual Safety Report ation

4055861-5-00-01

Domain Facsimile — Approved by FDA on 3/22/94
Mfr report # 200222305BWH
UF/Dist report #
FDA Use Only

A. Patient information

1. Patient identifier: (b) (6) in confidence
2. Age at time of event: 45 yrs or Date of birth: (b) (6)
3. Sex: ☒ female ☐ male
4. Weight: 163 lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☒ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr): 28-AUG-2002
4. Date of this report (mo/day/yr): 10-FEB-2003
5. Describe event or problem

ITCHING
JOINT PAIN
MUSCLE PAIN
FINGERS WERE TINGLING
FINGERS WERE NUMB
DECREASED FINE MOTOR SKILLS - LEFT HAND
TONGUE TINGLING
DECREASED PERIPHERAL VISION
HEADACHE
WEAKNESS
FATIGUE
INSOMNIA

Global narrative:
This spontaneous report was received from a physician in the United States via telephone on 16-September, 2002. *

6. Relevant tests/laboratory data, including dates

DSS
FEB 12 2003

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concomitant disease(s): depression, anxiety, hyperlipidemia, hypoglycemia

FEB 11 2003

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 Cipro (CIPROFLOXACIN HYDROCHLORIDE)
   #2
2. Dose, frequency & route used
   #1 500 MG, BID, ORAL
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1 26-AUG-2002 to 28-AUG-2002
   #2
4. Diagnosis for use (indication)
   #1 urinary tract infection
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 NI
   #2
7. Exp. date (if known)
   #1 NI
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # - for product problems only (if known)
   #1 NI #2
10. Concomitant medical products and therapy dates (exclude treatment of event)

Name: ZOLOFT Dates: NI Duration: 1 month, ??-SEP-1999, continuing

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

2. Phone number: 888-765-3203
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☒ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer (mo/day/yr): 31-JAN-2003
5. (A)NDA # 19-537
   IND # ____
   PLA # ____
   pre-1938 ☐ yes
   OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☒ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☒ follow-up # 2
8. Adverse event term(s)

PRURITUS, ARTHRALGIA, MYALGIA, PARAESTHESIA, HYPOAESTHESIA, COORDINATION ABNORMAL NOS, PARAESTHESIA ORAL, VISUAL FIELD DEFECT NOS, HEADACHE, ASTHENIA, *

9. Mfr. report number: 200222305BWH

E. Initial reporter

1. Name, address & phone #

(b) (6)

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FEB 11 2003
CDR/CDER

2. Health professional? ☒ yes ☐ no
3. Occupation: Medical Doctor
4. Initial reporter also sent report to FDA: ☒ yes ☐ no ☐ unk

FDA
Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

Individual Safety Report

4055861-5-00-02

MED WATCH	(b) (6)	G.9. Mfr. report number 200222305BWH	Page 2 of 3

B.5. Describe event or problem

[continuation:]
A 45-year-old female consumer, with history remarkable for allergy to codeine, was treated with CIPRO (ciprofloxacin HCL) tablets, 500 mg BID for a urinary tract infection from 26 to 28 August, 2002. Following the third dose, the consumer experienced onset of ITCHING, JOINT PAIN, MUSCLE PAIN, FINGERS WERE TINGLING, FINGERS WERE NUMB, DECREASED FINE MOTOR SKILLS - LEFT HAND, TONGUE TINGLING, DECREASED PERIPHERAL VISION, HEADACHE, WEAKNESS, FATIGUE, and INSOMNIA. The events were treated with MEDROL (methylprednisolone) dose pack, after which the ITCHING, JOINT PAIN & MUSCLE PAIN worsened. On 12-September, 2002, the consumer was started on CLONOPIN (clonazepam), 0.5 mg. as of the date of the physician's report, the consumer's events were ongoing. No other information was provided.

[From follow-up information received on 31-JAN-2003:] The MedWatch form was returned form the physician with additional information. The consumer has a history of depression, anxiety, hyperlipidemia and hypoglycemia.

The patient takes ZOLOFT (sertraline) and began at a dose of 25 mg daily for one month, then 50 mg daily since SEP-1999.

The patient was prescribed CIPRO for treatment of a urinary tract infection.

Bayer global comment:
ITCHING, JOINT PAIN, MUSCLE PAIN, FINGERS TINGLING, TONGUE TINGLING, HEADACHE, WEAKNESS, INSOMNIA, and FATIGUE are listed while FINGERS NUMB, DECREASED FINE MOTOR SKILLS - LEFT HAND, and DECREASED PERIPHERAL VISION are not listed in the international product information for CIPRO (ciprofloxacin HCl). The events DECREASED PERIPHERAL VISION and DECREASED FINE MOTOR SKILLS are considered serious due to disability. Due to the temporal association of the reported events with the use of ciprofloxacin, a potential causal association between the drug and the events cannot be excluded. However, as of the report date, there is no evidence of a positive dechallenge. Follow-up information has been requested.

[From follow-up information received on 31-JAN-2003:] Based on the follow-up information received for this case, a causal relationship between the reported events and treatment with ciprofloxacin cannot be excluded because of temporal association, although an alternative explanation of concomitant drug (sertraline - known to be associated with pruritus, arthralgia, myalgia, paresthesia, visual field defect, headache, asthenia, and insonmia) may have been the cause of the reported ITCHING, JOINT PAIN, MUSCLE PAIN, FINGERS WERE TINGLING, TONGUE TINGLING, DECREASED PERIPHERAL VISION, HEADACHE, WEAKNESS, FATIGUE, and INSOMNIA. In addition, one may speculate that ciprofloxacin interacted on a pharmacokinetic level (e.g., urinary excretion) with sertraline. This cannot, however, be proven on the evidence available.

(No further information is expected.)

G.8. Adverse event term(s)

[continuation:] FATIGUE, INSOMNIA

DSS
FEB 12 2003

FEB 11 2003

rporation

4055861-5-00-03*

H	(b) (6)	200222305BWH	Page 3 of 3

phone #

tion:] Phone: (b) (6)

FEB 1 1 2003

DSS

FEB 1 2 2003

Individual Safety Report

4069515-2-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

FOR VOLUNTARY reporting of adverse events and product problems

CDER

Form Approved: OMB No. 0910-0230 Expires: 09/30/05
See OMB statement on reverse

Internet Submission - Page 1

FDA Use Only
Triage unit sequence # 188185

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 44 Years or Date of birth: (b) (6)
3. Sex: ☐ female ☑ male
4. Weight: 220 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☑ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr): 02/10/2003
4. Date of this report (mo/day/yr): 03/06/2003
5. Describe event or problem

Reaction to Levaquin: Extreme joint pain,all joints effected. Fatigue, tightness in all motor operations. I have taken this drug on and off for 3 years and thought that the adverse effects were part of the general infection I had. Until I did some research and had this bad of an episode did i realize it was the Levaquin.

6. Relevant tests/laboratory data, including dates

DSS

MAR 0 7 2003

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Allergic to Ceclor and Biaxin.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 Levaquin 500 mg ?
   #2
2. Dose, frequency & route used
   #1 500 mg Oral
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1 02/10/2003 02/19/2003
   #2 11/19/2000 11/28/2000
4. Diagnosis for use (indication)
   #1 Sinus Infection , persistant
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☑ no ☐ doesn't apply
   #2 ☐ yes ☑ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☑ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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MAR 0 7 2003

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4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model #
   catalog #
   serial #
   lot #
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address / phone # (b) (6)
2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (11/02) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3925907

U.S. Department of Health and Human Services

Individual Safety Report

4080176-9-00-01

VOLUNTARY reporting of se events and product problems

CDER

rnet Submission - Page 1

Form Approved: OMB No. 0910-0230 Expires: 09/30/05
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 187418

A. Patient information

1. Patient identifier (b) (6) In confidence

2. Age at time of event: 32 Years or Date of birth: (b) (6)

3. Sex: ☑ female ☐ male

4. Weight: 110 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☑ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr): 03/11/2003

4. Date of this report (mo/day/yr): 03/24/2003

5. Describe event or problem

I was prescribed a 15 day treatment of Levaquin -500mg- for sinusitis. I took only 7 of the 15 pills prescribed to me, because I did not like the way they were making me feel. I experienced dizziness, light-headedness, drowsiness, and a general malaise. I am now experiencing moderate to severe tendonitis in my left wrist, right ankle, right knee, and neck pain. I am a healthy 32 year old female with no medical history of joint pain. After reviewing the precautionary insert that came with the Levaquin, and after reading posts on adverse reactions to Levaquin on the internet, I am convinced that this drug is responsible for my sudden pains.

6. Relevant tests/laboratory data, including dates

DSS
MAR 25 2003

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

I have no other significant medical history that would contribute to this report.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Levaquin 500mg orth
#2

2. Dose, frequency & route used
#1 500mg bid Oral
#2

3. Therapy dates (if unknown, give duration) (from/to (or best estimate))
#1 02/17/2003 02/23/2003
#2

4. Diagnosis for use (indication)
#1 sinusitis
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☑ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☑ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)
Flonase - BID, Allegra - BID

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other: ____

6.
model # ____ RECEIVED
catalog # ____ MAR 25 2003
serial # ____
lot # ____ MEDWATCH CTU
other #

5. Expiration date (mo/day/yr)

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

(b) (6)

2. Health professional? ☐ yes ☑ no

3. Occupation: Consumer/Non-Health Prof

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500 (11/02)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

U.S. Department of Health and Human Services

Individual Safety Report

4114570-4-00-01

LUNTARY reporting of
ents and product problems

Submission - Page 1

Form Approved: OMB No. 0910-0230 Expires: 09/30/05
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 193426

A. Patient information

1. Patient identifier (b) (6)
In confidence

2. Age at time of event:
or
Date of birth: (b) (6)

3. Sex
☑ female
☐ male

4. Weight
140 lbs
or
kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death (mo/day/yr)
☐ life-threatening
☐ hospitalization - initial or prolonged
☑ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event (mo/day/yr) 01/01/2000

4. Date of this report (mo/day/yr) 05/19/2003

5. Describe event or problem

Prescribed Levaquin for frequent sinus infections, beginning January, 2000. Developed serious and disabling complications, including severe joint pain and neurological problems -confusion, inability to concentrate, depression.-

6. Relevant tests/laboratory data, including dates

Diagnosed with "rheumatoid-like arthritis of unknown origin" Summer, 2000. Sent to (b) (6) for further evaluation. Further extensive testing could not explain crippling arthritis.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

50-year-old white female in excellent health. Physically active. B.S. Biology. School teacher. Never smoked. No alcohol. Allergic to aspirin.

DSS

MAY 2 0 2003

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Levaquin 500 mg generic
#2

2. Dose, frequency & route used
#1 1 tab day Oral
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 01/01/2000 03/01/2003
#2

4. Diagnosis for use (indication)
#1 sinus infection
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☑ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☑ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

RECEIVED
MAY 2 0 2003
MEDWATCH CTU

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other:

5. Expiration date (mo/day/yr)

6.
model #
catalog #
serial #
lot #
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

(b) (6)

2. Health professional?
☐ yes ☑ no

3. Occupation
Consumer/Non-Health Prof

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 (11/02)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3952082

Individual Safety Report

4120686-9-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

FOR VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

CDER DER

Form Approved: OMB No. 0910-0230 Expires: 09/30/05
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 194445

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
(b) (6) In confidence	43 Years or Date of birth:	☑ female ☐ male	155 lbs or kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☑ hospitalization - initial or prolonged
- ☑ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 05/30/2003

4. Date of this report (mo/day/yr): 05/30/2003

5. Describe event or problem

Was prescribed Levaquin while on anti-inflammatories. Also given prednisone. Have had tremors, heart palpitations, numbness, tingling, dry mouth, brain fog.

6. Relevant tests/laboratory data, including dates

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7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

I have never smoked, I do not use alcohol. I have never used illegal drugs. I was in perfect health prior to use of Levaquin, which I was given for a sinus infection I did not even know I had.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Levaquin 500 mg Ortho/McNeill
#2

2. Dose, frequency & route used
#1 1xper day oral
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 03/05/2003 03/13/2003
#2

4. Diagnosis for use (indication)
#1 sinus infection
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☑ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☑ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other:

5. Expiration date (mo/day/yr)

6.
model #
catalog #
serial #
lot #
other #

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7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

(b) (6)

2. Health professional? ☐ yes ☑ no

3. Occupation: Consumer/Non-Health Prof

4. Also reported to
- ☑ manufacturer
- ☐ user facility
- ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (11/02)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::3999816

U.S. Department of Health and Human Services

Individual Safety Report

4183519-0-00-01

VOLUNTARY reporting of
se events and product problems

rnet Submission - Page 1

CDER

Form Approved: OMB No. 0910-0230 Expires: 09/30/05
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 2014/12

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 54 Years or Date of birth: (b) (6)
3. Sex: ☑ female ☐ male
4. Weight: 145 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ____
3. Date of event (mo/day/yr): 12/27/2002
4. Date of this report (mo/day/yr): 09/06/2003
5. Describe event or problem

Took cipro for one week as prescribed by physician for bladder infection. Subsequently have been suffering with sensory neuropathy and joint pain. Testing has not revealed any other source of my problems. Symptoms have not responded to prescribed remedies, medication, physical therapy etc.

6. Relevant tests/laboratory data, including dates

MRI's, spinal tap, blood tests, nerve conduction studies, EMG, cat scan Jan.-July 2003

DSS

SEP 0 8 2003

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

none, very healthy until 2003. Caucasian.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   - #1 cipro 500 mg Bayer?
   - #2
2. Dose, frequency & route used
   - #1 2X day 1 week Oral
   - #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   - #1 12/27/2002 01/03/2003
   - #2
4. Diagnosis for use (indication)
   - #1 bladder infection
   - #2
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☐ no ☑ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   - #1
   - #2
7. Exp. date (if known)
   - #1
   - #2
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☐ doesn't apply
   - #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only) - -
10. Concomitant medical products and therapy dates (exclude treatment of event)

Prior to cipro was taking macrobid for a few days with no response.

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____
5. Expiration date (mo/day/yr)
6. model # ____ catalog # ____ serial # ____ lot # ____ other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

(b) (6)

2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (11/02) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::4000632

U.S. Department of Health and Human Services

Individual Safety Report

4186987-3-00-01

VOLUNTARY reporting of e events and product problems

CDER

Form Approved: OMB No. 0910-0230 Expires: 09/30/05
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 201619

...iet Submission - Page 1

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 47 Years or Date of birth: (b) (6)
3. Sex: ☑ female ☐ male
4. Weight: 127 lbs or ___ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr): 07/07/2003
4. Date of this report (mo/day/yr): 09/10/2003
5. Describe event or problem

Saw PCP end 7/7/2003 regarding a sinus/bronchial infection. He handed me samples of Levaquin 500 mg and told me to take them once daily for a week. Upon first dose I experienced rapid heartbeat, insomnia, sweating, nighmares. The following day I also experienced joint pain,dizziness,confusion,fatigue, "lifelessness", in addition to the palpitations, anxiety. I called my PCP and he prescribed Xanax for the anxiety/insomnia. After 3 days on the drug I returned to physician to ask to be put on another antibiotic, as I was clearly having adverse side effects. He advised me to continue course of treatment, but that I could cut the dose in half to 250 mg. At one point I nearly fainted while driving a car. I stopped taking Levaquin after six doses. In the 2 months post treatment, I

6. Relevant tests/laboratory data, including dates

N/A.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Have allergic rhinitis, predisposing me to sinus problems.

DSS
SEP 11 2003

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 Levaquin 500 mg
   #2
2. Dose, frequency & route used
   #1 once daily
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1 07/07/2003 07/11/2003
   #2
4. Diagnosis for use (indication)
   #1 sinus and bronchial infection
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☑ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☑ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
   - -
10. Concomitant medical products and therapy dates (exclude treatment of event)

Ibuprofen 1000 mg daily 7/6 - 7/12/2003.
DuraTuss -Guavent- - 1 tablet daily 7/8 - 7/12/2003.

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model # / catalog # / serial # / lot # / other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

(b) (6)

2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☑

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (11/02) **Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.**

Individual Safety Report

4186987-3-00-02

MEDWATCH

201619

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page 2

B5. Describe event or problem continued

continue to experience joint pain, anxiety, insomnia, numbness/tingling in my arms, legs and tremors/twitching in my hands, as well as flareups of tendon pain in my ankle. Have also had inflamed colon that a gastro-enterologist believes is related to the Levaquin use. I never had these symptoms before taking Levaquin. I note that PCP did not at any time advise me of this drug's potential side effects, nor did he tell me not to use caffeine, NSAIDs during Levaquin treatment.

DSS
SEP 11 2003

CaseID::4007439

Individual Safety Report

4194001-9-00-01

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The FDA Safety Information and Adverse Event Reporting Program

VOLUNTARY reporting of adverse events and product problems

CDER Internet Submission - Page 1

Form Approved: OMB No. 0910-0230 Expires: 09/30/05
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 202175

A. Patient information

1. Patient identifier: (b) (6) — In confidence
2. Age at time of event: 43 Years or Date of birth:
3. Sex: ☑ female ☐ male
4. Weight: 155 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☑ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☑ other: neurologica l problem
3. Date of event (mo/day/yr): 03/13/2003
4. Date of this report (mo/day/yr): 09/21/2003
5. Describe event or problem

Took Levaquin with prednisone. Continue to have hot flashes, tremors, muscle spasms, burning in feet, arthritis, nausea, diarrhea, and pain in achilles tendons.

6. Relevant tests/laboratory data, including dates

Tested for carcinoid tumors, thyroid disease, menopause, among others. All tests came back normal.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

DSS

SEP 22 2003

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   - #1 Levaquin 500 mg
   - #2 Prednisone 10mg
2. Dose, frequency & route used
   - #1 1 pill once/day Oral
   - #2 4 pills once per Oral
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   - #1 03/05/2003 03/13/2003
   - #2 03/05/2003 03/13/2003
4. Diagnosis for use (indication)
   - #1 Sinus Infection I didn't even know I had
   - #2 Sinus infection I didn't even know I had
5. Event abated after use stopped or dose reduced
   - #1 ☐ yes ☑ no ☐ doesn't apply
   - #2 ☐ yes ☑ no ☐ doesn't apply
6. Lot # (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction
   - #1 ☐ yes ☐ no ☑ doesn't apply
   - #2 ☐ yes ☐ no ☑ doesn't apply
9. NDC # (for product problems only) - -
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

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4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model # catalog # serial # lot # other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   - ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

(b) (6)

2. Health professional? ☐ yes ☑ no
3. Occupation: Consumer/Non-Health Prof
4. Also reported to
   - ☑ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (11/02)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4254393-9-00-01

CDER

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

FDA USE ONLY
Triage unit sequence # 208365

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) In confidence
2. Age at Time of Event: 42 Years or Date of Birth:
3. Sex: [x] Female [ ] Male
4. Weight: 150 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [x] Adverse Event and/or [ ] Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- [ ] Death: ____ (mo/day/yr)
- [ ] Life-threatening
- [ ] Hospitalization - initial or prolonged
- [x] Disability
- [ ] Congenital Anomaly
- [ ] Required Intervention to Prevent Permanent Impairment/Damage
- [ ] Other: ____

3. Date of Event (mo/day/year): 07/01/2003

4. Date of This Report (mo/day/year): 12/17/2003

5. Describe Event or Problem

I took three rounds of Levaquin in 7/03 - almost immediately after starting round one, I began to have a muscle spasm in my back which only subsided in 12/03. I also began to have buzzing and tingling, random muscle spasms, blurry vision, dizziness, foggy brain, inabilty to concentrate, memory loss, anomia, and depression and anxiety -cause or effect ??-. I first took Cipro in about 1999 and had a round of flares ups like this then, but never made a connection. The Doctors have tested me for averytning in the world, and I do mean everything, and the closest that my symptoms come to anything else is MS, but my spinal fluid is fine. I used to pride myself on my strength as a woman. I used to play baseball with my son and move furniture and remodel houses, but now I cannot open up a jar. I also have muscle weakness, and am tired all the time.

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6. Relevant Tests/Laboratory Data, Including Dates

MRI, 4/99, 4/00, 7/03, VER, 4/00, 7/03, Blood work -CPK, B12/Folic Acid, TSH, ANA, etc-, SPinal tap -protein, Lyme disease, Herpes, etc-, all 11/03 and 12/03

DSS
DEC 18

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Have allergies to codeine and gluten. White. One pregnancy in 1981. No smoking, very little alcohol consumption, am sensitve or allergic to organic solvents.

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 Cipro
#2 Levaquin

2. Dose, Frequency & Route Used
#1 one packet round Oral
#2 three 10 rounds each ro Oral

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 01/01/1999 – 01/01/1999
#2 07/01/2003 – 10/11/2003

4. Diagnosis for Use (Indication)
#1 bronchitis
#2 bronchitis

5. Event Abated After Use Stopped or Dose Reduced?
#1 [x] Yes [ ] No [ ] Doesn't Apply
#2 [ ] Yes [x] No [ ] Doesn't Apply

6. Lot # (if known)
#1
#2

7. Exp. Date (if known)
#1
#2

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [x] Doesn't Apply
#2 [ ] Yes [ ] No [x] Doesn't Apply

9. NDC# (For product problems only)

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
Advair -continuous- since about 2000, CLaritin, Singular

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot #
Catalog # / Expiration Date (mo/day/yr)
Serial # / Other #
5. Operator of Device
[ ] Health Professional
[x] Lay User/Patient
[ ] Other:
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
[ ] Yes [ ] No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA)
[ ] Yes [ ] No [ ] Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? [ ] Yes [x] No
3. Occupation: Consumer/Non-Health Professional
4. Also Reported to:
[ ] Manufacturer
[ ] User Facility
[ ] Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [ ]

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::4053411

MedWatch — Individual Safety Report

For VOLUNTARY reporting of events and product problems

Form Approved: OMB No. 0910-0230 Expires: 09/30/0
See OMB statement on reverse

FDA Use Only
Triage unit sequence # 208788

CDER

4259013-5-00-01

Page 1 of 1 CDER

A. Patient Information

1. Patient Identifier	2. Age at time of event: / or Date of birth:	3. Sex	4. Weight
In confidence	27 / (b) (6)	☑ female ☐ male	155 lbs or ____ kgs

B. Adverse event or product problem

1. ☑ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)
- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☑ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. **Date of event** (mo/day/yr): July 13th, 2003

4. **Date of this report** (mo/day/yr): 12.17.03

5. **Describe event or problem**

Initial tendon pain in right wrist, then jaw, knee, feet, rash on abdomen & thighs (raised red bumps, itchy). Swelling in face, feet, knee, wrist, fingers, then shoulder, neck pain. Severe headaches, insomnia, night sweats, visual hallucinations, agitation, depression, heart palpitations, numbness in feet, fingers & arms. Jaw clenching - ongoing numbness and tendon pain (occasionally sporadic.) One incident of spontaneous falling asleep after shooting pain in base of head. (NECK)

6. **Relevant tests/laboratory data**, including dates

7/15/03 ESR 40
7/24/03 ESR 28
8/4/03 ESR 80
7/15/03 CBC Comp Metabolic Panel (Normal)
DSS 7/28/03 LDH / CK Normal
DEC 26 2003

7. **Other relevant history, including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

was 6 months post partum - and nursing 6 month old child -

Diagnosed with acute sinusitis and ear infection on July 11th, 2003.

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known)
#1 Avelox 400mg Bayer Pharma
#2

2. **Dose, frequency & route used**
#1 400mg, 1 per day Oral
#2

3. **Therapy dates** (if unknown, give duration) from/to (or best estimate)
#1 July 11th, 12th, 13th (2003)
#2

4. **Diagnosis for use** (indication)
#1 Sinusitis
#2

5. **Event abated after use stopped or dose reduced**
#1 ☐ yes ☑ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. **Lot #** (if known)
#1 2500 5 SX
#2

7. **Exp. date** (if known)
#1 8/03
#2

8. **Event reappeared after reintroduction**
#1 ☐ yes ☐ no ☑ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. **NDC #** (for product problems only)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)
Celexa 40mg/day July 11th, 12th, 13th (2003)
Zyrtec D July 11th, 12th, 13th (2003)

D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

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4. **Operator of device**
- ☐ health professional
- ☐ lay user/patient
- ☐ other: ____

5. **Expiration date** (mo/day/yr)

6. model # / catalog # / serial # / lot # / other #

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

(b) (6)

2. **Health professional?** ☐ yes ☑ no

3. **Occupation** social worker

4. **Also reported to**
- ☑ manufacturer
- ☐ user facility
- ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (11/02) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event

Individual Safety Report

4268078-6-00-01

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

For VOLUNTARY reporting of adverse events and product problems

The FDA Safety Information and Adverse Event Reporting Program

Page 1 of 2 CDER

FDA USE ONLY
Triage unit sequence # 209619

A. PATIENT INFORMATION

1. Patient Identifier (b) (6) In confidence
2. Age at Time of Event: 59 YRS. or Date of Birth: (b) (6)
3. Sex: ☒ Female ☐ Male
4. Weight: 91 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
   - ☐ Death: ____ (mo/day/yr)
   - ☐ Life-threatening
   - ☐ Hospitalization - initial or prolonged
   - ☒ Disability
   - ☐ Congenital Anomaly
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage
   - ☐ Other: ____
3. Date of Event (mo/day/year): 10/13/03
4. Date of This Report (mo/day/year): 12/29/03
5. Describe Event or Problem

- BURNING PAIN IN MUSCLES, TENDONS AND JOINTS THROUGHOUT WHOLE BODY.
- SWELLING IN LEGS, KNEES, ANKLES AND FEET.
- IMPAIRED VISION
- IRREGULAR AND RAPID HEARTBEAT
- DIZZINESS
- MENTAL/MOOD CHANGES
- BREATHING DIFFICULTY
- STOMACH PAIN *
- NAUSEA *

* EVENT OCCURRED ONE TIME ONLY ON FIRST DAY

6. Relevant Tests/Laboratory Data, Including Dates

NI

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MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

NI ON MEDICAL CONDITIONS
WHITE RACE

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
   #1 AVELOX 400MG BAYER
   #2
2. Dose, Frequency & Route Used
   #1 1 TAB/DAY ORAL
   #2
3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
   #1 09/12/03 TO 10/13/03
   #2
4. Diagnosis for Use (Indication)
   #1 SINUS INFECTION
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☒ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # (If known)
   #1 UNK
   #2
7. Exp. Date (If known)
   #1 10/07/04
   #2
8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☒ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# (For product problems only)
   0026-8581-69
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
    NI

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other: ____
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
JAN 09 2004

10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4268078-6-00-02

209619

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

Page 2 of 2

FDA USE ONLY
Triage unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier (b) (6) — In confidence
2. Age at Time of Event: or Date of Birth: (b) (6)
3. Sex: [X] Female [ ] Male
4. Weight: ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [X] Adverse Event and/or [ ] Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- [ ] Death: ____ (mo/day/yr)
- [ ] Life-threatening
- [ ] Hospitalization - initial or prolonged
- [ ] Disability
- [ ] Congenital Anomaly
- [ ] Required Intervention to Prevent Permanent Impairment/Damage
- [ ] Other: ____

3. Date of Event (mo/day/year): 10/1/03

4. Date of This Report (mo/day/year): 1/5/04

5. Describe Event or Problem

Myalgias, fatigue onset 2 days following Avelox 400mg daily for sinusitis

6. Relevant Tests/Laboratory Data, Including Dates

10/25/03 CPK 34 (NL <201)
Hgb 11.4
TSH 0.02
ESR 64

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Hypothyroidism
Post concussion Syndrome

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 Avelox 400mg
#2 Avelox 400mg

2. Dose, Frequency & Route Used
#1 400mg qd
#2 400mg qd

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 9/12-16/03
#2 10/8-14/03

4. Diagnosis for Use (Indication)
#1 Myalgia
#2 Fatigue

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [ ] No [X] Doesn't Apply
#2 [ ] Yes [X] No [ ] Doesn't Apply

6. Lot # (If known)
#1
#2

7. Exp. Date (If known)
#1
#2

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

9. NDC# (For product problems only)
- -

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
Medication list and supplements attached

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device: [ ] Health Professional [ ] Lay User/Patient [ ] Other:
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? [ ] Yes [ ] No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor: DSS
10. Device Available for Evaluation? (Do not send to FDA) [ ] Yes [ ] No [ ] Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

1. [X] Yes [ ] No
3. Occupation: Physician
4. Also Reported to: [ ] Manufacturer [ ] User Facility [ ] Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [X]

PLEASE TYPE OR USE BLACK INK

JAN 09 2004

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4277370-0-00-01

CDER

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 21543

A. PATIENT INFORMATION

1. Patient Identifier (b) (6) In confidence
2. Age at Time of Event: 46 Years or Date of Birth: (b) (6)
3. Sex: [x] Female [ ] Male
4. Weight: 128 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [x] Adverse Event and/or [ ] Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
   - [ ] Death: ____ (mo/day/yr)
   - [ ] Life-threatening
   - [ ] Hospitalization - initial or prolonged
   - [x] Disability
   - [ ] Congenital Anomaly
   - [ ] Required Intervention to Prevent Permanent Impairment/Damage
   - [ ] Other: ____
3. Date of Event (mo/day/year): 10/19/2003
4. Date of This Report (mo/day/year): 01/19/2004
5. Describe Event or Problem

3-4 weeks after having taken a total of 2500 mg of Cipro, and being treated for yeast, the fun began. Tremors: hands shaking like an 80-year-old. Weakness: Arms unable to hold a phone. Anxiety: Feeling like I'd drunk 50 cups of coffee. Calf muscles: Aching when standing still - as if bulging from my legs.Night sweats. Fatigue: Immense. Depression.

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6. Relevant Tests/Laboratory Data, Including Dates

December 2003 MRI = normal. January 2004 MRI = normal. Needles show tremors in neck, legs, arms -where tested-. Labs = normal, except "ANA", which doctor says shows nothing.

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Healthy, non-smoking, social drinker -wine-. Excercised 2-3 x week on treadmill.

DSS
JAN 21 2004

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
   #1 Cipro 250 mg Bayer
   #2
2. Dose, Frequency & Route Used
   #1 2x/day
   #2
3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
   #1 09/23/2003 – 12/28/2003
   #2 –
4. Diagnosis for Use (Indication)
   #1 UTI
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 [ ] Yes [ ] No [x] Doesn't Apply
   #2 [ ] Yes [ ] No [ ] Doesn't Apply
6. Lot # (if known)
   #1
   #2
7. Exp. Date (if known)
   #1
   #2
8. Event Reappeared After Reintroduction?
   #1 [ ] Yes [ ] No [x] Doesn't Apply
   #2 [ ] Yes [ ] No [ ] Doesn't Apply
9. NDC# (For product problems only)
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
    no other drugs used

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device
   - [ ] Health Professional
   - [ ] Lay User/Patient
   - [ ] Other:
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   [ ] Yes [ ] No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA)
    [ ] Yes [ ] No [ ] Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? [ ] Yes [x] No
3. Occupation: Consumer/Non-Health Professional
4. Also Reported to:
   - [ ] Manufacturer
   - [ ] User Facility
   - [ ] Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [ ]

Mail to: MEDWATCH -or- FAX to:
5600 Fishers Lane
Rockville, MD 20852-9787
1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4485271-8-00-01

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Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1 of 2

FDA USE ONLY
Triage unit sequence # 230268

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event / Date of Birth	3. Sex	4. Weight
(b) (6) in confidence	41 Years or (b) (6)	☐ Female ☑ Male	258 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: ____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: ____

3. Date of Event *(mo/day/year)*: 08/07/1904

4. Date of This Report *(mo/day/year)*: 10/20/2004

5. Describe Event or Problem

DescriveEvent , Iwas prescrive cipro xr 1000mg for a supose uti problem and after taiking this medicine for 3 days i was not able to walk do to the pain in my legs abdomen my skin was burning knees and in achiles tendon left bicep the problem folow up by muscle pain weaknes and more fatigue than usual i stop the medicine and i call my doctor she never call me bak .I saw her ten days latter but she was not helpful or provited me with any anser today i am steel having trouble weaknes fatigue pain in my legs tendon pain blurde vision pins and netles digestion problems .I blaime cipro for al of the problems that i am having after al this time i am not recovering or felling better the doctors are not are not helpful i told my doctor wat hapend but i am not sure she reported the insidence to the fda i dont think that will recover from this.like so many other people that have gone thru the same thing

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MEDWATCH CTU

6. Relevant Tests/Laboratory Data, Including Dates

On 10/13/04 blood test were done i was told results are normal not having insuranc is aproblem but i will get more testing done

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

enviromental alergies sleep apnea none smoker no alcohl hispanc

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
- #1: Cipro XR 1000mg Bayer
- #2:

2. Dose, Frequency & Route Used
- #1: 1000mg one a day Oral
- #2:

3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
- #1: 08/04/2004 08/06/2004
- #2:

4. Diagnosis for Use *(Indication)*
- #1: Urinary trac infection
- #2:

5. Event Abated After Use Stopped or Dose Reduced?
- #1 ☐ Yes ☐ No ☐ Doesn't Apply
- #2 ☐ Yes ☑ No ☐ Doesn't Apply

6. Lot # *(if known)*
- #1:
- #2:

7. Exp. Date *(if known)*
- #1:
- #2:

8. Event Reappeared After Reintroduction?
- #1 ☐ Yes ☐ No ☐ Doesn't Apply
- #2 ☐ Yes ☐ No ☑ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mo/day/yr)*

7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocesso DSS

OCT 2 2 2004

10. Device Available for Evaluation? *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health Professional	☑ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4485271-8-00-02

230268

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

B5. Describe event or problem continued

is hard to find help.

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OCT 2 2 2004

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Individual Safety Report

4518984-X-00-01

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The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 233645

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) In confidence
2. Age at Time of Event: 46 Years or Date of Birth: (b) (6)
3. Sex: [x] Female [ ] Male
4. Weight: 250 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [x] Adverse Event and/or [ ] Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   - [ ] Death: ____ *(mo/day/yr)*
   - [ ] Life-threatening
   - [ ] Hospitalization - initial or prolonged
   - [x] Disability
   - [ ] Congenital Anomaly
   - [ ] Required Intervention to Prevent Permanent Impairment/Damage
   - [ ] Other: ____

3. Date of Event *(mo/day/year)*: 12/16/2003
4. Date of This Report *(mo/day/year)*: 12/02/2004

5. Describe Event or Problem

Reaction to Avelox, first 2 months neurological symptoms including, dizziness, lethargy, confusion, fatique. From onset to present time, eye floater, severe knee and hip pain, muscle weakness in legs, instability of knee joints, daily headaches, and daily fever.

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6. Relevant Tests/Laboratory Data, Including Dates

Elevated CRP and borderline high Sedimentation Rate, all other lab tests normal. Done in 10/2004

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Previous reaction to Levaquin otherwise healthy, very active adult

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
   #1 Avelox 500 mg
   #2
2. Dose, Frequency & Route Used
   #1 one daily Oral
   #2
3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
   #1
   #2
4. Diagnosis for Use *(Indication)*
   #1 sinusitis
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 [ ] Yes [x] No [ ] Doesn't Apply
   #2 [ ] Yes [ ] No [ ] Doesn't Apply
6. Lot # *(if known)*
   #1
   #2
7. Exp. Date *(if known)*
   #1
   #2
8. Event Reappeared After Reintroduction?
   #1 [ ] Yes [ ] No [x] Doesn't Apply
   #2 [ ] Yes [ ] No [ ] Doesn't Apply
9. NDC# *(For product problems only)*
10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date *(mo/day/yr)* / Serial # / Other #
5. Operator of Device
   - [ ] Health Professional
   - [ ] Lay User/Patient
   - [ ] Other:
6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   [ ] Yes [ ] No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
DEC 0 3 2004

10. Device Available for Evaluation? *(Do not send to FDA)*
    [ ] Yes [ ] No [ ] Returned to Manufacturer on: ____ *(mo/day/yr)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional? [x] Yes [ ] No
3. Occupation: Other Health Professional
4. Also Reported to:
   - [ ] Manufacturer
   - [x] User Facility
   - [ ] Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [x]

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::5699626

Individual Safety Report

4530290-6-00-01

CDER

CBR

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1 of 2

FDA USE ONLY

Triage unit sequence # 234491

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) — In confidence
2. Age at Time of Event: 49 Years or Date of Birth:
3. Sex: [x] Female [ ] Male
4. Weight: 205 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [x] Adverse Event and/or [ ] Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- [ ] Death: ____ (mo/day/yr)
- [ ] Life-threatening
- [ ] Hospitalization - initial or prolonged
- [x] Disability
- [ ] Congenital Anomaly
- [ ] Required Intervention to Prevent Permanent Impairment/Damage
- [ ] Other: ____

3. Date of Event (mo/day/year): 02/15/2003

4. Date of This Report (mo/day/year): 12/15/2004

5. Describe Event or Problem

STILL DISABLED 22 MONTHS AFTER LEVQUIN THERAPY I took the Fluoroquinolone aka -Quinolone- Drug, LEVAQUIN, to treat the medical condition of acute sinusitis on February 15, 2003. Prior to taking this drug, I was a healthy 49 year old, an advanced downhill skier, with NO medical problems until I sought treatment for a sinus infection. I was given a 10 day supply of LEVAQUIN by my physician. The Adverse Drug Reactions that happened to me started on February 17, 2003. I could barely walk, had to crawl up my staircase. I had severe muscle weakness, muscle burning and joint pain in all my limbs. I almost fell several times when walking. I ached and burned in what seemed every tendon/muscle in my body. I told my family and friends that I didn¿t know what was happening to me. I felt like I had MS. After researching this drug online and finding the ¿Drugvictims.org¿ website, as well as the Quinolone Yahoo

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DEC 16 2004

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6. Relevant Tests/Laboratory Data, including Dates

I have been treated by the following physicians in 2004, and all have diagnosed me with Fibromyalgia. --a Rheumatologist-- a General Practioner-- a Spine Specialist-- an Infectious disease specialist--and a Neurologist

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Sinus infection and high cholesterol. No allergies. Race=Caucasion, not pregnant, non-smoker, no alcohol, no other medical conditions.

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 Levofloxacin -Levaquin-, 500 mg, Ortho-McNeil Pharmaceuticals
#2

2. Dose, Frequency & Route Used
#1 1 tablet per day Oral
#2

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 02/15/2003 02/21/2003
#2

4. Diagnosis for Use (Indication)
#1 sinusitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [x] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot # (If known)
#1 13A767
#2

7. Exp. Date (If known)
#1 10/31/2005
#2

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

9. NDC# (For product problems only)

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device: [ ] Health Professional [ ] Lay User/Patient [ ] Other:
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? [ ] Yes [ ] No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS

10. Device Available for Evaluation? (Do not send to FDA) [ ] Yes [ ] No [ ] Returned to Manufacturer on: DEC 16 2004 (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? [ ] Yes [x] No
3. Occupation: Consumer/Non-Health Professional
4. Also Reported to: [ ] Manufacturer [ ] User Facility [ ] Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [x]

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4530290-6-00-02

234491

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 2

B5. Describe event or problem continued

Group, I realized I was having an Adverse Drug Reaction to Levaquin. I had then and continue to suffer, now 22 months after the Levaquin therapy, the following disabling conditions: ¿ Severe tendon/muscle pain and tightness ¿ Tendonitis ¿ Tingling, numbness, prickling, pins and needles sensations in my extremities. ¿ Electrical sensations ¿ Feeling of worms crawling under my skin ¿ Severe arm and leg weakness ¿ Muscle twitching, spasms and contractions ¿ Severe muscle tenderness. To poke my muscles feels like a bee sting! ¿ Inability to sleep due to pain 24 hours per day 7 days per week. ¿ Inability to work due to pain and weakness. ¿ Difficulty thinking clearly, confusion. ¿ Chronic fatigue

DSS

DEC 16 2004

U.S. Department of Health and Human Services

CDER

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

Individual Safety Report

4566500-9-00-01

VOLUNTARY reporting of e events and product problems

Page 1 of 2 (D&R

FDA USE ONLY
Triage unit sequence # 238030

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
In confidence	or 56 / (b) (6)	☒ Female ☐ Male	130 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- ☐ Death: ____ (mo/day/yr)
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☒ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: ____

3. Date of Event (mo/day/year)	4. Date of This Report (mo/day/year)
11/10/04	1/16/05

5. Describe Event or Problem

Since taking Cipro for 6 days beginning November 10, I have totally become a different person. I previously walked over 2 miles per day, but I now have become stiff and sore with debilitating aching joints; muscle pain; smarting, tingling and burning in my legs and a loss of energy and interest in so many things I so enjoyed before. Each day I awaken with

6. Relevant Tests/Laboratory Data, Including Dates

Urinalysis & blood tests - 11/17/04
Blood tests - 12/27/04
Checked for liver function, blood clotting, anemia

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

None

RECEIVED
JAN 26 2005
MEDWATCH CTU

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 Ciprofloxacin - 250mg. TEVA
#2

2. Dose, Frequency & Route Used	3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 1 Tablet twice/day	#1 11/10/04 - 11/16/04
#2	#2

4. Diagnosis for Use (Indication)
#1 Bladder Infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # (if known)	7. Exp. Date (if known)
#1	#1 11-10-05
#2	#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# (For product problems only)
- -

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

None

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mo/day/yr)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mo/day/yr)	7. If Explanted, Give Date (mo/day/yr)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

DSS

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

JAN 27 2005

10. Device Available for Evaluation? (Do not send to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mo/day/yr)

11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	Homemaker/ Housewife	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

pain that only intensifies as the day goes on, and by evenings I am overcome with total stiffness that makes any movement painful and almost impossible.

My husband recently retired, and instead of enjoying our years together travelling, he now takes care of me.

I believe this medication should not be available to ruin other's lives.

DSS
JAN 27 2005

CaseID::5735951

CDER

Individual Safety Report

4572002-6-00-01

The FDA Safety Information and Adverse Event Reporting Program

UNTARY reporting of
nts and product problems

Page 1 of 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 239173

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier (b) (6) In confidence
2. Age at Time of Event: or Date of Birth: (b) (6)
3. Sex: ☒ Female ☐ Male
4. Weight: ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mo/day/yr)
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☒ Disability
☐ Congenital Anomaly
☐ Required Intervention to Prevent Permanent ~~Impairment/Damage~~
☐ Other: ____

3. Date of Event (mo/day/year): 12/05/2004
4. Date of This Report (mo/day/year): 01/20/2005

5. Describe Event or Problem

ON 12/05/2004 - BEGAN EXPERIENCING HALLUCINATIONS AND TREMORS.
AFTER 1 WEEK STILL EXPERIENCING WEAKNESS, LOSS OF APPETITE, ATAXIA, AND CONFUSION
AFTER 1 MONTH - DEPRESSION REQUIRING PROZAC AND INSOMNIA REQUIRING AMBIEN
CONTINUE TO EXPERIENCE
- BLURRING OF VISION
- NUMBNESS OF FINGERTIPS
- PAINFUL JOINTS IN HANDS

6. Relevant Tests/Laboratory Data, Including Dates

RECEIVED
FEB 0 3 2005
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

MYOFASCIAL PAIN SYNDROME VS FIBROMYALGIA WITH CHRONIC FATIGUE
NEUROMEDIATED HYPOTENSION
ATTENTION DEFICIT DISORDER
ALL: SULFA ϕTOXICS ϕETOH
MEDS AT ONSET OF SYMPTOMS: RITALIN SR 20mg, PROZAC 10mg, TYLENOL #3

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 CIPRO XR 500mg
#2

2. Dose, Frequency & Route Used
#1 1 PO EACH DAY
#2

3. Therapy Dates (if unknown, give duration) from/to (or best estimate)
#1 NOV 30 - DEC 5
#2

4. Diagnosis for Use (Indication)
#1 PROTEUS UTI
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☒ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # (if known)
#1
#2

7. Exp. Date (If known)
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# (For product problems only)
- -

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # | Lot #
Catalog # | Expiration Date (mo/day/yr)
Serial # | Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS

10. Device Available for Evaluation? (Do not send to FDA) FEB 0 4 2005
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? ☒ Yes ☐ No
3. Occupation: UROLOGIST
4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☒

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::5744746

Individual Safety Report

4586775-X-00-01

Adverse Event Reporting Program

...NTARY reporting of
...ts and product problems

...ation Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 240723

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	46 Years / (b) (6)	☑ Female ☐ Male	117 lbs / kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: (mo/day/yr)
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☑ Other: hallucination

3. Date of Event *(mo/day/year)*: 01/15/2005

4. Date of This Report *(mo/day/year)*: 02/16/2005

5. Describe Event or Problem

I had stomach pain while taking Cipro, I only took half the dose, 5 days. After one week, I had chills, nightmares, hallucinations, numbness, tingling, joint pain in knees and elbows, tinnitus, muslce weakness, nausea, flashing lights in my eyes, ear pressure, burning rash on my hands. The joint pain has gone, but the numbness, muscle weakness, tinnitus, tingling, flashing lights still remain, one month later. I am a rather stoic person, I take very good care of myself and my children, and I am shocked that this has happened to me. Everyone I speak to who has taken this drug is shocked also when I tell them what has happened to me. I am terrified that these adverse reactions will not go away. This drug should be taken off the market. You must be aware of these reactions, as I have become informed by searching the internet. There certainly is not a lack of people out there who are furious at the adverse

6. Relevant Tests/Laboratory Data, Including Dates

RECEIVED
FEB 17 2005
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

I am allergic to penicillin, otherwise I am healthy and very active.

DSS
FEB 17 2005

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1 Cipro 250 mg.
#2

2. Dose, Frequency & Route Used
#1 orally twice daily
#2

3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
#1 01/10/2005 01/14/2005
#2

4. Diagnosis for Use *(Indication)*
#1 UTI
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(If known)*
#1
#2

7. Exp. Date *(If known)*
#1 01/05/2006
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to Manufacturer on: (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA

Mail to: **MedWatch** 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4586775-X-00-02

240723

WATCH

ofessionals of adverse events and product problems

B5. Describe event or problem continued

reactions they have had from this class of antibiotics. As for me, I'll just keep praying to God, it's in his hands now.

DSS

FEB 17 2005

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::5762113

U.S. Department of Health and Human Services

Individual Safety Report

4603662-9-00-01

VOLUNTARY reporting of events and product problems

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 242288

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier: In confidence
2. Age at Time of Event: or Date of Birth: 61 (b) (6)
3. Sex: [x] Female [ ] Male
4. Weight: 108 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [x] Adverse Event and/or [ ] Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
[ ] Death: ____ (mo/day/yr)
[ ] Life-threatening
[ ] Hospitalization - initial or prolonged
[x] Disability
[ ] Congenital Anomaly
[ ] Required Intervention to Prevent Permanent Impairment/Damage
[ ] Other: ____

3. Date of Event (mo/day/year): 6-10-04 to PRESENT
4. Date of This Report (mo/day/year): 2-15-05

5. Describe Event or Problem

Took one (1) 750mg Levaquin with in 2 hours - pain in right wrist, knee, ankle + foot. Pain in left shoulder, hip, calf, ankle + foot. Sensation of electricity in both feet. Also left heart pounding, shortness, major pain + anxiety. Ringing in both ears, plugged up feeling, horrible headaches. Burning rash when exposed to sun or heat. Muscles in both feet + calves very painful. Cannot walk for lengthy periods. My feet feel like I'm walking on rocks. Can't "digest" anymore without severe pain. Feet are still painful. Bottom of right foot does not feel feet - they are numb.

6. Relevant Tests/Laboratory Data, Including Dates

NONE

RECEIVED
MAR 0 8 2005
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

hypothyroidism, osteoporosis

DSS
MAR 0 9 2005

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 LEVAQUIN (LEVOFLOXACIN)
#2

2. Dose, Frequency & Route Used
#1 750mg-1X day
#2

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 6-10-2004
#2

4. Diagnosis for Use (Indication)
#1 BRONCHITIS
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [x] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot # (if known)
#1 3KA237
#2

7. Exp. Date (if known)
#1 7/06
#2

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [x] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

9. NDC# (For product problems only)
- -

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device: [ ] Health Professional [ ] Lay User/Patient [ ] Other:
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? [ ] Yes [ ] No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) [ ] Yes [ ] No [ ] Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? [ ] Yes [x] No
3. Occupation: Homemaker
4. Also Reported to: [x] Manufacturer [ ] User Facility [ ] Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [ ]

FDA Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Pg. 2 - Marjorie Powell - Lexapro
Item #5 Continued 2402288

- Ball of right foot very painful.
Muscles in both legs twitch and jump - feel "wiggly".
Had diahhrea for 2 weeks following one 750 mg tablet & a sample packet.

As of this date, 2-15-05, I still have pain in muscles and joints, pain in left hand and right wrist. Depression & panic come & go. The "foggy" brain feeling is slightly better but I still have trouble concentrating. I am very lonely and jumpy.

My vision has also changed. I had a near prescription and suddenly it felt like I had my old glasses on. I also get sharp pains in eyes.

This 2 pack sample of Lexapro was given to me with no warning labels, no side effect signs, just take these great tablets!

This drug should only be given for life threatening illnesses - NOT handed out like candy for every little thing that a person may have.

P.S.S
MAR 09 2005

Individual Safety Report
4603662-9-00-02

CaseID::5780149

Individual Safety Report

4634762-5-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of ~~adverse~~ events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 245995

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	or ____ Date of Birth: (b) (6)	☑ Female ☐ Male	____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: ____ *(mo/day/yr)*
- ☑ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☑ Required Intervention to Prevent Permanent Impairment/Damage
- ☑ Other: pain and suffering

3. Date of Event *(mo/day/year)*	4. Date of This Report *(mo/day/year)*
01/11/2005	04/11/2005

5. Describe Event or Problem

My name is (b) (6) I am writing this report for my mother, who was the patient in this case. My mother was given a free sample of a drug called Factive for her bronchitis. Within weeks of taking the drug she broke out in SEVERE hives, and suffered many of the symptoms described with the drugs side effects, to a severe degree at that. Even to this day she suffers the side effects, despite the fact she stopped taking the drug months ago. She can no longer taste food, and it is painful to eat, she has chronic hives -of which she has been told are permanent- and is in constant pain and suffering every day!! The possibility of death exists! My mother did not deserve this. The FDA should be ashamed that this drug even made it to market. How could this happen?? This drug needs to be IMMEDIATELY recalled!! I am writing to anyone who will listen to get this drug recalled. I would like to know what the FDA is

6. Relevant Tests/Laboratory Data, Including Dates

RECEIVED
APR 12 2005
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

None .

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1 Factive
#2

2. Dose, Frequency & Route Used	3. Therapy Dates *(If unknown, give duration)* from/to (or best estimate)
#1	#1
#2	#2

4. Diagnosis for Use *(Indication)*
#1 bronchitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*	7. Exp. Date *(if known)*
#1	#1
#2	#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mo/day/yr)*	7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
APR 13 2005

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4634762-5-00-02

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 2

245995

B5. Describe event or problem continued

going to do about this, since it was the FDA that allowed this drug on the market.

DSS

APR 13 2005

Individual Safety Report

4666186-9-00-01

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TARY reporting of
and product problems

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 248943

The FDA Safety Information and Adverse Event Reporting Program

Internet Submission - Page 1

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	23 Years or	☐ Female ☑ Male	150 lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other:

3. Date of Event *(mo/day/year)*: 01/11/2005

4. Date of This Report *(mo/day/year)*: 05/16/2005

5. Describe Event or Problem

Physical: Diffuse joint pain -every joint and tendon-, plantar fasciitis and achilles tendonitis severely limit ability to stand/walk, heart palpitations, symptoms of neuropathy in legs/feet-tingling, burning, buzzing-, muscle spasms, popping/cracking joints, sensitivity/inability to exercise, severe arm/wrist/elbow pain which severely limits use of hands, severe abdominal muscle/tendon pain, headaches, feeling of pressure in right ear. Mental: cognitive difficuly, memory loss, difficulty finding words, fatigue, generalized anxiety, mild insomnia and sleep disturbances, depression, occasional buzzing feeling in head, mood disturbances, feeling disconnected and disoriented, lightheadedness, inability to focus.

6. Relevant Tests/Laboratory Data, Including Dates

Had tests done to check for kidney problems, came back negative, don't know date.

RECEIVED
MAY 17 2005
MEDWATCH CTU

DSS
MAY 18 2005

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Allergies, irritable bowel syndrome, asthma, smoker -1/2 pack/day-, social anxiety disorder.

DSS
MAY 18 2005

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1 Levaquin 500 mg Ortho-McNeil
#2

2. Dose, Frequency & Route Used
#1 500mg Once/Day Oral
#2

3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
#1 12/02/2004 12/27/2004
#2

4. Diagnosis for Use *(Indication)*
#1 Bronchitis, Sinus Infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*
#1
#2

7. Exp. Date *(if known)*
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*
Dicyclomine 10mg 2x/day

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Type of Device

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mo/day/yr)*

7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to Manufacturer on: *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

-or-

FAX to:
1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::5817946

Individual Safety Report
4683542-3-00-01

CDER 250372

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1 QER

FDA USE ONLY
Triage unit
sequence #

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	50 Years / or — / (b) (6)	☑ Female ☐ Male	110 lbs / or / kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: _____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☑ Required Intervention to Prevent Permanent Impairment/Damage
- ☑ Other: RT CTR

3. Date of Event *(mo/day/year)*	4. Date of This Report *(mo/day/year)*
12/13/2004	06/05/2005

5. Describe Event or Problem

LEVAQUIN 750/5DAY.SEVERE H.A, NECK,SHOULDER,ELBOW,WRIST,BACK,HIP,KNEE,ANKLE PAIN.HAD RT.CTR..NO HELP.SEVERE RT SHOULDER ELBOW,WRIST PAIN,AND LFT BACK,KNEE PAIN..UNRESOLVED.,ANYBODY LISTENING??

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JUN 0 6 2005
MEDWATCH CTU

6. Relevant Tests/Laboratory Data, Including Dates

XRAYS,NERVE CONDUCTION TEST,MRIX2,LAB..12/04,01/05

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

ALL/NSAIDS,WHITE,SMOKE,ALCOHOL MINIMAL

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1 LEVAQUIN 750MG ORTO/MCNEIL
#2

2. Dose, Frequency & Route Used	3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
#1 750MG PO	#1 12/13/2004 12/18/2004
#2	#2

4. Diagnosis for Use *(Indication)*	5. Event Abated After Use Stopped or Dose Reduced?
#1 R/O PNEUMONIA..FINAL DX. BRONCHITIS	#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*	7. Exp. Date *(if known)*	8. Event Reappeared After Reintroduction?
#1	#1	#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2	#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. If Implanted, Give Date *(mo/day/yr)*	7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
DSS
JUN - 6 2005

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☑ Yes ☐ No	Nurse	☑ Manufacturer ☑ User Facility ☑ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4707939-8-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

CDER

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

CDER

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 252486

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) in confidence	29 Years or	☑ Female ☐ Male	150 lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: ____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☑ Other: pain

3. Date of Event *(mo/day/year)*	4. Date of This Report *(mo/day/year)*
03/02/2004	07/04/2005

5. Describe Event or Problem

Took one dose of Avelox for sinus infection. Woke up 2 hours later very disoriented and confused. 8 hours later my left shoulder, arm, and hand swelled. My left middle finger became semi-permanently flexed for one week. My arm burned, tingled, and caused a great deal of pain. For months I had limited use of my left arm. Physical therapy has helped with use, but has not diminished the pain.

DSS

JUL 0 5 2005

6. Relevant Tests/Laboratory Data, Including Dates

Xray of hand and wrist, MRI of shoulder and neck. All negative.

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JUL 0 5 2005

MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

none

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1 Avelox 500 mg
#2

2. Dose, Frequency & Route Used
#1 1 per day Oral
#2

3. Therapy Dates *(If unknown, give duration)* from/to (or best estimate)
#1 03/02/2004 03/03/2004
#2

4. Diagnosis for Use *(Indication)*
#1 sinusitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*
#1
#2

7. Exp. Date *(if known)*
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*
oral contraceptive

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Type of Device

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mo/day/yr)*

7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☑ Yes ☐ No	Other Health Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::5840679

Individual Safety Report

4626789-4-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

CDER

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 245082

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	50 Years or (b) (6)	☑ Female ☐ Male	90 lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other:

3. Date of Event *(mo/day/year)*: 12/01/2005

4. Date of This Report *(mo/day/year)*: 03/30/2005

5. Describe Event or Problem

Levaquin for sinusitis following viral illness which resulted in bilateseal hip, buttock, leg and foot pain and burning. Paresthesias, neuropathy, myalgia, arthralgia, tendonitis. Unable to sit or drive, after 3 months of mis-diganosis and all negative testing, took medical leave of absence from work - anxiety and depression symptoms afterwards.

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APR 0 1 2005
MEDWATCH CTU

6. Relevant Tests/Laboratory Data, Including Dates

ANA, RA factor, lyme, thyroid negative 11/05 and 3/24/05 -CPK negative 3/26/05, MRI pevlis, L hip and lumbar spine negative except for mild L4 arthritis, disc bulge. No signs sciatic on PE.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

DSS
APR 0 4 2005

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1 Levaquin
#2

2. Dose, Frequency & Route Used	3. Therapy Dates *(if unknown, give duration)* from/to *(or best estimate)*
#1 Oral	#1 11/22/2005 12/01/2005
#2	#2

4. Diagnosis for Use *(Indication)*
#1 sinusitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*	7. Exp. Date *(if known)*
#1	#1
#2	#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*
Physical therapy in December 04 through January 05, held for testing and resumed in March 05 with little benefit, possible ex

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to Manufacturer on: *(mo/day/yr)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☑ Yes ☐ No	Nurse	☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

Mail to: MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4626789-4-00-02

245082

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 5

C10. Concomitant medical products and therapy dates continued

acerbation.

D11. Concomitant medical products and therapy dates continued

DSS

APR 0 4 2005

CaseID::5852274

Individual Safety Report

4731191-0-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

CDER

CBR

Page 1 of 2

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 254738
TELEPHONE REPORT

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
In confidence	or _____ Date of Birth: (b) (6)	☐ Female ☒ Male	175 lbs or _____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: _____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☒ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: _____

3. Date of Event *(mo/day/year)*	4. Date of This Report *(mo/day/year)*
03/03/2005	07/14/2005

5. Describe Event or Problem

The reporter started (on 3/1/05) and completed a 10-day course of the drug. One or two days later, he began a second 10 day course the doctor prescribed, and also finished that. He experienced multiple adverse events. Beginning 3/3, he had tingling, prickling, and itching. Symptoms moved around and affected him head to toe. Sometimes it was in an arm, or the bottoms of a leg, or his groin, for example. He took Benadryl, but it provided little relief. On 3/23, he had gone to the ER because the sensations were so bad. They treated him with a steroid shot and oral steroids, but they didn't help. The drug wasn't suspected. He thought he might have some allergy and continued taking the drug.
Another serious event he had began with a feeling of pain in both shoulders, right greater than left. Onset was gradual and occurred later on. He thought he'd hurt himself exercising, but didn't recall any injury. He can't pinpoint exactly when pains started, but it was after he started the drug. Had he ruptured a tendon or torn his rotator cuff? He consulted an orthopedic surgeon. 15 x-rays were taken. No problems were seen with his bones. The doctor prescribed Mobic, but he only used it about a week.
CONT, see P 2

6. Relevant Tests/Laboratory Data, Including Dates

X-rays of affected areas yielded no bone abnormalities.

DSS
AUG 0 1 2005

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JUL 2 9 2005
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Race: White. Ht/Wt: 5'7"/175 lbs. No known prior drug allergies. Has a history of sinus infections, gets 1 or 2 per year. Also has a history of IBS, high blood pressure. No prior history of shoulder ailments. No history of kidney or liver dysfunction.
Non-smoker. Alcohol use-minimal, occasional beer on weekend.

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1 Levaquin
#2

2. Dose, Frequency & Route Used	3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
#1 500 mg once daily	#1 20 days total/Mar 2005
#2	#2 see B5

4. Diagnosis for Use *(Indication)*
#1 sinus infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*	7. Exp. Date *(if known)*
#1	#1
#2	#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*
- -

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*
Toprol 25 mg, Clidinium, Centrum Silver.

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	Consumer/Non-Health Professional	☒ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

U.S. Department of Health and Human Services

Individual Safety Report

4731191-0-00-02

(CONTINUATION PAGE)

VOLUNTARY reporting of events and product problems

854738

5. **Describe Event or Problem** *(continued)*

He continued to have sharp, stabbing pains when he moved or was in certain positions. Sometimes pains occurred while just walking and swinging his arms. The pain in his left shoulder lasted a few weeks. The right shoulder pain persists and has subsided slightly, but he still doesn't have the original use of his arm/shoulder. He can't even throw a baseball.
He'd also had some days with the feeling of pressure in his right ear. He'd had a sun sensitivity (photophobia) as well on several occasions (3 to 4 times), where his eyes were very sensitive to the sunlight and he couldn't go outside.
To date, he has transient pains that migrate from his right shoulder to the right neck and then to the right side of his skull. When he gets this feeling, he gets fatigued and lies down and in 1 to 2 hours it subsides.

6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Concomitant Medical Products and Therapy Dates *(Exclude treatment of event) (continued)*

DSS
AUG 0 1 2005

Individual Safety Report

4751244-0-00-01

CDER

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

OER

FDA USE ONLY
Triage unit sequence # 256 736

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event:	3. Sex	4. Weight
(b) (6) In confidence	or Date of Birth: (b) (6)	☐ Female ☑ Male	185 lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: _____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: _____

3. Date of Event *(mo/day/year)*	4. Date of This Report *(mo/day/year)*
02/20/2005	08/22/2005

5. Describe Event or Problem

Shortly after completing a regimen of ten days using the drug Ciprofloaxicin, I developed a severe weakening of the left Achilles tendon and developed neuropathy in my feet. I was unaware of the potential cause until I had a repeat infection requiring the use of the same drug again. This time, I looked at the potential side effects of this drug after noticing that my right foot was involved with increasing neuropathy and pain in the tendons. It has become necessary for me to obtain some relief with physical therapy, but walking has become difficult for more than a short distance. Before the February occurence, I was able to walk a mile or more each day for exercise.

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AUG 2 3 2005
MEDWATCH CTU

6. Relevant Tests/Laboratory Data, Including Dates

Physical therapists found that the tendons had softened and lost their strength.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

DSS
AUG 2 4 2005

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
- #1 ciprofloxacin 500MG TAB DR.R unknown
- #2

2. Dose, Frequency & Route Used
- #1 two tablets daily for ten days po
- #2

3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
- #1 01/25/2005 02/04/2005
- #2 07/13/2005 07/22/2005

4. Diagnosis for Use *(Indication)*
- #1 bladder infection
- #2 bladder infection

5. Event Abated After Use Stopped or Dose Reduced?
- #1 ☑ Yes ☐ No ☐ Doesn't Apply
- #2 ☑ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*
- #1
- #2

7. Exp. Date *(if known)*
- #1
- #2

8. Event Reappeared After Reintroduction?
- #1 ☐ Yes ☐ No ☐ Doesn't Apply
- #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Type of Device

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. If Implanted, Give Date *(mo/day/yr)*

7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::5882021

U.S. Department of Health and Human Services

Individual Safety Report

4771493-5-00-01

VOLUNTARY reporting of events and product problems

CDER

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 258733

Page 1 of 2 CBER

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event:	3. Sex	4. Weight
(b) (6) In confidence	or 53 Date of Birth: (b) (6)	☑ Female ☐ Male	110 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- ☐ Death: ____ (mo/day/yr)
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☑ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: ____

3. Date of Event (mo/day/year): 3/11/05

4. Date of This Report (mo/day/year): 9/8/05

5. Describe Event or Problem

For First 12 days or so - Dark urine, dizziness, hiperactivity, tremors, restlessness, anxiety, confusion nightmares, insomnia, manic, rapid heart rate, heart palpitations, extream weakness underlined
For First 3 months - 6 months still happening
skin rash, sensativity to SUN, extreme muscle pain and weakness, bone pain night sweats every night, nausea light headed, nerve pain, confusion, insomnia, extreme fatigue, muscle twitching, anxiety, restlessness, rapid pounding irregular heartrate, extreme sinusitis, ringing in ears, abnormal dreaming -
* now allergic to most medications & supplements - still having awful reactions

6. Relevant Tests/Laboratory Data, Including Dates

5/9/05 - Saw DR. - Neurologist & Lab Tests confirmed Levaquin reaction
4/6/05 saw DR. Psychiatry - believed it to be levaquin reaction
- Symptoms still persistent today -

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Disabeled for 10 years for Chronic Fatique Syndrome. Became ill 1987 disabeled 1994. Allergic to penicillin and sensative to many medicattions Should never have been given this awful medication. S/E Warning labels or taken off market.

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 Levaquin 500 mg daily
#2

2. Dose, Frequency & Route Used
#1 500 mg daily *
#2 250 mg daily

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 2/8/05 - 3/11/05
#2 1/29 - 2/3

4. Diagnosis for Use (Indication)
#1 Bronchitis w/fever
#2 Bronchitis

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # (if known)
#1 —
#2

7. Exp. Date (if known)
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# (For product problems only)
N/A

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
Asprin for fever
Seroquel for sleep occasionally

D. SUSPECT MEDICAL DEVICE

1. Brand Name N/A
2. Type of Device
3. Manufacturer Name, City and State

DSS
SEP 15 2005

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mo/day/yr)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

RECEIVED
SEP 14 2005
MEDWATCH CTU

10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Disabled	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

258233

LabCorp®

(b) (6) (b) (6) Pg 1 XE N 01 R SEQ 9570

Misc Source | Total Urine Volume | Report Status: S / Final

Individual Safety Report

4771493-5-00-02

Date Collected: 05/09/05 | Time Collected: 15:50 | Date Entered: 05/09/05 | Date Reported: 05/10/05

(b) (6) (b) (6) (b) (6) (b) (6) (b) (6)

Sex: F | Date of Birth: (b) (6)

PATIENT AGE: 053/11

MCAID#: (b) (6)

Phy Name: (b) (6)

Comp. Metabolic Panel (14); CBC, Platelet; No Differential; Hepatic Function Panel (7); Vitamin B12 and Folate; TSH; Sedimentation Rate-Westergren; Creatine Kinase, Total, Serum; Magnesium, Serum; Venipuncture; Laguna Hills,CA

Comp. Metabolic Panel (14)					
Glucose, Serum	98		mg/dL	65 - 99	SC
BUN	16		mg/dL	5 - 26	SC
Creatinine, Serum	0.8		mg/dL	0.5 - 1.5	SC
BUN/Creatinine Ratio	20			8 - 27	
Sodium, Serum	139		mmol/L	135 - 148	SC
Potassium, Serum	4.2		mmol/L	3.5 - 5.5	SC
Chloride, Serum	102		mmol/L	96 - 109	SC
Carbon Dioxide, Total	25		mmol/L	20 - 32	SC
Calcium, Serum	9.7		mg/dL	8.5 - 10.6	SC
Protein, Total, Serum	7.3		g/dL	6.0 - 8.5	SC
Albumin, Serum	4.8		g/dL	3.5 - 5.5	SC
Globulin, Total	2.5		g/dL	1.5 - 4.5	
A/G Ratio	1.9			1.1 - 2.5	
Bilirubin, Total	0.4		mg/dL	0.1 - 1.2	SC
Alkaline Phosphatase, Serum	82		IU/L	25 - 150	SC
AST (SGOT)	15		IU/L	0 - 40	SC
ALT (SGPT)	13		IU/L	0 - 40	SC
CBC, Platelet; No Differential					
White Blood Cell (WBC) Count	8.9		x10E3/uL	4.0 - 10.5	SC
Red Blood Cell (RBC) Count	5.03		x10E6/uL	3.80 - 5.10	SC
Hemoglobin		16.6 H	g/dL	11.5 - 15.0	SC
Hematocrit		48.8 H	%	34.0 - 44.0	SC
MCV	97		fL	80 - 98	SC
MCH	32.9		pg	27.0 - 34.0	SC
MCHC	34.0		g/dL	32.0 - 36.0	SC
RDW	12.9		%	11.7 - 15.0	SC
Platelets	268		x10E3/uL	140 - 415	SC
Hematology Comments:	Note:				SC
Verified by repeat analysis					
Hepatic Function Panel (7)					
Bilirubin, Direct	0.09		mg/dL	0.00 - 0.40	SC
Vitamin B12 and Folate					
Vitamin B12	361		pg/mL	211 - 911	SC
Folates (Folic Acid), Serum	11.8		ng/mL	>5.4	SC
			Indeterminate:	3.4 - 5.4	
			Deficient:	<3.4	
TSH	1.776		uIU/mL	0.350 - 5.500	SC
Sedimentation Rate-Westergren	8		mm/hr	0 - 30	SC
Creatine Kinase, Total, Serum	43		U/L	24 - 173	SC

DSS

SEP 15 2005

(b) (6) REPORT (b) (6)

Report DATE: 05/10/05 Report Time: 13:08 ET

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CaseID::5891511

CDER

Individual Safety Report

4784682-0-00-01

...r VOLUNTARY reporting of ...rse events and product problems

Adverse Event Reporting Program

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 259162

Page ___ of ___ CDER

A. PATIENT INFORMATION

1. Patient Identifier: In confidence
2. Age at Time of Event: 72yrs 10½ mo. or ___ Date of Birth: (b) (6)
3. Sex: ☒ Female ☐ Male
4. Weight: 127 ± lbs or ___ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ___ (mo/day/yr)
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☒ Disability
☐ Congenital Anomaly
☐ Required Intervention to Prevent Permanent Impairment/Damage
☐ Other: ___

3. Date of Event (mo/day/year): 1-11-05
4. Date of This Report (mo/day/year): 9-6-05

5. Describe Event or Problem: Went thru 10 day course with common side effects diarrhea, gas headache / sinus pressure.

PROBLEM: Chronic left hip joint pain and left Calf pain.
Sudden onset with stabbing pain through calf followed by sharp pain in hip joint (buttock area), almost couldn't stand.
Calf pain progressed to intense burning, cramping, radiating.
Hip also burning with or without weight bearing.
Pain persists in varying degrees use walking cane as needed.
Never had problem with leg before this sudden onset on 1/11/05.

6. Relevant Tests/Laboratory Data, Including Dates
2/16/05 hip XRay - osteoarthritis -
4/15/05 ultra sound leg vascular / normal
5/3ps Spine XRay Fractures - (old?)
5/24/05 Bone Density Scan / osteoporosis

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
Allergies - iodine IV, Pyridines? Sulfa based drugs? Ketoconaloze, hygroton, Bismuth.
Lactose intolerant
Race: ASIAN

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
#1 500 mg. generic Cipro, mfr Ranbaxy
#2

2. Dose, Frequency & Route Used
#1 500 mg. 2x day oral
#2

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 12/06/04 to 12/16/04
#2

4. Diagnosis for Use (Indication)
#1 UTI
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # (if known)
#1
#2

7. Exp. Date (if known)
#1 4-06
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# (For product problems only)
- -

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other: ___
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-Use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☒ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: ___ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

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SEP 29 2005
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DSS
SEP 30 2005

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? ☐ Yes ☒ No
3. Occupation
4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☒

PLEASE TYPE OR USE BLACK INK

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

4854168-3-00-01

rt LEVAQUIN® (levofloxacin) TABLETS

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

Johnson & Johnson Pharmaceutical

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Approved by FDA on 10/25/2002

Mfr report # US-JNJFOC-20050604083

UF/Dist report #

FDA use only

A. Patient information

1. Patient identifier: (b) (6) — In confidence
2. Age at time of event: or Date of birth: 57 Year ??/??/????
3. Sex: ☐ female ☒ male
4. Weight: UNK lbs or UNK kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse (check all that apply)
- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☒ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 04/01/2005

4. Date of this report (mo/day/yr): 11/17/2005

5. Describe event or problem

Report received from a Consumer or Other Non Health Professional. 1-154705923.

A 57 year old man, (weight unspecified), with a history of irritable bowel and elevated blood pressure, was prescribed levofloxacin 500 mg tablets daily, initiated on 01-Mar-05 to 24-Mar-05 for the treatment of sinusitis.

Concomitant medication included mesalazine, clindamycin, and metoprolol succinate.

The patient was originally prescribed a 10 day course of levofloxacin. After

(Cont.)

6. Relevant test/laboratory data, including dates

No Relevant Test/Laboratory Data Reported

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

HYPERTENSION
IRRITABLE BOWEL SYNDROME

(Cont.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 LEVAQUIN (LEVOFLOXACIN) Tablets
#2

2. Dose, frequency & route used
#1 500 mg, 1 in 1 Day, Oral
#2

3. Therapy dates (from/to (or best estimate))
#1 03/01/2005-03/24/2005
#2

4. Diagnosis for use (indication)
#1 SINUSITIS
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☒ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
1) ASACOL () MESALAZINE
2) CLINDAMYCIN () CLINDAMYCIN
3) TOPROL () METOPROLOL SUCCINATE

(Cont.)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
Johnson & Johnson Pharmaceutical
100 Tournament Drive
Horsham
PA 19044
UNITED STATES

2. Phone number
1-2153257691

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☒ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 07/12/2005

5. (A) NDA # 20-634
IND #
PLA #
pre - 1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☒ periodic
- ☐ initial ☐ follow-up # ___

8. Adverse event term(s)
1) PRURITUS
2) SHOULDER PAIN
3) PARAESTHESIA
4) DRUG INEFFECTIVE

(Cont.)

9. Mfr. report number
US-JNJFOC-20050604083

E. Initial reporter

1. Name & address

phone #
(b) (6)

2. Health professional? ☐ yes ☒ no

3. Occupation: Unknown

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

NOV 2 5 2005

Individual Safety Report
4854168-3-00-02

port LEVAQUIN® (levofloxacin) TABLETS

Johnson & Johnson Pharmaceutical
100 Tournament Drive

Horsham PA 19044

Mfr. report#: US-JNJFOC-20050604083

Continuation Sheet for FDA-3500A Form | Page 2 of 3 | Date of this report : 11/17/2005

B5. Describe event or problem (Cont...)

completion of the course, sinus symptoms remained and patient continued an additional 10 day course of levofloxacin therapy. On 01- Apr-05 the patient experienced," tingling all over that comes and goes, pain in both shoulders(right greater than left), fatigue, pain up into neck with ear aches and itching all over that comes and goes".

Outcome: sinus symptoms-recovered.

all other events: not recovered/not resolved.

This report is not serious.

Additional information received from the patient on 12-Jul-05:

The patient reported," intense skin irritation, burning, itching, pricking, tingling, severe pain deep in right shoulder, (seems to be in joint) remain". He also complains of blurred vision, confusion and anxiety. The patient stated, "xrays eliminated any bone damage. Intense skin problem stays with me most days-more intense depending on what I eat". He feels tired with a general ill feeling which did not exist before taking levofloxacin. He reported the symptoms have, "altered his life style-at least for now".

Outcome: not recovered.

confusion, blurred vision and anxiety listed as non serious events.

Based on the information received revealing the length of time the symptoms have persisted, this case has been revised to serious; disability.

B.7 Other relevant history, including preexisting medical conditions (Cont...)

C10. Concomitant medical products

Seq No.	: 1
C.10 Concomitant medical	: ASACOL (MESALAZINE)
C.10 Diagnosis for use(indication)	: 1) IRRITABLE BOWEL SYNDROME
C.10 dose,frequency & route used	: 1) Oral
C.10 therapy Dates(or duration)	: 1) ??/??/???? - Ongoing
Seq No.	: 2
C.10 Concomitant medical	: CLINDAMYCIN (CLINDAMYCIN)
C.10 Diagnosis for use(indication)	: 1) IRRITABLE BOWEL SYNDROME
C.10 therapy Dates(or duration)	: 1) ??/??/???? - Ongoing
Seq No.	: 3
C.10 Concomitant medical	: TOPROL (METOPROLOL SUCCINATE)
C.10 Diagnosis for use(indication)	: 1) HYPERTENSION
C.10 dose,frequency & route used	: 1) Oral
C.10 therapy Dates(or duration)	: 1) ??/??/???? - Ongoing

G8. Adverse event term (Cont...)

5) CONFUSIONAL STATE
6) FATIGUE
7) EAR PAIN

NOV 2 5 2005

Individual Safety Report
4854168-3-00-03

port LEVAQUIN® (levofloxacin) TABLETS

Johnson & Johnson Pharmaceutical
100 Tournament Drive

Horsham PA 19044

Mfr. report#: US-JNJFOC-20050604083

Continuation Sheet for FDA-3500A Form

Page 3 of 3

Date of this report : 11/17/2005

G8. Adverse event term (Cont...)

8) VISION BLURRED
9) ANXIETY

NOV 2 5 2005

Periodic Adv Individual Safety Report ABLETS

4855149-6-00-01

U.S. Department of Health and Human ... Pharmaceutical

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page 1 of 2

Approved by FDA on 10/25/2002

Mfr report # US-JNJFOC-20040304963

UF/Dist report #

FDA use only

A. Patient information

1. Patient identifier: (b) (6) In confidence
2. Age at time of event: or 52 Year; Date of birth: ??/??/????
3. Sex: [X] female [ ] male
4. Weight: 128 lbs or ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse (check all that apply)
- [ ] death ____ (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization - initial or prolonged
- [X] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other: ____

3. Date of event (mo/day/yr): ??/??/????

4. Date of this report (mo/day/yr): 11/17/2005

5. Describe event or problem

Report received from a consumer. 1-92826012.

A 52 year old woman, (weight 128 pounds), was treated with levofloxacin 500mg (formulation unspecified) from 11-Mar-04 to 18-Mar-04 for cystitis. Concomitant medication included zolpidem tartrate.

On 17-Mar-04 she experienced muscle pain in both knees. By 18-Mar-04 she had "pain in back of tendons in knees", could not walk and had difficulty sleeping. She also reported swelling bilaterally started with right leg

(Cont.)

6. Relevant test/laboratory data, including dates

No Relevant Test/Laboratory Data Reported

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

No Relevant History Reported

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 LEVAQUIN (LEVOFLOXACIN) Unspecified
#2

2. Dose, frequency & route used
#1 500 mg, 1 in 1 Day
#2

3. Therapy dates (from/to (or best estimate))
#1 03/11/2004-03/18/2004
#2

4. Diagnosis for use (indication)
#1 CYSTITIS
#2

5. Event abated after use stopped or dose reduced
#1 [ ] yes [ ] no [ ] doesn't apply
UNK
#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 [ ] yes [ ] no [ ] doesn't apply
UNK
#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
1)AMBIEN () ZOLPIDEM TARTRATE

(Cont.)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
Johnson & Johnson
Pharmaceutical
100 Tournament Drive
Horsham
PA 19044
UNITED STATES

2. Phone number 1-2153257691

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [X] consumer
- [ ] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other: ____

4. Date received by manufacturer (mo/day/yr): 01/28/2005

5. (A)NDA # 20-634
IND # ____
PLA # ____
pre - 1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
- [ ] 5-day [ ] 15-day
- [ ] 10-day [X] periodic
- [ ] initial [ ] follow-up # ____

8. Adverse event term(s)
1) PAIN IN EXTREMITY
2) JOINT SWELLING
3) ABASIA
4) INSOMNIA

9. Mfr. report number
US-JNJFOC-20040304963

E. Initial reporter

1. Name & address: (b) (6)

phone #

2. Health professional? [ ] yes [X] no

3. Occupation: Unknown

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Page No. : 14

NOV 2 5 2005

Periodic Adverse Drug

Individual Safety Report

4855149-6-00-02

Johnson & Johnson Pharmaceutical
100 Tournament Drive

Horsham PA 19044

Mfr. report#: US-JNJFOC-20040304963

Continuation Sheet for FDA-3500A Form

Date of this report : 11/17/2005

B5. Describe event or problem (Cont...)

first.

outcome: unknown

Additional information received from consumer 28-Jan-05: The woman reports that she has seen her physician and multiple sclerosis has been ruled out. The pain in her right hand has subsided but pain in the left hand continues. Her physician prescribed gabapentin in Nov-04 which she took for 3 weeks with relief of the pain. The physician told her that "nerves are misfiring". The pain in her left hand returned.

Based upon information received 28-Jan-05 the event pain is considered serious.

C10. Concomitant medical products

Seq No.	: 1
C.10 Concomitant medical	: AMBIEN (ZOLPIDEM TARTRATE)
C.10 Diagnosis for use(indication)	: 1) INSOMNIA

NOV 2 5 2005

Periodic Adverse Drug Experience Report LEVAQUIN® (levofloxacin) TABLETS

Individual Safety Report
4855081-8-00-01

U.S. Department of H...
MEDWATCH
The FDA Safety ... and Adverse Event Reporting Program

MANDATORY reporting

Page 1 of 4

Approved by FDA on 10/25/2002

Mfr report #: US-JNJFOC-20041200896
LR/Dist report #:
FDA use only

A. Patient information

1. Patient identifier: (b) (6) In confidence
2. Age at time of event: 46 Year or Date of birth: (b) (6)
3. Sex: ☐ female ☒ male
4. Weight: UNK lbs or UNK kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse (check all that apply)
☐ death (mo/day/yr)
☐ life-threatening
☐ hospitalization - initial or prolonged
☒ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event (mo/day/yr): 11/02/2004
4. Date of this report (mo/day/yr): 11/17/2005

5. Describe event or problem

Report forwarded by sales representative from a Patient who is also pharmacist. 1-140331339.

A man, (weight and age unspecified), was treated with levofloxacin 500 mg,(formulation unspecified), initiated on 30-Oct-04 to 02-Nov-04 for bronchitis.

On 31-Oct-04 the patient experienced ringing in the ears. On 01-Nov-04, he developed shooting pain in his leg muscles. Over the next several days, the patient noted deep muscle pain and joint pain in left ankle, bilateral wrist and finger pain and tendinitis in

(Cont.)

6. Relevant test/laboratory data, including dates

03-Nov-04 Aldolase 2.6 U/L (0.0-8.1)

18-Nov-04 RF (rheumatoid factor) <20IU/ml (<20.0 IU/ml)

(Cont.)

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

BACK PAIN
CLAVICLE FRACTURE
SEASONAL ALLERGY

(Cont.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 LEVAQUIN (LEVOFLOXACIN) Unspecified
#2

2. Dose, frequency & route used
#1 500 mg, 1 in 1 Day
#2

3. Therapy dates (from/to (or best estimate))
#1 10/30/2004-11/02/2004
#2

4. Diagnosis for use (indication)
#1 BRONCHITIS
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☒ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # -for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
1) FLONASE () FLUTICASONE PROPIONATE
2) CLARITIN () LORATADINE

(Cont.)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
Johnson & Johnson Pharmaceutical
100 Tournament Drive
Horsham
PA 19044
UNITED STATES

2. Phone number
1-2153257691

3. Report source (check all that apply)
☐ foreign
☐ study
☐ literature
☒ consumer
☒ health professional
☐ user facility
☒ company representative
☐ distributor
☐ other:

4. Date received by manufacturer (mo/day/yr): 03/16/2005

5. (A)NDA # 20-634
IND #
PLA #
pre - 1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☒ periodic
☐ initial ☐ follow-up #

8. Adverse event term(s)
1) MYALGIA
2) VASCULITIS
3) NEUROPATHY PERIPHERAL
4) PARAESTHESIA

(Cont.)

9. Mfr. report number
US-JNJFOC-20041200896

E. Initial reporter

(b) (6)

2. Health professional? ☒ yes ☐ no
3. Occupation: Physician
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☒ unk

FDA 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Page No. : 166

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NOV 2 5 2005

Periodic Adverse Drug Experience Report LEVAQUIN® (levofloxacin) TABLETS

Individual Safety Report

4855081-8-00-02

Johnson & Johnson Pharmaceutic
100 Tournament Drive

Horsham PA 19044

Mfr. report#: US-JNJFOC-20041200896

Continuation Sheet for FDA-3500A Form

Date of this report : 11/17/2005

B5. Describe event or problem (Cont...)

shoulders. The patient also reported CNS effects, "felt as if he were zoning out". The patient discontinued levofloxacin on 03-Nov-04 and was seen by health care provider. He requires the use of crutches and symptoms have not resolved as of 01-Dec-04.

Tinnitus and CNS effects are considered non-serious events.

This report is serious (disability)

9-Feb-05: Medical authorization received. Request for physicians letters sent.

Additional information received from physicians on 28-Feb-05:

On 03-Nov-04 the patient was seen by a physician with symptoms of myalgias and neuropathic pain mainly involving his calves; left side>right side. Physical exam was normal with the exception of tenderness in his calves and Achilles tendon areas. Cranial nerves II through XII were intact.

Diagnostic testing was done with the following results:

Laboratory Studies: Comprehensive Metabolic Panel and CBC (complete blood count) were normal.

ESR (sedimentation rate) 3mm/Hr. (ref range 0-15mm/Hr.)

CRP (C-reactive protein) 5.1mg/L (ref range <10.0mg/L)

RF(QN) (rheumatoid factor) <20 (ref range<20.0 IU/mL)

CK(creatine kinase) 42U/L (ref range 0-200U/L)

ANA screen negative

Aldolase 2.6U/L (ref range 0.0-8.1U/L)

Magnesium 1.9mg/dl (ref range 1.5-2.5mg/dl)

Report from 07-Dec-05: patient was experiencing difficulty with muscle cramps/irritability treated with clonazepam. He was using crutches while walking.

Electromyography and nerve conduction studies performed on 13-Dec-04

revealed normal bilateral lower extremity sensorimotor nerve conduction studies, F responses and H reflexes. The electromyographic examination of both lower extremities was normal. No evidence for the presence of peripheral neuropathy, nor myopathy.

MRI (magnetic resonance imaging) of the lumbar spine without contrast performed on 17-Dec-04:

Very minimal facet degenerative changes at L4-5 and L5-S1.

MRI of thoracic spine without contrast on 17-Dec-04:

mild disc desiccation change seen at multiple levels with a few minimal bulges. No spinal stenosis or foraminal narrowing identified.

Treatment consisted of ibuprofen 800mg q.i.d. and calcium and magnesium supplements. Patient had initial physical therapy evaluation done on 07-Jan-05.

Outcome: not recovered/not resolved.

NOV 2 5 2005

Periodic Adverse Drug Experience Report LEVAQUIN® (levofloxacin) TABLETS

Johnson & Johnson Pharmaceutical
100 Tournament Drive

Horsham PA 19044

Individual Safety Report

4855081-8-00-03

Mfr. report#: US-JNJFOC-20041200896

Continuation Sheet for FDA-3500A Form

Date of this report : 11/17/2005

B5. Describe event or problem (Cont...)

Reporter causality: related

Muscle cramps reported as a non-serious event.

Additional information received from a physician (neurologist) 16-Mar-05:

The patient's history of present illness was reported but is stated above.

A neurological examination was normal except:

Sensory examination: Is intact except for decreased temperature sensation in his feet. Reflexes were normal.

Gait: Gait is slightly antalgic but non-localizing. He seems to indicate discomfort in his lower legs when he walks. His balance is normal. He is able to walk in tandem and his Romberg sign is negative.

His feet are red and discolored and cold to touch. He stated that this is relatively new since the levofloxacin exposure.

Neurologist impression: The patient has bilateral calf pain and paresthesias in his feet. Clinically the suspicion is that levofloxacin is responsible for his symptoms. His nerve conduction study was normal, however he has vasomotor changes in his feet and some decreased sensation there as well. There is suspicion of a small fiber neuropathy, possibly caused by levofloxacin. He may also have a component of Achilles tendinitis, also potentially related to levofloxacin. "I have concerns about a potential vasculitic process, perhaps affecting his muscles and nerves in his distal lower extremities and he did initially have some symptoms in his upper extremities but, fortunately, he has had resolution of these. As his symptoms seem to be improving I do not think that steroid therapy at this point would be appropriate. I think that physical therapy with an aim at treating any tendinopathy that he has in his lower extremities and, also, trying to improve his range of motion, would be his best bet right now. For symptomatic relief of his paresthesias I would like to give him some gabapentin. I will start at a low dose and gradually titrate it." The patient was told by the neurologist that he was optimistic for improvement over the next 6 months to 1 year and hopefully will get back to normal.

B.6 Relevant tests/laboratory data, including dates (Cont...)

Lab Result:

Test name	Test date	Test result	Normal high	Normal low
ANA/ANF Titers	11/18/2004	negative		
C-Reactive Protein	11/18/2004	5.1 mg/L (milligram/liter)		
Complete Blood Count	11/05/2004	normal		
Creatine Kinase	11/03/2004	54	200 U/L	0 U/L
	11/18/2004	42 U/L		
Sed Rate	11/05/2004	3 MM/HR (millimeter/Hour)	15	0
	11/18/2004	2 MM/HR (millimeter/Hour)		

B.7 Other relevant history, including preexisting medical conditions (Cont...)

Medical History

SINUS OPERATION

NOV 2 5 2005

Periodic Adverse [redacted] Report LEVAQUIN® (levofloxacin) TABLETS

Individual Safety Report

4855081-8-00-04

Johnson & Johnson Pharmaceutical
100 Tournament Drive

Horsham PA 19044

Mfr. report#: US-JNJFOC-20041200896

Continuation Sheet for FDA-3500A Form | Page 4 of 4 | Date of this report : 11/17/2005

Medical History

SINUSITIS

SLEEP APNOEA SYNDROME

Drug History

Drug: BACTRIM

Reaction: HYPERSENSITIVITY

Drug: QUINOLONES

Reaction: HYPERSENSITIVITY

Drug: SULFA

Reaction: HYPERSENSITIVITY

C10. Concomitant medical products

Seq No. : 1
C.10 Concomitant medical : FLONASE (FLUTICASONE PROPIONATE)

Seq No. : 2
C.10 Concomitant medical : CLARITIN (LORATADINE)

Seq No. : 3
C.10 Concomitant medical : SINGULAIR (MONTELUKAST SODIUM)

G8. Adverse event term (Cont...)

5)ASTHENIA
6)ARTHRALGIA
7)TENDONITIS
8)MUSCLE SPASMS
9)NERVOUS SYSTEM DISORDER
10)TINNITUS

NOV 2 5 2005

Feb 06 06 12:01p (b) (6) p.1

Individual Safety Report

4906097-4-00-01

CDER OSW

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

VOLUNTARY reporting of adverse events and product problems

Page 1 of ___

FDA USE ONLY
Triage unit sequence # 268864

A. PATIENT INFORMATION

1. Patient Identifier (b) (6) In confidence
2. Age at Time of Event: 52 or Date of Birth:
3. Sex: ☐ Female ☑ Male
4. Weight: 195 lbs or ___ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
   - ☐ Death: ___ (mo/day/yr)
   - ☑ Life-threatening
   - ☐ Hospitalization - initial or prolonged
   - ☑ Disability
   - ☐ Congenital Anomaly
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage
   - ☐ Other: ___
3. Date of Event (mo/day/year): JUNE 11, 2005
4. Date of This Report (mo/day/year): Feb. 6, 2006
5. Describe Event or Problem

Took AVELOX for Sinusitis in MARCH (2005). JUNE 11th, I woke up with extreme fatigue, weak, with "foggy brain" and visual perception problems. Symptoms appearing later were: peripheral Neuropathy (hands + feet) later spreading to whole body, insomnia, tinitis, dehydration, Achy joints, short-term memory loss.

6. Relevant Tests/Laboratory Data, Including Dates

ALL MEDICAL tests for traditional medical diagnoses came back NEGATIVE.

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

NONE

RECEIVED
FEB 07 2006
MEDWATCH CTU

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & mfr/labeler, if known)
   #1 AVELOX (BAYER - MFR.)
   #2
2. Dose, Frequency & Route Used
   #1 400 mg - 1 x Day - 041
   #2
3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
   #1 Feb. 21 - MAR. 7, 2005
   #2
4. Diagnosis for Use (Indication)
   #1 SINUSITIS
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☑ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # (if known)
   #1 —
   #2
7. Exp. Date (if known)
   #1 2-21-06
   #2
8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☑ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# (For product problems only)
   00026-8581-69
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

NONE

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mo/day/yr) / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☑ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mo/day/yr)
7. If Explanted, Give Date (mo/day/yr)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: ___ (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? ☐ Yes ☐ No
3. Occupation: teacher
4. Also Reported to: ☑ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178 332

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

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DSS
FEB 08 2006

Individual Safety Report

4951701-8-00-01

...NTARY reporting of ...its, product problems and ...oduct use errors

Internet Submission - Page 1 of 3 CDER

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 272472

...The FDA Safety Information and
Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 32 Years	☑ Female ☐ Male	135 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/05/2005	03/21/2006

5. Describe Event, Problem or Product Use Error

PLEASE review the drugs Levaquin and Avelox - soo many people are being disabled and injured long term from taking the toxic drugs like fluroquinolones. The symptoms come on slowly as I was prescribed this drug 4 times by my doc over the course of a 5 year period - but by the 3 time I took it in the past 3 I knew it had to be the drug causing the problem because everytime I took it the past 3 times I had tendonitis and could not exercise walk without getting it. I took this horrible drug and I was only 30 and good shape as well. My last experience or toxic buildup of this drug made the most impact - I experienced tingeling and other

6. Relevant Tests/Laboratory Data, Including Dates

diganosed with tendonitis at age 31 a mo or two after taking drug Again dignosed with tendonitis in hip gluteous shortky after taking drug - age 32 Presently haveing nerve problems sleep distubance and aches and pains - cartlidge in both my knees damaged as shown on x-ray and turning into

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

no other previous problems before taking the fluoroquinolone drug

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Levaquin 500 mg

#2 Avelox 500mg

2.	Dose or Amount	Frequency	Route
#1	1 dose	1 a day 10 days	
#2	1 dose	1 a day 10 days	

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)* 10 days

#1 03/22/2003 – 04/01/2003

#2 04/12/2004 – 04/22/2004

4. Diagnosis or Reason for Use *(Indication)*

#1 sinus infection

#2 sinus infection

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☑ No ☐ Doesn't Apply

#2 ☐ Yes ☑ No ☐ Doesn't Apply

6. Lot #

#1 don''t know

#2 don;t know

7. Expiration Date

#1

#2

8. Event Reappeared After Reintroduction?

#1 ☑ Yes ☐ No ☐ Doesn't Apply

#2 ☑ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

don''t know

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

RECEIVED
MAR 22 2006

3. Manufacturer Name, City and State

4. Model # | Lot # | 5. Operator of Device

Catalog # | Expiration Date *(mm/dd/yyyy)* | ☐ Health Professional ☐ Lay User/Patient ☐ Other:

Serial # | Other #

MEDWATCH CTH

6. If Implanted, Give Date *(mm/dd/yyyy)*

7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
MAR 23 2006

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

(b) (6)

Phone # | E-mail (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report
4951701-8-00-02

MEDWATCH

272472

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page 2

B5. Describe event or problem continued

odd sensations - disrupted dream - sleeplessnes all of a sudden which scared me enough to look up the internet and see what the side effect of Levaquin where- along with the tendonitis of course it listed every other scary side effect I was having. I went to my doc ea time and they said I had tendonitis when I have NEVER had any tendonitis before taking the drug. Plus the tendonitis takes 6 mo to go away and then all the aches and pains and other sensations never go away and just cause more medical health preoblems... Putting all my facts togetether and making the drug connection I would like this drug pulled or at the very least not just given out like candy from docs when a person has a slight sinus infection and no other drugs have been tried. I am still suffering from numbness and aches similar to what fibormyalgia is - could most cases of fibormyalgia be related to people being given quinolone drugs in the past - many people think so 1,000's of people know for sure this drug is toxic and caused problems and other just think they are having aches and pain --- having yet to make the connection until they take the drug again in the future. I am not crazy the quilone drugs are at fault. If anything - PLEASE send out a notice to doctors about this drug and its ill effects in BOLD print. The tendon problem is not for just elderly people and a drug that caused tendon problems is not just limited to the tendons - but the nerves and all parts of the body. Young adults who are active and even normal sedentary people are just as suspectible from this damage caused from this drug. Please - make sure doctors are not just handing this "last resort" drug out like it is a first line defense drug as my doctor did everytime. I am never going back to him now due to this. It is a matter of someones life and longterm health. I have kids and a family --- my health has been damaged and I feel due to this toxic drug. I have demanded NEVER to be given this drug again - but fear the cumaltive damage of this toxic drug may never go away -- PLESE make sure this is investigated, Thank You

DSS
MAR 2 3 2006

272472

Individual Safety Report
4951701-8-00-03

WATCH
ofessionals of adverse events and product problems
net Submission - Page 3

B6. Relevant tests/laboratory data, including dates continued

osteo artritis per oerthopedist. Side effect of drug -- most likely.

DSS
MAR 2 3 2006

Individual Safety Report

4970499-0-00-01

The FDA Safety Information and Adverse Event Reporting Program

TARY reporting of product problems and product use errors

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY

Triage unit sequence # 273721

CDER

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 49 Years	☐ Female ☑ Male	162 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - Initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
09/15/2005	04/07/2006

5. Describe Event, Problem or Product Use Error

Avelox was taken in mid Sept. 2005 at 400mg for 10 days for sinus infection. Many side effects where experienced since then to now. I could hardly move for days, had a couple months where I had to relieve urin every 2 hours, had a week long headach for forst time in my life, very sore neck for a week, unable to do more than 20% of prior work load, Tendonitis diagnosis about 4 months after believed to be associated with starting to exercise after my longest layoff of exercise in my life. I have been cycling 10,000 miles a year for the last 8 years.

6. Relevant Tests/Laboratory Data, Including Dates

Much blood work, MRI, nuerology test

RECEIVED
APR 11 2006
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Picture of health up to this point.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 avelox 400mg Bayer?
#2

2. Dose or Amount	Frequency	Route
#1 400 mg	1/day x 10 days	po
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 09/10/2005 -- 09/20/2005
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 sinus infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1 ?	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

APR 12 2006
DSS
APR 12 2006

G. REPORTER *(See confidentiality section on back)*

(b) (6)

Phone # (b) (6)
E-mail (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::6031267

U.S. Department of Health and Human Services

4/13/06 Revised

Individual Safety Report

4973408-3-00-01

...NTARY reporting of ..., product problems and ...uct use errors

...of ... DSS

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 27412

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
In confidence	(b) (6)	☑ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
   ☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
   ☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
3/16 on	4/10/06

5. Describe Event, Problem or Product Use Error

Difficulty breathing
Chest pain
extreme ear/jaw pain
suicidal ideation/psychosis
limb tingling

4/13/06 – Forgot to list hip + leg pain/extreme

6. Relevant Tests/Laboratory Data, including Dates

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APR 13 2006
MEDWATCH OTU

7. Other Relevant History, including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Hashimoto's/hypo

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
   #1 LEVAQUIN
   #2

2.	Dose or Amount	Frequency	Route
#1	500 mg	1 daily	mouth
#2			

3. Dates of Use *(if unknown, give duration) from/to (or best estimate)*
   #1 3/16 – 3/19 ? or 20
   #2

4. Diagnosis or Reason for Use *(Indication)*
   #1 sinus infection
   #2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☑ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Homemaka	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (10/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Faxed 4/12/06

Rec'd via Fax

DSS
APR 14 2006

(b) (6)

Apr 13 06 07:48a p.1

Individual Safety Report

5094328-2-00-01

CDER

JNTARY reporting of
ts, product problems and
product use errors

Internet Submission - Page 1 /3

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 283986

The FDA Safety Information and Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	51 Years	☐ Female ☑ Male	220 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: _____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
   ☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
   ☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
04/01/2006	08/29/2006

5. Describe Event, Problem or Product Use Error

took levaquin for persistant sinus infection. It helped the infection, but caused the following problems during the 15 days on the pills, which persist to this date, almost 5 months: 1. Extremely sore achilles tendon; have greatly reduced activity in fear of rupture 2. sore hands and fingers; painful to close hands. Felt painful sensations in fingers upon gripping strongly; afraid something was tearing. that part is better, but my grip is weaker and hurts more. 3. Other sore joints, inluding hip. Has improved. 4. increased numbness in finger tips -some numbness ensued several years ago following a viral infection-. 5. muscle

More

6. Relevant Tests/Laboratory Data, Including Dates

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Allergies -cat is now gone- seem to have triggered the asthma, bronchitis, and nasal problems I was having, as well as a bad cold at christmas time.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
   #1 Levaquin not sure
   #2

2. Dose or Amount	Frequency	Route
#1 tablet	2 x a day	
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
   #1 04/01/2006 -- 04/15/2006
   #2 --

4. Diagnosis or Reason for Use *(Indication)*
   #1 Sinus infection; augmentin failed to help it.
   #2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☑ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☑ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor:

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AUG 30 2006
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F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DSS
AUG 31 2006

More

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
   (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Administrator	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report
5094328-2-00-02

MEDWATCH
professionals of adverse events and product problems
ternet Submission - Page 2

783986

B5. Describe event or problem continued

twitches--not just little skin muscles but major muscles. this has decreased, but whole fingers will bend periodically still. 6. Increased shoulder pain in weak right shoulder 7. Prickly-numb-burning sensation in lips that started with first pill, including swollen lips, which decreased during the course of the meds. The prickly sensation still comes, however, several times a day. Upon discussion of these symptoms with my Doctor's office, the advice was to keep taking it so I would get well. the doctor said, "Well, I've taken it and it didn't bother me."

DSS
AUG 3 1 2006

5094328-2-00-03

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 4

783986

B7. Other relevant history, including preexisting medical conditions continued

No smoking, diabetes, alchohol,kidney or liver problems. So far. Have mild hypertension, moderate cholesterol. Meds for both. Take theophylline for asthma. I Cut back when on the levaquin because I researched interactions.

DSS

AUG 31 2006

CaseID::6135374

3485799-3-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 1 of 5

CDER

Form Approved: OMB No. 0910-0291 Expires: 8/31/00
See OMB statement on reverse

FDA Use Only

Triage unit sequence # 120320

A. Patient information

1. Patient identifier (b) (6) In confidence

2. Age at time of event: 62 Years or Date of birth: (b) (6)

3. Sex: ☑ female ☐ male

4. Weight: 132 lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____ (mm/dd/yyyy)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☑ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mm/dd/yyyy): 03/06/1999

4. Date of this report (mm/dd/yyyy): 04/07/2000

5. Describe event or problem

I took 500mgs of Levaquin for 5 days for a bronchial infection. On the fifth day, I developed sudden excrutiating pains in both shin bones, knees, back, muscles, hips & joints. A month later, I developed severe burning pain under the left ribcage which was diagnosed as a large -3.5ct x 1.5 ct- stomach ulcer. I also still suffer total exhaustion, screaming nightmares, interrupted sleep, insomnia, mood swings, anxiety, debilitating dizzyness, depression, panic attacks. I lost 20 lbs quickly. Then the pain spread to my arms & fingers. Then I developed anemia & now I am having SEVERE colitis type symptoms. Ive never had these symptoms prior to taking Levaquin in March, 6, 1999. Prior to Levaquin, I was an active woman, a licenced psychotherpist at the masters level, working a full time

6. Relevant tests/laboratory data, including dates

Too many tests to list here. I will gladly forward exact dates, tests & results to you if any of this gets through to you - I fear it never will. Im under the care of a primary doctor, orthopedist, rheumatologist, gastroenterologist & psychiatrist. I am consulting a registered dietician. Ive had numerous XRays, bone scan, copious blood tests, MRI, endoscopy. Im now sc

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Im allergic & intolerant to many drugs, foods, environmental pollutants. I have a history of Interstitial Cytitis since 1985 & it is stabilized by a drug regime that has remained the same for 10 years & has not caused any ADRs No hepatic, renal, or other system dyfunctions before Levaquin.. Im caucasion, menopausal, stopped cigarettes in 1976, s

C. Suspect medication(s)

1. Name (Product Name) / (Labeled Strength) / (Mfr/Labeler)
- #1 Levaquin / 500 mg / /
- #2 / / /

2. Dose/Frequency/Route used
- #1 500 mg / TID / Oral
- #2 / / Buccal

3. Therapy dates (if unknown, give duration) From – To (or best estimate)
- #1 03/06/1999 – 04/07/2000
- #2 –

4. Diagnosis for use (separate indications with commas)
- #1 Bronchitis
- #2

5. Event abated after use stopped or dose reduced
- #1 ☐ yes ☑ no ☐ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1 03/11/1999
- #2

8. Event reappeared after reintroduction
- #1 ☑ yes ☐ no ☐ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only) – –

10. Concomitant medical products and therapy dates (exclude treatment of event)

Medication regime for Interstitial Cystits since 09/01/1985. Hormone replacement therapy since menopause in 1985. TENS unit

D. Suspect medical device

1. Brand name NA

2. Type of device NA

3. Manufacturer name & address

NA

DSS

APR 11 2000

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APR 10 2000

MEDWATCH CTU

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other: ____

5. Expiration date (mm/dd/yyyy): 03/06/1999

6.
- model # NA
- catalog # NA
- serial # NA
- lot # NA
- other #

7. If implanted, give date (mm/dd/yyyy): 03/06/1999

8. If explanted, give date (mm/dd/yyyy): 03/06/1999

9. Device available for evaluation? (Do not send device to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mm/dd/yyyy)

10. Concomitant medical products and therapy dates (exclude treatment of event)

NA

E. Reporter (see confidentiality section on back)

(b) (6)

2. Health professional? ☑ yes ☐ no

3. Occupation: Other Health Professional

4. Also reported to
- ☐ manufacturer
- ☑ user facility
- ☐ distributor

5. If you do not want your identity disclosed to the manufacturer, place an "X" in this box. ☐

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

4Tu120320

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3485799-3-00-02

120320

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page 2 of 5

B5. Describe event or problem continued

job & a private practice in the evenings. I worked out regularly & enjoyed a robust satisfying sex life with my husband. Now Im unable to work, am in debt for $50,000, the quality of my sex life is sharplyl deminished. Many days I am unable to leave my home. My husband is frantic with worry about my health.

DSS
APR 11 2000

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Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

120320

3485799-3-00-03

120320

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page 3 of 5

B6. Relevant tests/laboratory data, including dates continued

heduled for another endoscope & colonoscopy. I see a psychiatrist once a week. He is attempting to find a drug-s- to treat the depression, anxiety, screaming nightmares, panic attacks, insomnia, interrupted sleep patterns.

DSS
APR 11 2000

RECEIVED MEDWATCH HF-2

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

120320



120320

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page 4 of 5

B7. Other relevant history, including preexisting medical conditions continued

topped alcohol in 1984. I was otherwise very healthy & active.

DSS
APR 11 2000



Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

120320

Individual Safety Report

3485799-3-00-05

120320

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

C10. Concomitant medical products and therapy dates continued

for Interstitial Cystitis.

D10. Concomitant medical products and therapy dates continued

DSS
APR 11 2000

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM
HF-2

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

120320 APR 10 '00 1:11

5211578-2-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

NTARY reporting of adverse events, product problems and product use errors CDER

Page ___ of ___

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 2934468

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	42	☐ Female ☒ Male	160 lb or ___ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ___ (mm/dd/yyyy) ☒ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☒ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
05-27-1997	12-27-2006

5. Describe Event, Problem or Product Use Error 45 lbs WT Loss
Violent Vomiting of green Bile - Dizzyness, Confusion, Loss of Bowel Motility "Constipation" Chronic Numbness Weakness in Arms. Burning. Exhaustion, Fatigue. Anxiety. Neck Shoulder hip Back problems requiring Physical Therapy Surgery. Wasting Weight Loss. Tremors Hallucinations have subsided but the other Symptoms Above Persist today 9 years After Exposure.

6. Relevant Tests/Laboratory Data, Including Dates
N/A

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JAN 16 2007
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
ERCP Injury 1987 (Pancreas)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on: ___ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 CIPROFLOXICIN Bayer
#2

2.	Dose or Amount	Frequency	Route
#1	500 mg	2x day x 10 d	ORAL
#2			

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 MAY 1997
#2 Sept 1997

4. Diagnosis or Reason for Use (Indication)
#1 UTI
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☒ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy) 7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

DSS
JAN 17 2007

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	Disabled	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CDER

Individual Safety Report

5243751-1-00-01

Adverse Event Reporting Program

...NTARY reporting of ..., product problems and ...uct use errors

...sion - Page 1

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 296335

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 47 Years	☑ Female ☐ Male	215 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
09/29/2006	02/19/2007

5. Describe Event, Problem or Product Use Error

I was prescribed Levaquin 500mg on September 21,2006 because of bronquitis for one week, by September 29 I experienced: diarrhea nausea numbness in arms, hands, fingers extreme swelling in joints insomnia difficulty to stand up, walk bruses in eyes and arms no strength tingly or electric sensation in hands extreme pain I have been retaining water I have been attending to many doctors, but none of them knew what was happening to me, until one of them told me this was called Serum Sickness or Steven Johnson, which is an extreme reaction to the drug. FIVE MONTHS HAVE PASSED AND I STILL HAVE THE SYMPTOMS. It is affecting my

More

6. Relevant Tests/Laboratory Data, Including Dates

October: High level on C protein
RA Joegrins ANA test
U/A SSB TSH
DSS

FEB 21 2007

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Heart Problems High blood pressure
Recurent bronquitis

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Levaquin ortho
#2

2. Dose or Amount	Frequency	Route
#1 500mg	7 days/ 1 daily	po
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 09/21/2006 -- 09/28/2006
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 bronquitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID
00045-1525-50

E. SUSPECT MEDICAL DEVICE

1. Brand Name
Levofloxacin

2. Common Device Name
Levaquin

3. Manufacturer Name, City and State
ORTHO

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☑ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☑ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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FEB 20 2007
MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☑ Yes ☐ No	Nurse	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report
5243751-1-00-02

WATCH

:ofessionals of adverse events and product problems
rnet Submission - Page 2

7246335

B5. Describe event or problem continued

life, because I depend of others to do certain things for me, because of the extreme pain, and weakness I´m experiecing.

DSS

FEB 2 1 2007

Individual Safety Report

5258918-6-00-01

-evofloxacin Tablets

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

Johnson & Johnson Pharmaceutical R&D

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page 1 of 3

Approved by FDA on 10/25/2002

Mfr report # US-JNJFOC-20060103915

UF/Dist report #

FDA use only

A. Patient information

1. Patient identifier: (b) (6) In confidence

2. Age at time of event: or 53 Year; Date of birth: (b) (6)

3. Sex: [X] female [ ] male

4. Weight: 190 lbs or ____ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse (check all that apply)

- [ ] death ____ (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization - initial or prolonged
- [X] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [X] other: Med Signif

3. Date of event (mo/day/yr): 12/03/2005

4. Date of this report (mo/day/yr): 10/23/2006

5. Describe event or problem

Spontaneous Report received from a Physician. 1-182593564.

A 53 year old woman, 170 pounds, with a history of hypertension, non-smoker, back problems, no known drug allergies and occasional alcohol use, was prescribed levofloxacin tablets, 500 mg, initiated on 02-Dec-05 to 09-Dec-05 for the treatment of a sinus infection.

Concomitant medication include metoprolol succinate, vitamins, magnesium, calcium, folic acid, and methylsulfonal.

(Cont.)

6. Relevant test/laboratory data, including dates

Rh factor both negative and positive results Dec-05

9-Jan-06: Rh factor 18H while previous

(Cont.)

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

BACK DISORDER
HYPERTENSION
Comments:mild
NON-SMOKER

(Cont.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEVAQUIN (LEVOFLOXACIN) Tablets

#2

2. Dose, frequency & route used

#1 500 mg, 1 in 1 Day, Oral

#2

3. Therapy dates (from/to (or best estimate))

#1 12/02/2005-12/08/2005

#2

4. Diagnosis for use (indication)

#1 SINUSITIS

#2

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [X] doesn't apply

#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)

#1

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [X] doesn't apply

#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

1) TOPROL () METOPROLOL SUCCINATE
2) VITAMINS () VITAMINS
3) MAGNESIUM () MAGNESIUM
4) CALCIUM () CALCIUM

(Cont.)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Johnson & Johnson
Pharmaceutical R&D
100 Tournament Drive
Horsham
PA 19044
UNITED STATES

2. Phone number: 1 - 2153257691

3. Report source (check all that apply)

- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer (mo/day/yr): 04/04/2006

5. (A) NDA # 20-634; IND # ____; PLA # ____; pre-1938 [ ] yes; OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)

- [ ] 5-day
- [ ] 15-day
- [ ] 10-day
- [X] periodic
- [ ] initial
- [ ] follow-up # ____

8. Adverse event term(s)

1) MUSCLE SPASMS
2) MUSCULAR WEAKNESS
3) PARAESTHESIA
4) JOINT EFFUSION

(Cont.)

9. Mfr. report number: US-JNJFOC-20060103915

E. Initial reporter

(b) (6)

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Initial reporter also sent report to FDA: [ ] yes [ ] no [X] unk

FDA 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

NOV 17 2006

Individual Safety Report

5258918-6-00-02

evofloxacin Tablets

Johnson & Johnson Pharmaceutical R&D
100 Tournament Drive

Horsham PA 19044

Continuation Sheet for FDA-3500A Form

Mfr. report#: US-JNJFOC-20060103915

Date of this report : 10/23/2006

B5. Describe event or problem (Cont...)

On 03-Dec-05 the patient experienced severe leg cramps, along with weakness of legs and numbness and tingling of legs, knees and thighs,which progressively worsened. Levofloxacin was discontinued on 9-Dec-05 due to the symptoms. The patient was treated with steroids. The patient's pain level, "was as high as a 10; and has now improved to level 4." Rh factor was negative at the beginning of symptoms and are currently positive.

Outcome: (recovering/resolving).

This report is serious(medically significant).

Additional information received from physician 14-Feb-06: After the second day of levofloxacin therapy the woman experienced lower leg cramps, weakness of legs and numbness and tingling of leg. She also experienced pain and cramps at superior and inferior tendon attachments of both legs. On 9-Jan-06 laboratory studies showed glucose 108mg/dl with a normal value of 65-99. Her "Rh factor" was 18H while her previous "Rh" was normal. The physician reports that she has not recovered and is disabled.

Rh factor increased and hyperglycemia are considered non-serious events.

Additional information received, as an update from previous report, from physician 4-Apr-06: The physician clarified that the woman experienced pain and cramps at superior and inferior tendon attachments of both knees. He reports that her condition has improved since the last report (14-Feb-06) about 20%. An MRI (magnetic resonance imaging) showed effusion at both suprapatellar recesses of both knees. All laboratory results are currently normal.

The physician reports the causality as related.

B.6 Relevant tests/laboratory data, including dates (Cont...)

B6. Other diagnostics

Rh was normal.

MRI (magnetic resonance imaging) showed effusion at both suprapatellar recesses of both knees

B.6 Relevant tests/laboratory data, including dates (Cont...)

Lab Result:

Test name	Test date	Test result	Normal high	Normal low
Glucose	01/09/2006	108 mg/dL (milligram/deciliter)	99	65

B.7 Other relevant history, including preexisting medical conditions (Cont...)

Other relevant medical history

no known drug allergies; occasional alcohol use

NOV 17 2006

Individual Safety Report

5258918-6-00-03

Report Levofloxacin Tablets

Johnson & Johnson Pharmaceutical R&D
100 Tournament Drive

Horsham PA 19044

Continuation Sheet for FDA-3500A Form

Page 3 of 3

Mfr. report#: US-JNJFOC-20060103915

Date of this report : 10/23/2006

C10. Concomitant medical products

Seq No.	: 1
C.10 Concomitant medical	: TOPROL (METOPROLOL SUCCINATE)
C.10 Diagnosis for use(indication)	: 1) HYPERTENSION
C.10 dose,frequency & route used	: 1) 10 mg
C.10 therapy Dates(or duration)	: 1) ??/??/???? - Ongoing
Seq No.	: 2
C.10 Concomitant medical	: VITAMINS (VITAMINS)
Seq No.	: 3
C.10 Concomitant medical	: MAGNESIUM (MAGNESIUM)
Seq No.	: 4
C.10 Concomitant medical	: CALCIUM (CALCIUM)
Seq No.	: 5
C.10 Concomitant medical	: FOLIC ACID (FOLIC ACID)
Seq No.	: 6
C.10 Concomitant medical	: MSM (METHYLSULFONAL)
Seq No.	: 7
C.10 Concomitant medical	: LISINOPRIL (LISINOPRIL)
C.10 Diagnosis for use(indication)	: 1) HYPERTENSION
C.10 dose,frequency & route used	: 1) 20 mg
C.10 therapy Dates(or duration)	: 1) ??/??/???? - ??/??/????

G8. Adverse event term (Cont...)

5) RHEUMATOID FACTOR
6) HYPERGLYCAEMIA

NOV 17 2006

Individual Safety Report

5298961-4-00-01

Adverse Event Reporting Program

...NTARY reporting of ... product problems and ... product use errors

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 390574

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☐ Female ☑ Male	174 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☑ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy) ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
06/28/2006	04/10/2007

5. Describe Event, Problem or Product Use Error

My ENT doctor gave me prescription of Avelox -a fluroquinolone antibiotic - 400 mg per day- on June 15, 2006 after a minor surgery. On June 28, 2006 same ENT doctor gave me a prescription of Levaquin -a fluroquinolone antibiotic- ¿ 750 mg for 21 days for sinusitis and a free sample of Levaquin. During and immediately after the course of Levaquin, I developed pain in my back, neck and right wrist, and intense pain and restricted movement in right rotator cuff -the shoulder-. My orthopedic surgeon gave me a steroid injection in my right rotator cuff and also send me for physical therapy for 4 weeks but nothing helped. My shoulder MRI was

More

6. Relevant Tests/Laboratory Data, Including Dates

DSS

APR 13 2007

More

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

None

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Levaquin 750 mg Otho-McNeil
#2

2. Dose or Amount	Frequency	Route
#1 750 mg	1 daily	po
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 22 days 06/28/2006 -- 07/18/2006
#2 --

4. Diagnosis or Reason for Use (Indication)
#1 Sinusitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
#1
#2

7. Expiration Date
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name: Levaquin
2. Common Device Name
3. Manufacturer Name, City and State: Ortho-McNeil Pharmaceutical Inc Raritan, NJ 08869

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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APR 12 2007
MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

My ENT doctor gave me prescription of Avelox -a fluroquinolone antibiotic - 400 mg per day- on June 15, 2006 after a minor surgery. On June 28, 2006

More

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Other Health	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

5298961-4-00-02

MEDWATCH

...professionals of adverse events and product problems

Internet Submission - Page 2

300574

B5. Describe event or problem continued

normal as biochemical injury to tendon fibers cannot be visualized in MRI. I also had several headaches. One night in December I had very intense headache while in sleep. My neurologist immediately sent me for a brain MRI, there was not any sign of stroke. Additionally I also developed inguinal hernia sometime in August 2006. I had bilateral hernia repair surgery on (b) (6) I strongly believe that all my problems -painful shoulder, intense headache and inguinal hernia- are adverse reaction caused by extended course of Levaquin. It is well documented in scientific literature that fluroquinolone damages connective tissues and is also neurotoxic. In PDR maximum recommended doses of Levaquin are 500 mg for 14 days OR 750 mg for 5 days to treat sinusitis, but my ENT gave me 750 mg per day for 21 days -plus 1 free sample- and that too immediately after 10-day course of Avelox. A medical doctor must know that fluroquinolone cannot be prescribed for 32 days under ANY circumstance. Please let me know what I should do. Thanks. (b) (6)

DSS

APR 13 2007

Individual Safety Report

5298961-4-00-03

WATCH

professionals of adverse events and product problems

Internet Submission - Page 5

300574

F. Other (Concomitant) medical products continued

same ENT doctor gave me a prescription of Levaquin -a fluroquinolone antibiotic- ¿ 750 mg for 21 days for sinusitis and a free sample of Levaquin. During and immediately after the course of Levaquin, I developed pain in my back, neck and right wrist, and intense pain and restricted movement in right rotator cuff -the shoulder-. My orthopedic surgeon gave me a steroid injection in my right rotator cuff and also send me for physical therapy for 4 weeks but nothing helped. My shoulder MRI was normal as biochemical injury to tendon fibers cannot be visualized in MRI. I also had several headaches. One night in December I had very intense headache while in sleep. My neurologist immediately sent me for a brain MRI, there was not any sign of stroke. Additionally I also developed inguinal hernia sometime in August 2006. I had bilateral hernia repair surgery on (b) (6) I strongly believe that all my prob

DSS

APR 13 2007

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::6326779

Individual Safety Report

5341540-0-00-01

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 304006

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☒ Female ☐ Male	150 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem (e.g., defects/malfunctions) ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
- ☐ Death: ____ (mm/dd/yyyy)
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
- ☒ Disability or Permanent Damage — Perhaps
- ☐ Congenital Anomaly/Birth Defect
- ☒ Other Serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
02/01/2007 - ongoing	05/14/2007

5. Describe Event, Problem or Product Use Error

Beginning 2/1/2007 my muscles and tendons have hurt and burned, especially in my arms. Shooting pain comes from my elbows. Local doctor sent me to a rheumatologist who suspects the ongoing Pain is connected to Levaquin. All the many blood tests come back fine. Pain began in the 3rd day of my second round of Levaquin. This was 3½ months ago! - Sleep disturbances - Arms swollen.
Bad DRUG-No Warning.

6. Relevant Tests/Laboratory Data, Including Dates

2-27-07 Tests Negative for Lupus, Rh. Arthritis, Polymyalgia, Myositis
3-8-07 - More negative tests
4-19-07 Blood tests with rheumatologist all negative
5-2-07 Lyme disease test Negative
5-10-07 Rheumatologist suspects Levaquin. All else ruled out

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

Nope! Was Very healthy.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

#1 Levaquin 250 Mg Jan 19, 07 ← Jan 23, 2007
#2 Levaquin 250 mg Jan 30 - Feb 3

2. Dose or Amount	Frequency	Route
#1 2 x daily	5 days	
#2 2 x daily	5 days	

3. Dates of Use (If unknown, give duration) from/to (or best estimate)

#1 1/19/07 - 1/23/07
#2 1/30/07 - 2/3/07

4. Diagnosis or Reason for Use (Indication)

#1 UTI
#2 UTI

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☒ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?

#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2 ☐ Yes ☐ No ☒ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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MAY 29 2007
MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confident (b) (6)

1. Name and Address (b) (6)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	Retired Teacher	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (10/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

DSS
MAY 31 2007

CaseID::6437033

Individual Safety Report

5474058-5-00-01

Adverse Event Reporting Program

...NTARY reporting of ..., product problems and ...uct use errors

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 314072

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) In confidence
2. Age at Time of Event, or Date of Birth: (b) (6)
3. Sex: ☐ Female ☑ Male
4. Weight: 210 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy) ☑ Disability or Permanent Damage
☑ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy): 2/20/2007
4. Date of this Report (mm/dd/yyyy): 09/16/2007

5. Describe Event, Problem or Product Use Error

acute Bowel inflammation
abdominal and muscle Tremors
40 pound wghtloss in 30 days
depression
Insomnia
muscle mass Loss
continual muscle pain
Diarrhea
Dehydration
Confusion
Hearing loss
Intense nightmares

6. Relevant Tests/Laboratory Data, including Dates

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SEP 28 2007
MEDWATCH CTU

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

DSS
SEP 29 2007

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Avelox
#2

2. Dose or Amount	Frequency	Route
#1 ONE	DAILY	ORAL
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 2/19/2007 5 Days
#2 3/16/2007 15 DAYS

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

4. Diagnosis or Reason for Use (Indication)
#1 Sinus Infection
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
#1
#2

7. Expiration Date
#1
#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name N/A
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional? ☐ Yes ☑ No
3. Occupation: Disabled
4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (10/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

5691441-3-00-01

NTARY reporting of
s, product problems and
product use errors

Internet Submission - Page 1

CDER

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 330769

The FDA Safety Information and Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 37 Years	☐ Female ☑ Male	225 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
09/17/2006	03/31/2008

5. Describe Event, Problem or Product Use Error

I was prescribed Levaquin for a "possible" urinary tract infection. I was told by Doctors that a urinary tract infection was probably not the prognosis due to never having one in my life. The doctor prescribed Levaquin "just in case" and never disclosed any potential side effects of the medication. I began taking the medication Levaquin and within 12 hours the following symptoms occured: rapid heartbeat, tingling in arms, dizziness, nausea, stomache cramps disentery, tightness in chest, sweats, blurred vision, mania, panic, light flashes when eyes are closed, sleeplessness, feeling of falling when eyes are closed, burning in bowels and

More

6. Relevant Tests/Laboratory Data, Including Dates

Stool, urine, blood,analysis, electro cardiogram, and eventually a colinoscopy. All tests came back normal-no health issues. Tests performed 09/2006 and 12/2006

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Completely healthy 37 year old male. No history of any psychological problems or medications. The only health issue was seasonal allergies and Rx

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Levaquin 500 MG ?
#2

2.	Dose or Amount	Frequency	Route
#1	500 MGS	1 X Day x 10 Days	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 09/15/2006 -- 09/20/2006 5 Days
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 Possible, Improbable Urinary Tract Infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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APR 01 2008

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F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

5691441-3-00-02

VATCH

330769

ssionals of adverse events and product problems

Internet Submission - Page 2

B5. Describe event or problem continued

anus, electrical shocks in fingers. Called the Doctor over a five day period -every day- and explained increasing symptoms. The nuses returned my calls and directed me -patient- to continue medication. The fifth day I called the Doctor and complained of all the afforementioneed symptoms and added "it feels like I am having a heart attack". The Doctors told me to come in immediately to be examined. He ordered the following tests: stool, urine, blood,analysis, electro cardiogram, and eventually a colinoscopy. After leaving the examining room the DOctor poked his head back in and stated "Oh yah, you can stop taking your medication-Levaquin-".All tests came back normal-no health issues. Lost 38 lbs in 45 days. Its been 2 1/2 and I have been on countless medications to control these ongoing symptoms. This drug is poison, it ruined my health and has made life a living HELL! I am in the process of writing a book exposing this drug and its thousands of victims~!

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APR 01 2008

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

5691441-3-00-03

330769

MEDWATCH

...essionals of adverse events and product problems

Internet Submission - Page 4

B7. Other relevant history, including preexisting medical conditions continued

for albuterol inhaler as needed. No heart disease, high blood pressure, liver or kidney issues, stomach conditions, or central nervous systems issues. Last physical -pre-levaquin-showed "good" on bloodwork for colosterol.

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Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::6617669

CDER

Individual Safety Report

5702622-4-00-01

The FDA ... Adverse Event Reporting Program...

For VOLUNTARY reporting of events, product problems and product use errors

Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY

Triage unit sequence # 33/9/3

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 31 Years	☑ Female ☐ Male	128 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*

☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/19/2008	04/09/2008

5. Describe Event, Problem or Product Use Error

Has been experiencing excruciating pain in right rotator cuff because of tendon damage caused by antibiotic levaquin, as well as know experiencing severe bouts of systematic lupus also diagnosed SINCE being treating by levaquin, ongoing anxiety and depression, numbness in extremities. Unable to work or sleep properly since administration, severely depressed and suicidal.

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More

6. Relevant Tests/Laboratory Data, Including Dates

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

NONE.

DSS
APR 10 2008

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 LEVAQUIN 500MG ORTHO

#2

2.	Dose or Amount	Frequency	Route
#1	ONE TABLET	DAILY	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*

#1 02/01/2008 -- 02/05/2008

#2 -- --

4. Diagnosis or Reason for Use *(Indication)*

#1 SINUS INFECTION

#2

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☑ No ☐ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?

#1 ☐ Yes ☐ No ☐ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::6709766

U.S. Department of Health and Human Services

Individual Safety Report

5811599-2-00-01

...Event Reporting Program

...NTARY reporting of ...ts, product problems and ...duct use errors

Page ___ of ___ CDER

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 343152

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	81 (b) (6)	[X] Female [ ] Male	118 lb or ___ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. [X] Adverse Event [ ] Product Problem *(e.g., defects/malfunctions)*
[ ] Product Use Error [ ] Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
[ ] Death: ___ *(mm/dd/yyyy)* [X] Disability or Permanent Damage
[ ] Life-threatening [ ] Congenital Anomaly/Birth Defect
[ ] Hospitalization - initial or prolonged [ ] Other Serious (Important Medical Events)
[ ] Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
4/10/08	6/30/08

5. Describe Event, Problem or Product Use Error

ON 4/19/08 MY ANKLES WERE STIFF AND PAINFUL. I AWOKE ON 6/30/08 TO "BURNING" ANKLES, SWOLLEN AND A RASH RUNNING FROM MY ANKLE BONE ABOUT 5" UP THE INNER LEG OF THE LEFT FOOT. STOPPED THE MEDICATION THAT DAY, AND THE ANKLE WAS X-RAYED (MY INTERNIST SUSPECTED A STRESS FRACTURE - NOT SO.) HEALING PROGRESSES SLOWLY, BUT HAD TO ACQUIRE A DISABILITY PARKING PLACARD. I REPORTED PROBLEM TO ORTHO,

6. Relevant Tests/Laboratory Data, Including Dates

X-RAY OF L. ANKLE 5/7/08.

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MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

NONE

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
[ ] Yes [X] No [ ] Returned to Manufacturer on: ___ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 LEVAQUIN
#2

2.	Dose or Amount	Frequency	Route
#1	500 mgs	DAILY	ORAL
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 FROM 4/10/08 TO 4/25/08
#2

4. Diagnosis or Reason for Use
#1 SINUSITIS
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [X] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [X] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
ORTHO NJ

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	[ ] Health Professional [ ] Lay User/Patient [ ] Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
[ ] Yes [ ] No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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JUL 15 2008

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

(b) (6)

Phone #	E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
[ ] Yes [ ] No		[X] Manufacturer [ ] User Facility [ ] Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [X]

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::6733832

Individual Safety Report

5849193-X-00-01

...rmation and
Adverse Event Reporting Program

JNTARY reporting of
ts, product problems and
product use errors CDER

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 346783

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 59 Years	☐ Female ☑ Male	205 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
06/15/2008	08/15/2008

5. Describe Event, Problem or Product Use Error

I was perscribed Avelox 400mg Qday X 21 days for a sinus infection. Immediately a became sensitive to sun exposure which still ezists.In june I developed tendonitis in both achilles with the left worse than the right. Also developed tendonitis in both thumbs, left worse than right and left elbow. I am presently on Prednisone and scheduled for Physical Therapy.

More

6. Relevant Tests/Laboratory Data, Including Dates

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Avelox 400mg Bayer
#2

2.	Dose or Amount	Frequency	Route
#1	400mg	Q Day	po
#2			

3. Dates of Use *(If unknown, give duration)* from/to (or best estimate)
#1 02/14/2008 -- 03/07/2008 (21 days)
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 Sinusitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

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AUG 18 2008

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::6946431

U.S. Dep

Individual Safety Report

6112302-1-00-01

...ARY reporting of roduct problems and t use errors

1 of 2

CDER

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

The F
Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 3691448

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☒ Female ☐ Male	114 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☒ Disability or Permanent Damage X
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
11-5 + 11-6-08	3-1-09

5. Describe Event, Problem or Product Use Error

Cipro prescribed by emergency room DR (b) (6) (b) (6) Med. Ctr - (b) (6), She Knew I was over 60 yrs - a risk. Pain began within 24 Hr. on 11-5-08 + Swelling - limping - left food badly affected + right foot lesser degree; X-rays Taken 12/08 after HMO Dr. (b) (6) stopped Cipro. Requested appt. with (b) (6) Podiatric - Dr. who prescribed pain killer + a stretch elastic support glove - for left foot. etc. - special foot inserts for shoes.

Eye vision also affected by drug & new prescription glasses were required (my expense)

6. Relevant Tests/Laboratory Data, Including Dates

I requested P.T. - approved by HMO for 12 sessions only. Dec. 08 (2) - Jan. 09 (6) - Feb. (2) & Mar. (1) 09 by HMO. I need more + must continue at home for extended Time + constantly use support items + Favor left foot. (Not Too much standing or walking)

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

n/A

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☒ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)* (See attached)

#1 CiproFloxacin HCL 500 mg. Tadrl

#2

2.	Dose or Amount	Frequency	Route
#1	1 Tab - orally	2 x day	
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*

#1 11-5 + 11-6-08

#2

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☒ No ☐ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

4. Diagnosis or Reason for Use Possible

#1 Urinary Infection

#2

8. Event Reappeared After Reintroduction?

#1 ☐ Yes ☐ No ☒ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1 See attached Copy	#1
#2 0/0 RX	#2

9. NDC # or Unique ID

#1 55111-0127-01

#2

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*

7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor:

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MAR 11 2009

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MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)* n/A

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	Retired	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

not yet

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::6955136

Form Approved: OMB No. 0910-0291, Expires:10/31/08
See OMB statement on reverse

Individual Safety Report

6129670-7-00-01

VOLUNTARY reporting of
...ts, product problems and
...oduct use errors

CDER

...age ____ of ____

FDA USE ONLY
Triage unit sequence # 370446

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	52	☐ Female ☑ Male	198 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
Feb. 24, 2009 to Present	03/10/2009

5. **Describe Event, Problem or Product Use Error**

Last day of a 20 day prescripton, I developed severe pain in my right knee - to the point where I could barely move my leg. Also pain in left shoulder, both forearms and right elbow. Pain also in right hip and periodically in left knee and calf as well as periodically in right calf, ankle and heel. Tightness and heaviness in right leg, sporadic sharp pain in right knee (nagging pain is always present. Uncomfortable to walk and also cannot stand for more than a few minutes without discomfort. The initial pain changed after being off the medicine for a day or two, but I still have severe pain in my right knee; have to walk gingerly because if I straighten my leg too much I will get a sharp pain. Also, if I move my leg or foot the wrong way I will get sharp pain. Also experience headaches. They seem to be coming less often now, but for the first 10 days they were constant (although the location of the headache in my head would change). At this point, I don't know if these side effects are permanent, but they are currently disabling.

6. ~~Relevant Tests/Laboratory Data, Including Dates~~

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MEDWATCH CTU

DSS
MAR 23 2009

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Only pre-existing condition I have are seasonal allergies. Never have had any muscular/skeletal problems before.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*
#1 Leavquin 500 mg.
#2

2.	Dose or Amount	Frequency	Route
#1	500 mg.	daily	
#2			

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 Feb. 4, 2009 to Feb. 24, 2009
#2

4. **Diagnosis or Reason for Use** *(indication)*
#1 Sinus Infection
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**
2. **Common Device Name**
3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)*
7. **If Explanted, Give Date** *(mm/dd/yyyy)*
8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?** ☐ Yes ☐ No
9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*
Zyrtec

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Non-Healthcare Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

CaseID::7029352

(9)

Individual Safety Report

6233772-4-00-01

1/2

TARY reporting of product problems and ct use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

Page 1 of 12

CDER

FDA USE ONLY
Triage unit sequence # 380710

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	45	☐ Female ☑ Male	205 lb or 93.2 kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
02/17/2009	05/31/2009

5. Describe Event, Problem or Product Use Error

10 DAYS AFTER USING LEVAQUIN I DEVOLOPED SEVER TENDONITIS IN MY HANDS AND FEET. 2 DAYS LATER MY FACE, EYELIDS, MOUTH, HANDS AND FEET WERE BURNING LIKE THEY WERE ON FIRE. I WENT TO THE EMERGENCY ROOM (b) (6) (b) (6) DUE TO THE PAIN. BY 12 MARCH 2009 I DEVOLOPED DRY EYE SYNDROME WITH DRIED OUT SINUS CAVITIES. I HAVE EYE FLOATERS AS OF 17 FEB 2009. I JUST HAD MY LAST VISIT MAY 09 WITH MY FOOT DR AND HE TOLD ME THE DAMAGE TO MY TENDONS IS PERMENANT. I AM IN THE MILITARY AND NOW I CANT WALK!!!! FOR SOME REASON MY SYMPTOMS HAVE GOTTEN WORSE SINCE 05/15/2009. NOW MY EARS ARE COMPLETELY DRIED UP, MY PALMS, SOLES, AND ARMPITS DO NOT SWEAT. I HAVE AN INTOLERANCE OF CHEMICAL ODORS. MY EARS RING TERRIBLY. I HAVE RH/LH UPPER QUADRANT PAIN.

6. Relevant Tests/Laboratory Data, Including Dates

EYE EXAM STATING I HAVE DRY EYE SYNDROME X 3 MONTHS MAY2009
LIPASE AND ALT HIGH MAY 2009
FEET AND ACHILLES EXAM FEB-MAY2009 CHRONIC TENDONITIS
EEG ABNORMAL MAY 2009

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

THRYOID LOW
NO SMOKING,
NO ALCHOHOL
NO LIVER/ KIDNEY PROBLEMS
WHITE MALE
ALL OF MY LABS WERE NORMAL IN DEC08 BEFORE I TOOK LEVAQUIN

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

(1)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: LEVOFLOXACIN
Strength: 500MG
Manufacturer: MP6641466

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 500	1 a day	047
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 24 JAN 2009
#2 05 FEB 2009

4. Diagnosis or Reason for Use *(Indication)*
#1 UTI
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1 MP6641466	#1 JAN 10	
#2	#2	

E. SUSPECT MEDICAL DEVICE

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JUN 15 2009
MEDWATCH CTU

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER *(See confidentiality section on back)*

(b) (6)

JUN 16 2009

State: (b) (6)

Phone #	E-mail
(b) (6)	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Non-Healthcare Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

6233772-4-00-02

NUATION PAGE)

VTARY reporting of
and product problems

380710

Adverse Event Reporting Program

B.5. **Describe Event or Problem** *(continued)*

THE MILITARY DR'S DO NOT KNOW WHAT TO DO OR HOW TO TREAT THIS. THEY PUT IN MY RECORD THAT I HAD AN ADVERSE REACTION TO LEVAQUIN (TENDINITIS) BUT HAVE NO IDEA WHAT ELSE TO DO. I HAVE ALSO DEVOLOPED TERRIBLE BRONCITIS SINCE MAY 09. I HAVE MY MILITARY MEDICAL RECORD AVAILABLE BECAUSE I HAD A 5 YEAR PHYSICAL IN DECEMBER 2008 WITH NO PROBLEMS. SIGNED OFF BY A COMMANDER AS NO HEALTH ISSUES WHATSOEVER. WITHIN 5 MONTHS THE LEVAQUIN HAS COMPLETELY DESTROYED A HEALTHY AND ACTIVE LIFE. WITH ALL THE COMPLAINTS (THOUSANDS OF REACTIONS ON THE INTERNET) YOU HAVE TO KNOW THEIR IS A PROBLEM WITH THIS DRUG? MY NEUROLOGIST SUSPECTS THE LEVAQUIN HAS DAMAGED THE PART OF MY CNS THAT CONTROLS SECRETIONS. HOW CAN I LIVE WITH THAT PORTION OF MY NERVOUS SYSTEM NO WORKING? ARE THE SIDE EFFECTS PERMANT? CAN YOU TELL ME ANYTHING SO I CAN EXPLAIN IT TO MY WIFE? SHE CANT COMPREHEND A DRUG DOING THIS TO ME. MY MILITARY CAREER IS OVER BECAUSE THEY WONT TOLERATE A SAILOR WHO CANT WALK, AND MY WIFE IS FINDING IT HARD TO TOLERATE ME BECAUSE SHE DOESNT BELIEVE ANY OF IT. MY SYMPTOMS HAVE GOTTEN WORSE SINCE 15 MAY 2009. ANY ADVICE WILL BE APPRECIATED.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

ALL TEST ARE DOCUMENTED BY THE USN AND ARE AVAILABLE UPON REQUEST.

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event) (continued)*

D66
JUN 16 2009

CaseID::7111554

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Individual Safety Report

6342755-5-00-01

...ITARY reporting of product problems and ...ict use errors

1 of 2 CDER

FDA USE ONLY
Triage unit sequence # 391106

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	54	☑ Female ☐ Male	226 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage (Possible)
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
8/2/09	08/24/09

5. Describe Event, Problem or Product Use Error

Took Avelox for 4 days quit taking it ankles started to ache/stevening of forearms began not taking it burning under skin, burning sensation spread to upper arms neck & face. Reported it to Dr. who of course is trying to blame it on other things sent me to a neurologist and gave me steroids to alleviate symptoms, Prescription is ending & now symptoms are returning Dont know what to do – dont want permanent damage and cant stand burning feeling HELP

6. Relevant Tests/Laboratory Data, Including Dates

Going for EEG or EMG Some Neurology test but cant do it felt Im done taking steroids have to wait 4 weeks so as not toget a false positive on test

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Found out wk after I began experiencing symptoms from Avelox that I have diabetes / high blood press + cholesterol

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Avelox 400 mg Schering Corp
#2

2. Dose or Amount	Frequency	Route
#1 400 mg	1 time a day	
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 7/29/09 to 8/2/09
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 SINUSITIS
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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SEP 04 2009
MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DSS
SEP 04 2009

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

USA

Phone # | E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.



AVELOX WEBSITE

Changes in sensation and possible nerve damage (Peripheral Neuropathy) 391106

Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including AVELOX. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

- pain
- burning
- tingling
- numbness

• weakness AVELOX may need to be stopped to prevent permanent nerve damage.

Hope this helps! Let me know what the Dr. says,

(b) (6)

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8/18/2009

DSS
SEP 04 2009

CaseID::7173279

Individual Safety Report

6428936-0-00-01

FARY reporting of
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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

Page 1 of 1 CDER

FDA USE ONLY
Triage unit sequence # 397428

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	71	☑ Female ☐ Male	148 lb or 67.3 kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☒ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
08/15/2009	10/25/2009

5. **Describe Event, Problem or Product Use Error**

After several days of taking Levaquin for a sinus infection, patient experienced tenderness and swelling in her left ankle. At that time we thought that she had unknowingly sprained her left foot. After the 5th day, she had increased swelling in the ankle and soreness in the Achilles area. She also became very tired, had pain in her right rotator cuff, tingling in right foot, shooting pains in right leg, pressure on right side of face and very low blood pressure (68/45). On 09/08/2009 an Orthopedic Surgeon placed her foot in a cast. On 09/29/2009 he replaced it with a "boot" which she continues to wear at this date.

6. **Relevant Tests/Laboratory Data, Including Dates**

08/24/2009: Ultra sound to check for blood clot. No clots detected.
08/31/2009: MRI on left foot. Torn Achilles tendon.
09/03/2009: X-ray on left foot. No broken bones.
09/08/2009: X-ray on left foot. 2nd opinion.

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

None

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: Levaquin
Strength: 750mg
Manufacturer: Ortho-McNeil

DSS

#2 Name:
Strength:
Manufacturer:

NOV 0 4 2009

2. Dose or Amount	Frequency	Route
#1 5 tablets	1/day	Oral
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*	5. Event Abated After Use Stopped or Dose Reduced?
#1 08/10/2009-08/15/2009	#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Sinus infection
#2

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

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2. **Common Device Name**

3. **Manufacturer Name, City and State**

MEDWATCH CTU

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)* 7. **If Explanted, Give Date** *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7237848

6524093-0-00-01

...Safety Information and
Adverse Event Reporting Program

...OLUNTARY reporting of
...vents, product problems and
product use errors

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Page ___ of ___

...Form approved: OMB No. 0910-0291; Expires: 12/31/20...
See OMB statement on reverse

FDA USE ONLY
Triage unit sequence # 403107

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	72	[X] Female [ ] Male	134 lb or ___ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. [X] Adverse Event [ ] Product Problem *(e.g., defects/malfunctions)*
[ ] Product Use Error [ ] Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*

[ ] Death: ___ *(mm/dd/yyyy)*
[ ] Life-threatening
[ ] Hospitalization - initial or prolonged
[ ] Required Intervention to Prevent Permanent Impairment/Damage (Devices)
[X] Disability or Permanent Damage
[ ] Congenital Anomaly/Birth Defect
[ ] Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*

5. Describe Event, Problem or Product Use Error

torn tendon in knee
Bruise + swelling. had
surgery to repair knee
July 10-2009 - still a problem.
Vision Change - depression
Bad dreams and nightmares

6. Relevant Tests/Laboratory Data, Including Dates

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DEC 30 2009
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Muscle Weakness

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

[X] Yes [ ] No [ ] Returned to Manufacturer on: ___ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 LEVAQUIN 500
#2

2.	Dose or Amount	Frequency	Route
#1	1 tablet	Each day	5 days
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*

#1 2-09-2009
#2

4. Diagnosis or Reason for Use *(Indication)*

#1 Urinary tract Infection
#2

5. Event Abated After Use Stopped or Dose Reduced?

#1 [ ] Yes [X] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

8. Event Reappeared After Reintroduction?

#1 [ ] Yes [ ] No [X] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	[ ] Health Professional [ ] Lay User/Patient [ ] Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
[ ] Yes [ ] No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

D86

Product names and therapy dates *(exclude treatment of event)*

DEC 30 2009

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
[ ] Yes [X] No	Retired	[ ] Manufacturer [ ] User Facility [ ] Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [ ]

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7280708

Individual Safety Report

6579871-9-00-01

CDER

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 407309

The FDA Safety Information and Adverse Event Reporting Program

ARY reporting of product problems and use errors

Internet Submission - Page 1

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 34 Years	☑ Female ☐ Male	284 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)

☐ Death: ____ (mm/dd/yyyy) ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
05/01/2009	02/04/2010

5. Describe Event, Problem or Product Use Error

I have taken Levaquin off and on for several years for different infections and prescribed by different doctors. I never received any warning about this drug. I have suffered from tendonitis of my feet, knee and shoulders. I recently had to get my rotator cuff repaired due to constant pain which interfered with my ability to work. I have also had to seek treatment for my heart racing. The doctor did not find anything wrong. I have had at least 3 EKGs with no abnormalities.

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FEB 09 2010
MEDWATCH CTU

More

6. Relevant Tests/Laboratory Data, Including Dates

I can present documentation from doctors.

More

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

I have type I diabetes. I am obese. I have no drug allergies and do not smoke or drink alcohol.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Levaquin 500mg
#2 Armor Thyroid 60mg

2.	Dose or Amount	Frequency	Route
#1	1	QD	po
#2	1	QD	po

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 02/01/2002 -- 02/01/2009
#2 02/05/2009 -- 01/31/2010

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply

4. Diagnosis or Reason for Use (Indication)
#1 Urinary tract infection, bronchitis, sinus infection.
#2 Hypothyroidism

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
FEB 11 2010

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

More

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7475693

6835802-5-00-01

The FDA Safety Information and Adverse Event Reporting Program

VOLUNTARY reporting of events, product problems and product use errors

Internet Submission - Page 1 CDER

FDA USE ONLY

Triage unit sequence # 423681

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	51 Years	☑ Female ☐ Male	140 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)* ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*

☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/14/2009	07/10/2010

5. Describe Event, Problem or Product Use Error

After taking Ciprofloxacin for three days, I developed tremors, heart palpitations, numbness, tingling, weakness, dizzines, anxiety, and worst of all, a ligament tear in my right foot upon simply rising from a chair. The tremors, heart arrhythmias, anxiety, and parasthesias still plague me after 16 months.

RECEIVED
JUL 12 2010
MEDWATCH CTU

More

6. Relevant Tests/Laboratory Data, Including Dates

MRI, March 2009 Echocardiogram, April 2009 Blood tests, March-April 2009 -revealed vitamin D level of 17-

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Fibromyalgia, age 31-41 -then it cleared up; asymptomatic alph 1 antitrypsin deficiency -pizz-; Mother had M.S.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Ciprofloxacin 500 mg Ranbaxy Generic

#2

2.	Dose or Amount	Frequency	Route
#1	500 mg	twice daily	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*

#1 03/14/2009 -- 03/16/2009 3 days

#2 --

4. Diagnosis or Reason for Use *(Indication)*

#1 Urinary tract infection

#2

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☑ No ☐ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?

#1 ☐ Yes ☐ No ☑ Doesn't Apply

#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1 103200? or JPA?	#1	103200? JPA?
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*

7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?

☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DSS
JUL 12 2010

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7547563

U.S. Department of Health and Human Services

Individual Safety Report

6930931-X-00-01

JNTARY reporting of
ts, product problems and
oduct use errors CDER

Page 1 of ____

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 427070

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	42	☑ Female ☐ Male	150 lb or 68.2 kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy) ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☒ Other Serious (Important Medical Events)
☐ Required intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)

4. Date of this Report (mm/dd/yyyy) 07/30/2010

5. Describe Event, Problem or Product Use Error

After taking Cipro, I started having severe, strange side effects. Most noticeable was excess fluid & severe pain in left ankle (which is still same 6 weeks later), as well as shooting nerve & tendon pain throughout entire body. Other side effects include extreme thirst, incapacitating joint pain (could not bend my fingers & can hardly walk), swelling down left arm accompanied by feeling of pressure where I could see my veins protruding, facial twitching & other continued neurological symptoms that are completely debilitating. In addition to ankle pain, have had neck, shoulder, back, gland, and leg pain, with spasms all over body. Extreme sensitivity to sunlight and heat, & "old" injuries seemed to have resurfaced.

6. Relevant Tests/Laboratory Data, Including Dates

Went to ER for ankle on (b) (6) and they tested for blood clots in leg which were negative. Bloodwork did not show any type of virus or anything else that could be causing these terrible symptoms. Nothing is broken in ankle but it remains swollen with fluid and immobile.

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

I am sensitive to steroid products and have an allergy to Penicillin (break out in hives). The side effects listed above are still happening, over six weeks after first taking Cipro. It has completely disabled me and I do not want this to happen to anyone else! I have a chronic back problem but this is completely different. Not only has it affected my health but is costing thousands of dollars in med. bills.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

(1)

#1 Name: Ciprofloxacin
Strength: 250 mg tablet
Manufacturer: Bayer (?)

DSS

#2 Name:
Strength:
Manufacturer:

AUG 18 2010

2. Dose or Amount	Frequency	Route
#1 250 mg	2x/day	
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 15 June 2010
#2 18 June 2010

4. Diagnosis or Reason for Use (Indication)
#1 UTI symptoms (Urinary Tract Infection)
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	8. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

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AUG 17 2010
MEDWATCH CTU

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Non-Healthcare Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7658371

7057816-5-00-01

CDER

VOLUNTARY reporting of ...events, product problems and product use errors

Internet Submission - Page 1/2

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 433064

The FDA Safety Information and Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 49 Years	☑ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☑ Hospitalization - initial or prolonged
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
07/28/2009	10/20/2010

5. Describe Event, Problem or Product Use Error

After taking CIPRO, I began having snapping sounds in my hips when I went up the stairs this occurred for about 2 weeks then came extreme pain in the hip and groin area, then the lower back I was unable to walk, shortly there after I had muscle twitching, pins and needles aching legs,shoulders, arms, neck and snapping sounds of my tendons all over my body. I was anxious, dizzy, hysterical I had night sweats, insomnia. I lost 20 lbs,I would drink ensure to try and keep my weight up, I had thoughts of suicide because of the extreme 24/7 pain, I was so sleep deprived I could not think straight. Please please please do something about this

More

6. Relevant Tests/Laboratory Data, Including Dates

Can't remember dates from 6/2009-12/2009 CT scan hips MRI hips and back, CT brain, MRI brain. Nerve conduction blood tests for MS, ALS,arthritis, lupus, cancer variuos autoimmune diseases, lukemia. I cannot remember all my tests I saw many many physicians, about 10-12 in all.

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

No preexisting medical condictions.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 CIPRO 500 MG
#2

2.	Dose or Amount	Frequency	Route
#1	500 mg	twice daily	
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 05/21/2009 7 days 05/28/2009
#2 02/20/2010 7 days 02/27/2010

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☑ No ☐ Doesn't Apply

4. Diagnosis or Reason for Use *(Indication)*
#1 UTI infection
#2

8. Event Reappeared After Reintroduction?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☑ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name: Ciprofloxin
2. Common Device Name: Cipro
3. Manufacturer Name, City and State: Tamarac, Florida

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

Physical therapy, counseling medications hosptalizations.

DSS
OCT 22 2010

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

7057816-5-00-02

MEDWATCH

433064

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 2

B5. Describe event or problem continued

terrible drug. It has ruined my life I am still suffering please. Presently I am having skin problems and insomnia as well as depression.

DSS

OCT 22 2010

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7704577

U.S. Department of Health and Human Services

Individual Safety Report

7115874-3-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 435984

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	62	[X] Female [ ] Male	149 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. [X] Adverse Event [ ] Product Problem (e.g., defects/malfunctions)
[ ] Product Use Error [X] Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
[ ] Death: ____ (mm/dd/yyyy)
[X] Disability or Permanent Damage
[ ] Life-threatening
[ ] Congenital Anomaly/Birth Defect
[ ] Hospitalization - initial or prolonged
[X] Other Serious (Important Medical Events)
[ ] Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
11-26-2009	8-13-2010

5. Describe Event, Problem or Product Use Error

I WAS PRESCRIBED CIPRO FOR A UTI. I TOOK IT FOR 3 DAYS AND WOKE UP ON THIRD NIGHT WITH BURNING LEGS + ARMS. THE EMERGENCY ROOM DOCTOR DIAGNOSED A CIPRO SIDE EFFECT. MY DOCTOR TREATED ME FOR TENDONITIS

6. Relevant Tests/Laboratory Data, Including Dates

NERVE CONDUCTION TEST FEB 2010. 2/5/2010 ON ARMS + LEGS.

UTI TEST 26th NOV 2009

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

NONE. I WAS HEALTHY AND ACTIVE BEFORE TAKING THIS MEDICATION.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
[X] Yes [ ] No [ ] Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Name: CIPROFLAXIN HCL 250MG
Strength:
Manufacturer: DR REDDY'S LAB.
#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 2X250MG	2X DAY	MOUTH (ORAL)
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 26th 27th 28th
#2 NOV. 2009.

4. Diagnosis or Reason for Use (Indication)
#1 POSSIBLE UTI
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [X] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [X] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1 8/30/2012	RX# 139816
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

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MEDWATCH CTU

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	[ ] Health Professional [ ] Lay User/Patient [ ] Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? [ ] Yes [ ] No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

NOV 18 2010

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
[ ] Yes [X] No	TEACHER	[X] Manufacturer [ ] User Facility [ ] Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [X]

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7704577

U.S. Department of Health and Human Services (CONTINUATION PAGE)

Individual Safety Report

7115874-3-00-02

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435984

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B.5. **Describe Event or Problem** *(continued)*

FOR A MONTH. MY SYMPTOMS WERE PAIN + BURNING IN MY ARMS + LEGS. I WAS NOT ABLE TO WALK, SLEEP, SIT OR FUNCTION. ANY WHERE NEAR NORMALLY. IT IS NOW 8 MONTHS LATER AND I AM STILL NOT ABLE TO WALK, DRIVE OR WORK. I HAVE NERVE DAMAGE THROUGHOUT MY ARMS AND LEGS AND HAVE BEEN IN CONSTANT PAIN SINCE I TOOK THIS MEDICATION.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

IT IS NOW ALMOST 11 MONTHS SINCE I TOOK THIS MEDICATION AND I STILL CANT WALK (EXCEPT AROUND THE ROOM I AM IN) I MUST USE A TRICYCLE TO GET AROUND. I CANT DRIVE AND HAVE NEEDED HELP TO FUNCTION (SHOPPING LAUNDRY ETC) SINCE NOV 2009

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)* *(continued)*

ALLERGIC TO SULFUR DRUGS.

DSS

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)* *(continued)*

NOV 18 2010

CaseID::7741243

Individual Safety Report

7138396-2-00-01

UNTARY reporting of
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Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 437391

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 36 Years	☑ Female ☐ Male	120 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy) ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
09/10/2010	12/01/2010

5. Describe Event, Problem or Product Use Error

Upon taking the 1st pill of Ciprofloxacin high dose 3day dosage, I had the following symptoms: rapid, pounding heartbeat of 130 beats/min. -tachycardia-, depersonalization, began having panic attacks, hypoglycemia & severe hunger/metabolism, burning body pain, unable to sleep with tachycardia present for 2 weeks, profuse sweating, pacing, joint/tendon pain, head burning, visual changes/distortion, poor memory/coordination, GI upset--gastritis & severe constipation pale yellow stools, moderate jaundice skin, muscles wasting & burning tendons, dizziness & vertigo.

More

6. Relevant Tests/Laboratory Data, Including Dates

I saw the following doctors, none including the primary care physician noticed that I was having an adverse reaction to Cipro! General Practitioner: Rx Valium & Xanax for the anxiety, did not notice DRUG REACTION! Endocrinologist: Suspected Reactive Hypoglycemia -High Insulin Readings-

More

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

Gluten, Soy, & Dairy sensitivities. Otherwise a very healthy diet & active 36 year old. Now unable to work or care for my family.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Ciprofloxacin 500 mg Cobalt
#2

2.	Dose or Amount	Frequency	Route
#1	2 tablets day	3	
#2			

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 09/10/2010 -- 09/12/2010
#2 --

4. Diagnosis or Reason for Use (Indication)
#1 Suspected Urinary Tract Infection -Few Red Blood Cells
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID
16252-0515-01

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

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DEC 02 2010
MEDWATCH CTU

4. Model # Lot # Catalog # Expiration Date (mm/dd/yyyy) Serial # Other #

5. Operator of Device
☐ Health Professional
☐ Lay User/Patient
☐ Other:

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
DEC 02 2010

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

More

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☑ Yes ☐ No	Other Health	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

7138396-2-00-02

MEDWATCH

professionals of adverse events and product problems

Internet Submission - Page 3

437391

B6. Relevant tests/laboratory data, including dates continued

High Night Cortisol Gastroenterologist: Endoscopy & Colonoscopy. DX: Gastritis & erythema in GI tract & Hiatal hernia Neurologist: MRI--normal (b) (6): unable to dx MD in Washington State: Reaction to Cipro diagnosis & tx for severe low ferritin levels, hospital IV's for iron infusions & drug reaction shots.

DSS

DEC 02 2010

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7798999

Individual Safety Report

7225667-4-00-01

VOLUNTARY reporting of events, product problems and product use errors

Page 1 of ___

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB Statement on reverse.

FDA USE ONLY
Triage unit sequence # 440717

1. Patient Identifier	2. Age at Time of Event or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☐ Female ☒ Male	95 lb or ___ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1 ☒ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death ___ (mm/dd/yyyy) ☒ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☒ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)

4. Date of this Report (mm/dd/yyyy) 11/6/11

5. Describe Event, Problem or Product Use Error

I have been seriously sick since approx 4/07 - 6/08. I took Levaquin A few times then, or before then. I cannot walk, bend, and function. I have A LOT of pain, fatigue, anxiety. I cannot work. No Quality of life.

6. Relevant Tests/Laboratory Data, Including Dates

tendonitis, RA., possible tendon tears, popping of knees. Scars from skin rashes and boils, pain in arms, ankles, toes, fingers, elbows, face

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

I have been on Anxiety medication

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☒ No ☐ Returned to Manufacturer on ___ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

(1)
#1 Name: Levaquin
Strength: 750 mg, 500 mg
Manufacturer: J.J. LEVAQUIN

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount / Frequency / Route

	Dose or Amount	Frequency	Route
#1			
#2			

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 4/08 6/08 ??
#2

4. Diagnosis or Reason for Use (Indication)
#1 Sinus Infections
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy) 7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	Self Employed Sales	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

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MEDWATCH CTU

DSS
JAN 07 2011

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event

CaseID::7800646

U.S. Department of Health and Human Services

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

Individual Safety Report

7227122-4-00-01

...NTARY reporting of ...s, product problems and ...duct use errors

...ession - Page 1 OQRS

FDA USE ONLY
Triage unit sequence # 441052

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 72 Years	☐ Female ☑ Male	235 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☑ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
12/13/2010	01/10/2011

5. Describe Event, Problem or Product Use Error

Started taking Levaquin, as directed by my physician, Dr. (b) (6) for a sinus infection. After taking it for 12 days I experienced severe pain in my left achilles tendon. I contacted Dr. (b) (6) and was directed to an orthopedist, Dr. (b) (6). I have been applying Voltaire cream and icing. However, this past week I have experienced pain in my right knee and tingling, numbness and pain in my left foot. I am going back to Dr. (b) (6) for further evalutaion. My discomfort and pain has been effecting my lifestyle for over a month now. I have difficulty walking, sleeping and carrying out everyday activities.

More

6. Relevant Tests/Laboratory Data, Including Dates

X-ray was taked on December 9th to determine that I had severe tendonitis by Dr. (b) (6) I am returning to Dr. (b) (6) office tomorrow to have him further evaluate my tendonitis and to examine my right knee and left foot. No doubt, further x-rays will be done at this time.

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

None

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 levaqin 750 mg. Janseen Pharmaceutical
#2

2. Dose or Amount	Frequency	Route
#1 one per day		po
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 11/19/2010 -- 12/01/2010
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 Sinus Infection
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID
50458-930-20

E. SUSPECT MEDICAL DEVICE

1. Brand Name
Levaquin

2. Common Device Name
Levofloxacin

3. Manufacturer Name, City and State
Janssen Pharmaceutical

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

Levaquin Taken November, 2010 to Dece... 2010

DSS
JAN 11 201

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7804996

U.S. Department of Health and Human Services

Individual Safety Report

7238259-8-00-01

...ARY reporting of ...product problems and ...t use errors

...on - Page 1 / 2

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 44/631

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	40 Years	☑ Female ☐ Male	135 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☑ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
   ☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
   ☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
   ☑ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
11/08/2010	01/14/2011

5. Describe Event, Problem or Product Use Error

After being prescribed Cipro for a bladder infection, I not only did not improve, but experienced headaches, back pain, severe abdominal pain, and extreme lethargy while on the drug. Since that time, I have not been able to work because my symptoms have been getting progressively worse, making it often difficult for me to: walk or use my hands, think clearly, recall recent events, have enough energy to stand for more than a few minutes, control my bladder, access words when speaking, sleep, and live without widespread muscle and joint pain. I was given no warning about this drug and was told to remain on it even after initial symptoms

More

6. Relevant Tests/Laboratory Data, Including Dates

Positive ANA results: 12/31/2011 CTU

JAN 19 2011

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

None.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
   #1 Cipro Unknown
   #2

2. Dose or Amount	Frequency	Route
#1		
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
   #1 11/08/2010 -- 11/15/2010
   #2 --

4. Diagnosis or Reason for Use *(Indication)*
   #1 Bladder Infection
   #2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☑ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☑ Doesn't Apply
   #2 ☐ Yes ☐ No ☑ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name: Ciproflolaxin
2. Common Device Name: Cipro
3. Manufacturer Name, City and State: Unknown

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☑ Health Professional ☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☑ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

DSS

JAN 19 2011

Phone (b) (6) E-mail (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health	☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

7238259-8-00-02

VATCH

44/631

reporting by health professionals of adverse events and product problems

B5. Describe event or problem continued

of reaction occurred.

DSS

JAN 19 2011

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7918609

Individual Safety Report

7420109-8-00-01

VOLUNTARY reporting of events, product problems and product use errors

CDER

Page ___ of ___

Form Approved: OMB No. 0910-0291, Expires: 12/31
See OMB statement on rev

FDA USE ONLY

Triage unit sequence # 450756

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	51	☑ Female ☐ Male	110 lb or ___ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)

☐ Death: ___ (mm/dd/yyyy)
☑ Life-threatening
☑ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy) 08/03/10

4. Date of this Report (mm/dd/yyyy) 04/05/11

5. Describe Event, Problem or Product Use Error

Took 1 dose of levaquin at 11:00 am AT (b) (6). Woke up from sleep with abdominal pain. Got out of bed and passed out. Back to bed. Woke up with tingling in hands & face. They also went numb. This occured for many nights went to ER. Continued tingling, rushing sensations, anxiety, insomnia, palpitations, muscle weakness and fatigue. Continue. Have not been able to work.

6. Relevant Tests/Laboratory Data, Including Dates

MRI-brain
EEG
blood work
echocardiogram
EKG
CATSCAN 24 hour halter monitor

Some symptoms have improved over long period of time.

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

past history of hives and swelling of face & lips.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

☐ Yes ☐ No ☐ Returned to Manufacturer on: ___ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

#1 Janseen Pharm (J) Levaquin

#2

2. Dose or Amount	Frequency	Route
#1		
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)

#1 August 3, 2010

#2

4. Diagnosis or Reason for Use (Indication)

#1 UTI

#2 early onset bronchitis

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☑ No ☐ Does Appl

#2 ☐ Yes ☐ No ☐ Does Appl

6. Lot #

#1

#2

7. Expiration Date

#1

#2

8. Event Reappeared After Reintroduction?

#1 ☐ Yes ☐ No ☐ Does Apply

#2 ☐ Yes ☐ No ☐ Does Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)

7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

DSS
APR 13 2011

G. REPORTER (See confidentiality section on back)

1. Name and Address

USA

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No	Teacher	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::7942111

Individual Safety Report

7457729-0-00-01

VOLUNTARY reporting of events, product problems, product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 452293

CDER

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A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	52 (b) (6)	☑ Female ☐ Male	145 lb or 65.9 kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☑ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)

☐ Death: _____ (mm/dd/yyyy) ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☒ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
dec. 26th 2010	04/18/2011

5. Describe Event, Problem or Product Use Error

Prescribed Levaquin 750mg for a sinus infection on 12/24/10. Within 2 day my right foot swelled up and my left arm kept dropping when I lifted it above shoulder to brush hair. 3rd day all muscles and bones hurt and could not stretch them it felt like they were being torn. 4th day my face and lips were swelling up and I started having big red blotches on my face. I reported to health care that prescribed and she said quit taking it but I had just finished the 5 day course. 2 weeks later I went back with all the same problems and along with the same sinus infection. She thought I was just depressed. I told her I was depressed because I could not walk and my arm would not work. I could

6. Relevant Tests/Laboratory Data, Including Dates

MRI left shoulder 2/28/2011

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

No known problems according to many tests.
I have been in pain for years in the stomach-lower right area.
I had surgery (Hysterectomy (b) (6) Also surgery to explore pain in right side area in (b) (6) and found I was

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

#1 Name: Levaquin
Strength: 750 mg
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 5 tablets 750 mg Levaquin	1 a day	
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)

#1 12/25/10 -12/29/10
#2

4. Diagnosis or Reason for Use (Indication)

#1 sinus infection
#2

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?

#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

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2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
		☐ Health Professional
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Lay User/Patient
		☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)	7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

1. Name and Address

(b) (6)

DSS
MAY 02 2011

City: (b) (6) State (b) (6) ZIP: (b) (6)

Phone #	E-mail
(b) (6)	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

B.5. **Describe Event or Problem** *(continued)*

could not walk up my stairs and now my hip was coming undone and shooting pains down my leg.She gave me Augmentin for the sinus infection and thought I should be put on Cymbalta for depression but I said no to Cymbalta. 3 weeks later I went back to her and the pharmacy and they said it should of been out of my system in 5 days and I said it was not. This time she the doctor listened to me and took notes. Sent me to a foot doctor and had an MRI on shoulder. MRI showed torn rotator cuff. The foot doctor said it could be from the Levaquin. I am still dealing with these effects and more.

Ringing in the ears
Extreme Body Oder
Headaches — Skin burning pains
Twitching and jerking
Hot and cold sweating
Hands swelling
Locked up Thumb joint-Trigger finger-left hand.
Depression with Anxiety
Pains in my right side
Hip pain shooting down my leg-Right

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

MRI for the left shoulder - 3/28/2011

Bisida Scan - 1/15/2011 -

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)* *(continued)*

given Levaquin 500mg during surgery intravenously. Never felt better and now this has happened.

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)* *(continued)*

I have had years of Physical Therapy - Chiropratic care - thousands of dollars since my hysterectomy in 2005. I have seen at least 10-15 doctors to no avail. I now know it was from Levaquin given to me during surgery & unaware. [redacted] (b) (6)

DSS MAY 02 2011

CaseID::7987954

7523525-9-00-01

...UNTARY reporting of ...nts, product problems and ...roduct use errors

Page 1 of 1

See OMB statement on reverse.

FDA USE ONLY

Triage unit sequence # 455279

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	(b) (6)	☐ Female ☒ Male	140 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)* ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☒ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
10/25/2009	05/27/2011

5. Describe Event, Problem or Product Use Error

I took 12 CIPRO PILLS IN OCT OF 2009 AND THEN BECAME COMPLETELY CRIPPLED EVER SINCE! I CANNOT WALK, I CANNOT WORK - I AM NOW ON SSDI BECAUSE OF THIS ABSOLUTE POISON. IT HAS DAMAGED EVERY JOINT & TENDON IN MY BODY, MY TEETH, MY VISION, MY HEARING, MY SKIN, MY HAIR, MY NAIL BEDS AND I ATE EVERY OUNCE OF FOOD OUT OF MY MOUTH. HORRIFIC

6. Relevant Tests/Laboratory Data, Including Dates

I HAVE BEEN TO MANY DOCTORS THAN YOU CAN IMAGINE. NONE OF THEM CAN DO ANYTHING FOR ME! WHY IS THIS POISON ON THE MARKET!

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

I WAS COMPLETELY HEALTHY BEFORE

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☒ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 CIPROFLOXACIN 500MG BAYER
#2

2.	Dose or Amount	Frequency	Route
#1	500 mg	2 X DAY	MOUTH
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 OCTOBER 2009
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 "SUSPECTED" UTI
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

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4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS
JUN 01 2011

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

NONE
THIS STUFF IS POISON!

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	DISABLED!	☒ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8022885

Individual Safety Report

7584007-1-00-01

CDER

VOLUNTARY reporting of events, product problems and product use errors

Page 1 of 1

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY

Triage unit sequence # 458051

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	(b) (6)	☒ Female ☐ Male	92 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
   ☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
   ☑ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
12-20-10	6-17-11

5. Describe Event, Problem or Product Use Error

SEVERE PAIN + LOSS OF STRENGTH IN BOTH THUMBS. SUBSEQUENT PROBLEMS: ~~[illegible]~~ TMJ, ALMOST CONSTANT HEADACHES, GROIN PAIN, PLANTAR-FACIATIS, KNEE PAIN, DIAHREA, THRUSH - ALL CONTINUE. HOSPITALIZED TWICE IN (b) (6) FOR CHEST PAIN, DIZZINESS, SHAKING, DISORIENTED, IMPAIRED THOUGHT PROCESS WHILE TAKING MEDICATION

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
   #1 LEVAQUIN 500 MG. JANSSEN
   #2

2.	Dose or Amount	Frequency	Route
#1	1 TABLET	EVERY 24 HRS	ORAL
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
   #1 12/8/10 - 12-17-10
   #2

4. Diagnosis or Reason for Use *(Indication)*
   #1 SINUS INFECTION & BRONCHITUS
   #2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☑ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☑ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1 ?	#1 12-8-11	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

DSS

JUN 28 2011

RECEIVED

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

JUN 28 2011

MEDWATCH CTU

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	ELEC. ENGINEER	☐ Manufacturer ☑ ~~User Facility~~ DR. ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☒

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8135973

Individual Safety Report

7744082-8-00-01

CDER

RY reporting of duct problems and ise errors

Page 1 of 1

Form Approved: OMB No. 0910-0291. Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 462479

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier: In confidence
2. Age at Time of Event or Date of Birth: (b) (6)
3. Sex: ☑ Female ☐ Male
4. Weight: 122 lb or ____ kg

B. ADVERSE EVENT PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy)
☐ Life-threatening
☑ Hospitalization - initial or prolonged
☑ Required intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☑ Other Serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy): 09-03-10

4. Date of this Report (mm/dd/yyyy): 08-30-11

5. Describe Event, Problem or Product Use Error

While pushing water dispenser on front of refrigerator, felt like lightening went into my fingers (R) hand, and up to my shoulder, throwing my (R) arm, elbow first up high and behind my head.
after surgery Dr Tom tendons (R) shoulder now have required tendon tearing

6. Relevant Tests/Laboratory Data, including Dates

X RAY (R) ARM (b) (6)
MRI (R) SHOULDER
MRI (L) SHOULDER (b) (6)

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

NO PREEXISTING MEDICAL CONDITIONS
NO TRAUMA

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

#1 Name: CIPRO
Strength: 500 MG
Manufacturer: UNKNOWN

#2 Name: LEVAQUIN
Strength:
Manufacturer: UNKNOWN

2. Dose or Amount / Frequency / Route

	Dose or Amount	Frequency	Route
#1	CIPRO	X 1 daily	ORALLY
#2	LEVAQUIN	X 1 daily	ORALLY

3. Dates of Use (If unknown, give duration) from/to (or best estimate)

#1 6-25-10 & 12-26-10
#2 1-22-11

4. Diagnosis or Reason for Use (Indication)

#1 BLADDER INFECTION
#2 BLADDER INFECTION

5. Event Abated After Use Stopped or Dose Reduced?

#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #

#1 UNKNOWN
#2 UNKNOWN

7. Expiration Date

#1 UNKNOWN
#2 UNKNOWN

8. Event Reappeared After Reintroduction?

#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

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MEDWATCH CTU

2. Common Device Name

3. Manufacturer Name, City and State

4. Model # / Lot # / 5. Operator of Device (☐ Health Professional ☐ Lay User/Patient ☐ Other:)
Catalog # / Expiration Date (mm/dd/yyyy)
Serial # / Other #

6. If Implanted, Give Date (mm/dd/yyyy)

7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

1. Name and Address
Name: (b) (6)
Address:
City: (b) (6) State (b) (6) ZIP: (b) (6)

DSS SEP 09 2011

Phone #: (b) (6)
E-mail

2. Health Professional? ☐ Yes ☑ No
3. Occupation: Retired
4. Also Reported to: ☑ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8269115

Individual Safety Report

7942143-1-00-01

CDER

VOLUNTARY reporting of events, product problems and product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

Page 1 of 1

FDA USE ONLY
Triage unit sequence # 466269

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
In confidence	(b) (6)	☑ Female ☐ Male	135 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ Adverse Event ☐ Product Problem (e.g., defects/malfunctions) ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy) ☒ Disability or Permanent Damage ☐ Life-threatening ☐ Congenital Anomaly/Birth Defect ☒ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events) ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy): 5-24-2011

4. Date of this Report (mm/dd/yyyy): JUNE 2011

5. Describe Event, Problem or Product Use Error
USED 2 CIPROFOXACIN 500 MG. BURNING STARTED IN MY BODY. ARMS & LEGS GOT WEAK & SORE. BOWEL GOT WHITE. COULD NOT SLEEP OR EAT EARS HAD PAIN & RAN WAS DIZIE. HARD TO BREATH HAVE SISTS ON MY KIONEYS ANKLE IS PAINFUL & WEAK

6. Relevant Tests/Laboratory Data, Including Dates
HOSPITALIZED NORTHWESTERN JUNE 13 TO JUNE 19 VARIOUS TESTS

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
ALLIGIES TO ANTIBOTICS IM WHITE DO NOT DRINK OR SMOKE - STILL HAVE RED BLOTCHES ON MY FACE ALL MY VEINS HAVE SWOLEN UP

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☒ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Name: CIPROFLOXICAN
Strength: 500 MG TABLETS
Manufacturer: DON'T KNOW DESIGN ON PILL
#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 2 500 MG	STOPED AFTER-2	
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 5-24-2011
#2

4. Diagnosis or Reason for Use (Indication)
#1 YOURANY TRACK INF
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☒ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

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2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other:
Catalog #	Expiration Date (mm/dd/yyyy)	
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

(b) (6)

Phone # | E-mail

2. Health Professional? ☐ Yes ☐ No
3. Occupation: CLERICAL
4. Also Report to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

DSS NOV 23 20

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8335481

Individual Safety Report

8035555-1-00-01

CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

LUNTARY reporting of
:nts, product problems and
product use errors

The FDA Safety Information and Adverse Event Reporting Program

Page 1 of 1

FDA USE ONLY
Triage unit sequence # 469517

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
In confidence	30	☐ Female ☒ Male	160 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy)
☒ Disability or Permanent Damage
☐ Life-threatening
☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
10/25/2009	12/27/2011

5. Describe Event, Problem or Product Use Error

THIS POISON COMPLETELY AND UTTERLY CRIPPLED ME!!!
ATTACKED EVERY SINGLE JOINT, MUSCLE, TENDON, TORE MY RETINAS, HORRIFIC NON-ABATING PAIN
SHAME ON THE FDA!!

6. Relevant Tests/Laboratory Data, Including Dates

I'VE BEEN TO SO MANY DR'S I CANNOT EVEN TELL YOU. THEY CANNOT HELP!!!

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

NONE

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☒ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Name: CIPROFLOXACIN
Strength: 500MG
Manufacturer: BAYER
#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 500MG	2X DAY	MOUTH
#2		

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 SIX DAYS IN OCT 2009
#2

4. Diagnosis or Reason for Use (Indication)
#1 SUSPECTED UTI
#2

6. Lot #	7. Expiration Date
#1	
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

1. Name and Address
Name: (b) (6)
Address:
City: (b) (6) State (b) (6) ZIP: (b) (6)

DSS
JAN 10 2012

Phone # (b) (6)
E-mail CIPRO IS POISON!!!

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	DISABLED!	☒ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8578803

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Individual Safety Report

8378900-X-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 475954

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	(b) (6)	☐ Female ☑ Male	170 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: ____ *(mm/dd/yyyy)*
   ☐ Life-threatening
   ☐ Hospitalization - initial or prolonged
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
   ☑ Disability or Permanent Damage
   ☐ Congenital Anomaly/Birth Defect
   ☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
01/02/2012	04/27/2012

5. Describe Event, Problem or Product Use Error

LEVOFLOXACIN WAS PRESCRIBED FOR SINUS INFECTION BY DR. (b) (6) (b) (6) OF (b) (6) CLINIC, (b) (6) RD., STE (b) (6) (b) (6) PHONE: (b) (6) I DEVELOPED SOME NUMBNESS IN RIGHT LEG AFTER 4 DAYS ON MED. FINISHED 10 DAY REGIMEN AND DEVELOPED NUMBNESS, TINGLING ON RIGHT SIDE-ARM AND FOOT AND ARCHILLES TENDON DIAGNOSIS: PERIPHERAL NEUROPATHY NO IMPROVEMENT TO DATE.

6. Relevant Tests/Laboratory Data, Including Dates

BLOOD TESTS IN JAN 2012

RECEIVED
MAY 22 2012
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
   #1 LEVOFLOXACIN 250 MG, DR. REDDY'S LAB
   #2

2.	Dose or Amount	Frequency	Route
#1	250 MG	1 PER DAY	
#2			

3. Dates of Use *(If unknown, give duration)* from/to *(or best estimate)*
   #1 30 DEC 2011 - 8 JAN 12
   #2

4. Diagnosis or Reason for Use *(Indication)*
   #1 SINUS INFECTION
   #2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☑ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
   #1
   #2

7. Expiration Date
   #1 12/30/2012
   #2

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☑ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID
   #1 BLOOD
   #2 RD4279 WHITE

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address (b) (6)

DSS
MAY 22 2012

Phone (b) (6) E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	RET.	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8679997

Individual Safety Report

8521252-2-00-01

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

VOLUNTARY reporting of adverse events, product problems and product use errors

Internet Submission - Page 1

CDER

FDA USE ONLY
Triage unit sequence # 481082

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☑ Female ☐ Male	34 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
05/25/2012	07/10/2012

5. Describe Event, Problem or Product Use Error

Within one hour of taking my first dose of Levofloxacin, my right big toe started hurting very badly. The pain then progressed to both legs and feet. It felt like they were going numb and I was experiencing extreme pressure. I called the doctor and they took me off the drug immediately. I was not able to walk at all for 2 days after my initial dose. About a week later my symptoms increased to include hallucinations, and pain in my hips, wrists, fingers, knees, and elbows. From the research I have done online, I believe to be suffering from Levoquin Tendonitis. I have not made much improvement since the initial dose.

More

6. Relevant Tests/Laboratory Data, Including Dates

The doctor did not run tests or have any idea what to do.

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

I took the antibiotic to fight off an upper urinary infection that was not responding to another antibiotic. I have gluten intolerance caused by

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Levofloxacin 25 mg/ml solution Hi-Tech
#2

2.	Dose or Amount	Frequency	Route
#1	20 ml	once every 24 hour	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 05/25/2012 one dose 05/25/2012
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 upper urinary infection
#2

6. Lot #	7. Expiration Date
#1 3238285-03633	#1 05/25/2013
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID
50383-0286-04

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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JUL 12 2012
MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

DSS
(b) (6)
JUL 12 2012

Phone # (b) (6)
E-mail (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

8521252-2-00-02

MEDWATCH

481082

FOR VOLUNTARY reporting by health professionals of adverse events and product problems

B7. Other relevant history, including preexisting medical conditions continued

Irritable Bowel Syndrome; never smoked or drank; Caucasian; allergic to tree nuts, iodine -x-ray dye-, penicillin; doctors always told me I was healthy.

DSS
JUL 12 20

CaseID::8708389

Individual Safety Report

8553661-X-00-01

CDER

LUNTARY reporting of
ents, product problems and
roduct use errors
omission - Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 482535

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☐ Female ☑ Male	195 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☑ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
06/15/2005	07/23/2012

5. Describe Event, Problem or Product Use Error

I have been disabled for over six years from being prescribed Levaquin. I have severe and permanent peripheral neuropathy. I was formally healthy, athletic, and had an MBA degree. My symptoms include severe burning, parasthesia, nerve damage, tendonosis, insomnia, head pressure, vision damage, suicidal ideation at one point early on. My life has been ruined by Levaquin. I obtained the FDA Freedom of Information Reports for Levaquin, Cipro, and Avelox. There are over 3,500 reports of peripheral neuropathy type symptoms when you add in all of the neuropathy type submitted medwatch reports. I have been to the FDA twice to give a presentation

More

6. Relevant Tests/Laboratory Data, Including Dates

EMG - 2005 Skin punch biopsy - 2006 QEEG test - 2009 MRI - 2005 CBC - multiple spinal tap - 2006

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

I was perfectly healthy and athletic prior to Levaquin. I was blessed with great family health genes until Levaquin ruined my life. My parents are 91

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Levaquin 500 mg Johnson & Johnson
#2

2.	Dose or Amount	Frequency	Route
#1	500 mg	once a day	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 05/15/2005 – 05/25/2005 (10 days)
#2 – –

4. Diagnosis or Reason for Use *(Indication)*
#1 possible urinary tract infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DSJ
JUL 25 2012

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health	☑ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

8553661-X-00-02

WATCH

professionals of adverse events and product problems

ernet Submission - Page 2

482535

B5. Describe event or problem continued

on fluoroquinolone induced severe and long term peripheral neuropathy. My meeting was chaired both times by Dr. Karen Weiss, head of the FDA Safe Use Committee. Dr. Weiss has since left the FDA to go to work for Johnson & Johnson, the manufacturer of Levaquin. I also had several conference calls with Dr. Deb Miller and Dr. David Banks. They both work at the FDA Office of Special Health Issues. Both of them agreed that fluoroquinolones should have a boxed warning for potential irreversible peripheral neuropathy. The package insert for all fluoroquinolones mentions that they can cause potential irrversible peripheral neuropathy. This information is not present on the prescribing literature given out at the pharmacy. It is imperative that physicians and consumers have informaed consent and better disclosure of potential severe and permanent peripheral neuropathy. My story has been on a recent national PBS news segment on fluoroquinolone toxicity along with an ABC news report on Levaquin adverse events. Why is their no dear doctor letter or boxed warning for Levaquin and other fluoroquinolones for potential irreversible peripheral neuropathy? Over half of the fluoroquinolones once on the market have now been removed from clinical practice. Johnson & Johnson's own clinical studies show delayed peripheral nervous system adverse events, yet on the label, there is no mention of this. Through all of my advocacy, I was given the position of FDA Patient Representative for Drug Safety. I would like to speak to someone at the FDA who is in charge of reviewing the medwatch data for fluoroquinolones. I have collected a wealth of documentation on this subject. Thank you very much for your time and consideration. Sincerely, (b) (6)

DSS

JUL 25 2012

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

8553661-X-00-03

H82535

MEDWATCH

professionals of adverse events and product problems

Internet Submission - Page 4

B7. Other relevant history, including preexisting medical conditions continued

and 86 and still in reasonably good health. I won many sports awards during my lifetime. I had an MBA degree and had a great work record in the medical field prior to Levaquin toxicity.

DSS

JUL 25 2012

CaseID::8726312

Individual Case Safety Report

8726312-03-00-01

oratories, Inc

ıse by user-facilities,
distributors and manufacturers
.NDATORY reporting

FDA Facsimile Approval: 05/09/2006 (ArisGlobal, LLC)

Mfr Report # USA/USA/12/0025042

UF/Importer Report #

FDA Use Only

FORM FDA 3500A (1/09)

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) — In confidence
2. Age at Time of Event: 17 Y or Date of Birth:
3. Sex: [X] Female [ ] Male
4. Weight: 400 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [X] Adverse Event and/or [ ] Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- [ ] Death: ____ (mm/dd/yyyy)
- [ ] Life-threatening
- [ ] Hospitalization - initial or prolonged
- [X] Disability or Permanent Damage
- [ ] Congenital Anomaly/Birth Defect
- [X] Other serious (Important Medical Events)
- [ ] Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy): 07/ /2012

4. Date of This Report (mm/dd/yyyy): 10/10/2012

5. Describe Event or Problem

This is a spontaneous case reported by a consumer's mother on 13 July 2012. A 17-year-old female patient experienced weakness, general malaise, leg and arm pain and was bed bound all day and was reduced activities daily while on levofloxacin tablets 500 mg for urinary tract infection.

The patient's medical history included pelvic inflammatory disease. Concomitant medications were not reported.

The patient started treatment with levofloxacin tablets 500 mg, orally, once daily, for urinary tract infection (Lot number; expiration date; NDC and UPC number: unknown) and the patient was currently on day 3 of treatment on 13 July 2012. The patient was 'bed bound all day and was reduced activities daily'. The patient was on levofloxacin 500 mg about 6 weeks ago (brand unknown was not sure if it was Dr. Reddy's) and stated her daughter had leg and arm pain; weakness and general malaise. At the time of reporting, the action taken with suspect drug was unknown and the

Cont...

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Past Disease:
PELVIC INFLAMMATORY DISEASE (Continuing: Unknown)

Concurrent Disease:
ALLERGIC TO PENICILLIN (Continuing: Unknown)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labeler)
#1 Levofloxacin Tablets 500 mg(LEVOFLOXACIN)
#2
Cont...

2. Dose, Frequency & Route Used
#1 500 mg, 1 in 1 D, Oral
#2

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 07/ /2012 -
#2

4. Diagnosis for Use (Indication)
#1 URINARY TRACT INFECTION
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [ ] No [ ] Doesn't Apply — UNK
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot #
#1 UNKNOWN
#2

7. Exp. Date
#1 Unknown
#2

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [ ] Doesn't Apply — UNK
#2 [ ] Yes [ ] No [ ] Doesn't Apply

9. NDC # or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
Unknown

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)
Dr.Reddys Laboratories,Inc
Pharmacovigilance
200 Somerset Corporate Boulevard,
7th Floor,
Bridgewater,,New Jersey 08807
USA
(Printing Unit)

2. Phone Number: 908 203 4900

3. Report Source (Check all that apply)
- [ ] Foreign
- [ ] Study
- [ ] Literature
- [ ] Consumer
- [X] Health Professional
- [ ] User Facility
- [ ] Company Representative
- [ ] Distributor
- [ ] Other:

4. Date Received by Manufacturer (mm/dd/yyyy): 10/09/2012

5. (A)NDA # 076710
IND #
STN #
PMA/510(k) #
Combination Product [ ] Yes
Pre-1938 [ ] Yes
OTC Product [ ] Yes

6. If IND, Give Protocol #

7. Type of Report (Check all that apply)
- [ ] 5-day
- [ ] 30-day
- [ ] 7-day
- [ ] Periodic
- [ ] 10-day
- [ ] Initial
- [X] 15-day
- [X] Follow-up # 4

9. Manufacturer Report Number: USA/USA/12/0025042

8. Adverse Event Term(s)
1) Asthenia
2) Malaise
Cont...

E. INITIAL REPORTER

1. Name and Address
Consumer
USA

Phone #

DSS
OCT 15 2012

2. Health Professional? [X] Yes [ ] No

3. Occupation: Nurse

4. Initial Reporter Also Sent Report to FDA [ ] Yes [ ] No [X] Unk.

OCT 12 2012

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Individual Case Safety Report

8726312-03-00-02

Mfr. Report # : USA/USA/12/0025042

Date of This Report : 10/10/2012

B. ADVERSE EVENT OR PRODUCT PROBLEM

B.5 Describe Event or Problem (Cont...)

outcome of the events were reported as not recovered. No further information was available from the reporter at the time of this report.

The case was considered as serious (Medically significant).

Company comment: This 17-year-old female adolescent patient experienced weakness, general malaise, leg and arm pain and was bed bound all day and had reduced activities daily while on levofloxacin tablets 500 mg for urinary tract infection. Based on the time to onset of events a causal role of levofloxacin cannot be excluded.

Follow-up information was received from a consumer (the patient's mother) on 24 July 2012.

Additional/new information: The patient's medical history and new events were added.

The reporter (the patient's mother) stated that, the patient was instructed by pharmacist not to take any further doses of levofloxacin. The patient continued to have bilateral swelling and bruising back of knees and down back of legs. The left leg was worse than right leg. The reporter stated that, the patient was allergic to penicillin. The reporter was unable to provide further information regarding the date of event onset and the outcome of the event. The patient was not given any other treatment. No further information was available from the reporter at the time of this report.

Company comment: This 17-year-old female adolescent patient experienced weakness, general malaise, leg and arm pain and was bed bound all day and was had reduced activities daily while on levofloxacin tablets 500 mg for urinary tract infection. Based on the time to onset of events and the fact that the patient was not given any other treatment a causal role of levofloxacin was assessed as possible.

Follow-up information was received from a consumer (the patient's mother) on 06 September 2012.

Additional/new information:

The reporter (patient's mother) stated that she and her daughter continued to experience leg pain associated with levofloxacin 500mg. Also refer (DRR-25851, USA/USA/12/0025789) for the reporter (mother) case also.

Follow up comment:
Follow up information does not change the previous assessment of this case.

Follow-up information was received from a Registered Nurse (patient's mother) on 10 September 2012.
Additional/new information: Primary reporter details changed and the case made medically confirmed. New events added (tendon pain and loss of mobility).

The reporter (patient's mother) was a Registered Nurse. The reporter stated that she and her daughter continue to experience tendon pain and weakness with subsequent loss of mobility and changes in quality of life as a result of having used levofloxacin. They have been medically evaluated and continued to have physical therapy without much change in condition. 13 July 2012 was day 3 of treatment with levofloxacin. The patient was a nursing school student who had to drop out due to the inability to be on her feet. No further information on this adverse event is available at this time.

This case was assessed serious due to disability and other medically significant events.

Follow up comment:
This 17-year-old female adolescent patient experienced weakness, malaise, leg and arm pain and was bed bound all day and was had reduced activities daily and had tendon pain while on levofloxacin tablets 500 mg for urinary tract infection. Based on the time to onset of events and the fact that the patient was not given any other treatment a causal role of levofloxacin was assessed as possible. Reduced mobility could have been due to tendon pain.

Follow-up information was received from a reporter on 09 October 2012.
Additional/new information: Information about Event outcome received.

The reporter contacted the Medical information department to request the contact address for Dr. Reddy's Laboratories legal department. During the discussion, the reporter disclosed that the symptoms of leg pain and weakness had persisted inspite of physical therapy. The reporter's physician had now referred the patient to a specialist for a surgical work-up. No further information regarding this event was available.

DSS
OCT 15 2012
OCT 12 2012

Individual Case Safety Report



8726312-03-00-03

Mfr. Report # : USA/USA/12/0025042

Date of This Report : 10/10/2012

Follow up comment:
Follow up information does not change the previous assessment of this case.

C. SUSPECT PRODUCT(S) (Cont...)

Seq No.	: 1
C.1 Suspect Product	: Levofloxacin Tablets 500 mg(LEVOFLOXACIN)
C.2 Dose, Frequency & Route Used	: 2) 500 mg, 1 in 1 D, Oral
C.3 Therapy Dates (or duration)	: 2) 07/11/2012 -
C.5 Dechallenge	: 2) UNK : 3) UNK : 4) UNK : 5) UNK : 6) UNK : 7) UNK : 8) UNK
C.8 Rechallenge	: 2) UNK : 3) UNK : 4) UNK : 5) UNK : 6) UNK : 7) UNK : 8) UNK

G. ALL MANUFACTURERS

G.8 Adverse Event Term(s)

3) Pain
4) Activities of daily living impaired
5) Swelling
6) Contusion
7) Tendon pain
8) Mobility decreased

DSS
OCT 15 2012

OCT 1 2 2012

CaseID::8729655

Individual Safety Report

8595304-5-00-01

VOLUNTARY reporting of events, product problems and product use errors

Page 1 of 3

CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 483903

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☑ Female ☐ Male	125 lb or 56.8 kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
05/06/2012	07/13/2012

5. **Describe Event, Problem or Product Use Error**

Saturday, 05/05/2012, I was prescribed Ciprofloxacin HCL 500 mg for a bladder infection. I told the doctor I was taking progesterone cream & adrenal support cream. I filled the prescription. Neither the doctor nor the pharmacist provided me informed consent, but the pharmacist told me not to take calcium with the drug. Three hours after taking the 1st dose on Saturday pm, my left groin tendon ached. Two hours after taking the 2nd dose on Sunday am, my left knee hurt. Two hours after taking the 3rd dose in the pm, my left middle left toe hurt. I woke up at 3:30 a.m. with pain in both Achilles tendons (bottom) as well as my arms (inside of the bend). I did not take another pill. On Monday, my groin, Achilles (near ankle), &

6. **Relevant Tests/Laboratory Data, Including Dates**

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MEDWATCH CTU

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

I was taking progesterone cream & adrenal support cream.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: Ciprofloxacin HCL
Strength: 500 mg
Manufacturer: Pack Pharmaceuticals

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 500 mg	2x/day for 5 days	oral
#2		

3. **Dates of Use** *(if unknown, give duration) from/to (or best estimate)*
#1 05/05/2012 and 05/06/2012
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Bladder Infection
#2

6. Lot #	7. Expiration Date
#1	#1 01/01/2016
#2	#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC # or Unique ID**
16571-0412-10

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**
2. **Common Device Name**
3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
(b) (6)

DSG
AUG 07 20

Phone #	E-mail
(b) (6)	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Non-Healthcare Professional	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☑

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

8595304-5-00-02

(CONTINUATION PAGE)

'OLUNTARY reporting of
events and product problems

483903

Adverse Event Reporting Program

B.5. **Describe Event or Problem** *(continued)*

arms (inside bend) were still hurting. On Tuesday, my Achilles were still hurting. This time the upper part of the Achilles was hurting as well. When I went to bed that night, the tendons running from behind my ears down my neck were hurting on both the left & right sides. I also noticed symmetrical sores on either side of my upper gums. On Wednesday, the pain in my right leg lessened, but my left leg still hurt (groin & upper & lower Achilles). This time my arms were hurting up at the shoulders as well as behind the ears & down the neck. I also had a headache & was extremely tired. I had to sleep most of the day, though it was restless. Then Thursday, the back (outer side) of both of my arms were hurting too. I continued to have a headache & was still exhausted even after sleeping 9 hours, though sleep was restless. After two days of sleeping, I was less tired. As the days went on, I became easily fatigued when doing the simplest things such as vacuuming & walking up stairs or inclines. I have not been able to resume my exercise since the event, & I can no longer wear high-heeled shoes. The effects of the drug seem to visit different parts of my body at different times. For instance, some days my right wrist aches terrible (which it NEVER did before the Cipro); some days the lightest lifting hurts my abdomen or my arms. Some days my Achilles barely hurt at all & other days they ache tremendously-symmetrically near ankle at in the calf area. In addition, since the event, I have not been able to sleep soundly at night without taking a sleep aid such as melatonin.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event) (continued)*

DSS
AUG 07 2012

CaseID::8732189

Individual Safety Report

8595588-3-00-01

rmaceuticals Inc.

For use by user-facilities,
rters, distributors and manufacturers
.or MANDATORY reporting

FDA Facsimile Approval: 05/09/2006 (ArisGlobal, LLC)

Mfr Report # E2B_00000252(1)

UF/Importer Report #

FDA Use Only

FORM FDA 3500A (10/05)

Page 1 of 2

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) — In confidence
2. Age at Time of Event: 45 Y or Date of Birth: (b) (6)
3. Sex: [X] Female [ ] Male
4. Weight: 165 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [X] Adverse Event and/or [ ] Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- [ ] Death: ____ (mm/dd/yyyy)
- [ ] Life-threatening
- [ ] Hospitalization - initial or prolonged
- [X] Required Intervention to Prevent Permanent Impairment/Damage (Devices)
- [X] Disability or Permanent Damage
- [ ] Congenital Anomaly/Birth Defect
- [X] Other serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy): UNK

4. Date of This Report (mm/dd/yyyy): 07/31/2012

5. Describe Event or Problem

Case reference no. E2B_00000252, is a spontaneous report from USA reported by a 45 year old female patient who experienced insomnia, musculoskeletal weakness, musculoskeletal inflammation, twitching and myoclonus (arms/legs jerking) while on Lupin 's Levofloxacin Tablets 750 mg.

No medical history and concomitant medication was reported.

On 12 January 2012, the patient started treatment with Lupin's Levofloxacin 750 mg tablets once daily per orally for bronchitis/pneumonia. From the same night the patient started experiencing insomnia. On 13 January 2012 and 14 January 2012, the patient continued taking Lupin's Levofloxacin and experienced insomnia on each night. On 15 January 2012, the patient realized that she had adverse event due to Lupin's Levofloxacin and stopped taking Lupin's Levofloxacin. On 16 January 2012, the patient contacted her physician who wanted her to continue treatment with Lupin s Levofloxacin but she refused. From 17 January 2012, the patient started

Cont...

6. Relevant Tests/Laboratory Data, Including Dates

2

Cont...

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

No Risk Factor Available

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labeler)
#1 Levofloxacin Tablets 750 mg(Levofloxacin)
#2
Cont...

2. Dose, Frequency & Route Used
#1 750 mg (750 mg,1 in 1 D),Per oral
#2

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 01/12/2012 - 01/15/2012
#2

4. Diagnosis for Use (Indication)
#1 BRONCHITIS
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [ ] No [X] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot #
#1 UNK
#2

7. Exp. Date
#1 UNK
#2

8. Event Reappeared After Reintroduction?
#1 [ ] Yes [ ] No [X] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

9. NDC # or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
Concomitant Drug No Available

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)
Lupin Pharmaceuticals Inc.
111, South Calvert Street, 21st floor
Baltimore,Maryland 21202
USA
(Initial Unit)

2. Phone Number: 410-576-2000

3. Report Source (Check all that apply)
- [ ] Foreign
- [ ] Study
- [ ] Literature
- [ ] Consumer
- [X] Health Professional
- [ ] User Facility
- [ ] Company Representative
- [ ] Distributor
- [ ] Other:

4. Date Received by Manufacturer (mm/dd/yyyy): 07/16/2012

5. (A)NDA # 78-424
IND #
STN #
PMA/510(k) #

6. If IND, Give Protocol #

7. Type of Report (Check all that apply)
- [ ] 5-day
- [ ] 30-day
- [ ] 7-day
- [ ] Periodic
- [ ] 10-day
- [X] Initial
- [X] 15-day
- [ ] Follow-up # ____

Combination Product [ ] Yes
Pre-1938 [ ] Yes
OTC Product [ ] Yes

9. Manufacturer Report Number: E2B_00000252(1)

8. Adverse Event Term(s)
1) Tendonitis [v.15.0]
2) Insomnia [v.15.0]
Cont...

E. INITIAL REPORTER

(b) (6)

2. Health Professional? [X] Yes [ ] No

3. Occupation: Physician

4. Initial Reporter Also Sent Report to FDA: [ ] Yes [ ] No [X] Unk.

AUG 02 2012

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

AUG 0 1 2012

Individual Safety Report

8595588-3-00-02

Mfr. Report # : E2B_00000252(1)

Date of This Report : 07/31/2012

B. ADVERSE EVENT OR PRODUCT PROBLEM

B.5 Describe Event or Problem (Cont...)

experiencing musculoskeletal events beginning in her knuckles of both hands and then within 24 hours radiating to her arms and legs/entire body. The patient stated that her tendons were not ruptured, but rather just inflamed. The patient identified that her joints were weak and inflamed with the ankles and wrists being the worst. In addition, the patient stated that she experienced "twitching" from the drug attacking her peripheral nerves and "myoclonus" because her arms and legs were jerky. On an unknown date in January 2012, the patient had MRI (magnetic resonance imaging) which revealed inflammation in her right Achilles tendon.

At the time of this report, treatment with Lupin's Levofloxacin was discontinued and the events had not resolved.

The patient had not consented to contact her physician; hence a follow up with the physician could not be performed.

Follow up information was received from the physician on 16 July 2012; in the follow up information, the event tendonitis was added. The case was reassessed as serious based on the follow up information.

On an unknown date, after 2-3 doses of Levofloxacin, the patient experienced symptoms of tendonitis. The patient had undergone numerous treatments but the symptoms persisted for six months. The reporting physician stated that the patient required intervention for tendonitis (intervention details were not reported). As per reporting physician, the manufacturer of Levofloxacin was unknown. No further information was available.

At the time of this report, the event had not resolved.

B.6 Relevant Tests/Laboratory Data, Including Dates (Cont...)

Lab Result :

Test name	Test date	Test result	Normal value	Classification
MRI	01/ /2012	Revealed inflammation in right achilles tendon.		

C. SUSPECT PRODUCT(S) (Cont...)

Seq No.	: 1
C.1 Suspect Product	: Levofloxacin Tablets 750 mg(Levofloxacin)
C.4 Diagnosis for Use (Indication)	: 2) PNEUMONIA
C.5 Dechallenge	: 2) -ve : 3) -ve : 4) -ve : 5) -ve : 6) -ve
C.8 Rechallenge	: 2) N/A : 3) N/A : 4) N/A : 5) N/A : 6) N/A

G. ALL MANUFACTURERS

G.8 Adverse Event Term(s)

3) Muscular weakness [v.15.0]
4) Myositis [v.15.0]
5) Muscle twitching [v.15.0]
6) Myoclonus [v.15.0]

Company Comments :

This case has been assessed as Serious and Unexpected.

Based on the presumed temporal relationship of drug and the events, a possible contributory role of the suspect drug cannot be ruled out, as such company causality is assessed as possible.

DSS

AUG 02 2012

AUG 01 2012

CaseID::8749635

Individual Safety Report

8621828-8-00-01

CDER

VOLUNTARY reporting of events, product problems and product use errors

Submission - Page 1/2

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 485168

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 23 Years	☑ Female ☐ Male	184 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
09/20/2011	08/19/2012

5. Describe Event, Problem or Product Use Error

ciprofloxacin 500mg 10 days, had severe reactin to drug caused joint/tendon pain that I still have to this day all over in my jaw, shoulders, neck, calves, neck, especially in knees all this a few hours after first dose, kept getting worse as the days went on, on last day developed electrical shocks and stabbing needle nerve pain that turned into peripheral neuoropathy, also developed severe anxiety/panic attacks/insomnia, then a week later severe digestive distress developed bleeding in stools and horrible pain on right and left sides, had liver issues also which did blood work and autoimmune issues popped up also liver cyst on ultrasound

More

6. Relevant Tests/Laboratory Data, Including Dates

A month after autoimmune markers popped up positive for ANA, AMA and SSA along with C4 complement possible primary billiary cirhosis of the liver diagnosed, vit D low, liver cyst appeared in an ultrasound

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 ciprofloxacin 500 mg for 10days Bayer Healthcare Pharmaceuticals I
#2

2.	Dose or Amount	Frequency	Route
#1	500mg	10 days	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 10 days 09/20/2011 -- 09/30/2011
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 urinary tract infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1 H0E306	#1
#2	#2

9. NDC # or Unique ID
0085-1754-02

E. SUSPECT MEDICAL DEVICE

1. Brand Name
ciprofloxacin -floroquinolone family-

2. Common Device Name
cipro

3. Manufacturer Name, City and State
Bayer pharmaceuticals 800 Dwight Way Berkeley, CA 94710

4. Model #	Lot # H0E306	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

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AUG 21 2012
MEDWATCH CTU

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

cipro has made me disabled now I still have many issues because of these pills!!

DSS
AUG 21 2012

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Safety Report

8621828-8-00-02

485168

MEDWATCH

h professionals of adverse events and product problems

B5. Describe event or problem continued

popped up, and experienced kidney stress and still experiencing frequent urination.

DSS

AUG 21 2012

CaseID::8896483

Individual Case Safety Report

8896483-01-00-01

CDER

VOLUNTARY reporting of events, product problems and product use errors

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 493251

...t Safety Information and Adverse Event Reporting Program

Internet Submission - Page 1

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
Unspecified in confidence	(b) (6) 30 Years	[✓] Female [ ] Male	125 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. [✓] Adverse Event [ ] Product Problem *(e.g., defects/malfunctions)*
[ ] Product Use Error [ ] Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
[ ] Death: ____ *(mm/dd/yyyy)*
[ ] Life-threatening
[✓] Hospitalization - initial or prolonged
[ ] Required Intervention to Prevent Permanent Impairment/Damage (Devices)
[✓] Disability or Permanent Damage
[ ] Congenital Anomaly/Birth Defect
[ ] Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
10/16/2005	11/06/2012

5. Describe Event, Problem or Product Use Error

Severe PNS/ANS -including, neuropathy, tremor, vertigo, and balance- issues, joint/tendon/fibro pain, and MCS/food allergies after only two doses of the fluoroquinolone antibiotic Avelox. This pain has lasted 7 years so far!

More

6. Relevant Tests/Laboratory Data, Including Dates

CTU
NOV 07 2012

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

No pre-existing conditions. No prior allergies.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
[ ] Yes [✓] No [ ] Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Avelox 400 mg Bayer
#2

2.	Dose or Amount	Frequency	Route
#1	1 pill	per day	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 10/15/2005 -- 10/15/2005
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 bronchitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 [ ] Yes [✓] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 [✓] Yes [ ] No [ ] Doesn't Apply
#2 [ ] Yes [ ] No [ ] Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name: Avelox
2. Common Device Name: moxifloxacin
3. Manufacturer Name, City and State: Bayer

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	[ ] Health Professional [ ] Lay User/Patient [ ] Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
[ ] Yes [ ] No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DSS
NOV 07 2012

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

Phone #	E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
[ ] Yes [✓] No		[ ] Manufacturer [ ] User Facility [ ] Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: [✓]

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8901852

Individual Case Safety Report

8901852-01-00-01

CDER

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oduct use errors

mission - Page 1 /3

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 493555

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
Unspecified In confidence	(b) (6) 46 Years	☑ Female ☐ Male	120 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
02/26/2007	11/08/2012

5. Describe Event, Problem or Product Use Error

Over 5 years ago I took 4 pills/ciprofloxacin and had a severe adverse reaction including; insomnia, severe head pressure, loss of balance, fatigue, increased temperature/pain sensitivity, tinnitis, vision/hearing loss, anxiety, cns/pns/ans damage, right hip labral tear, rhabdomylosis, muscle wasting, tendon/joint pain, difficulty walking, spasticity, clonus, IBS, etc. My neurological issues which began following my reaction to cipro have progressed to the point where I was recently diagnosed with PLS -primary lateral sclerosis-. Prior to taking cipro I was healthy and athletic.

More

6. Relevant Tests/Laboratory Data, Including Dates

Head/full spine MRIs in 2009 & again in 2011. Blood work, emg and lumbar puncture in 2009. x rays of right hip in 4/2009, 10/2009 and 5/2012. MRA of right hip Jan 2010. Surgery on good sized labral tear in May 2010. DNA test for HSP -hereditary spastic paraplegia- 10/2012 which came back

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Mild environmental allergies to pollens, dust, mold. Caucasian. 3 pregnancies resulting in healthy vaginal deliveries. NON smoker. Light alcohol use

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 ciprofloxacin 500 mgs generic
#2

2.	Dose or Amount	Frequency	Route
#1	500 mgs	2 times per day	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 02/26/2007 – 02/28/2007 (2 days)
#2 –

4. Diagnosis or Reason for Use *(Indication)*
#1 sinusitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name: cipro
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☑ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

CTU

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

NOV 09 2012

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DSS

NOV 09 2012

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

8901852-01-00-02

493555

WATCH

rofessionals of adverse events and product problems

B6. Relevant tests/laboratory data, including dates continued

negative/normal. Emg's in 2012.

DSS

NOV 09 2012

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

8901852-01-00-03

493555

MEDWATCH

professionals of adverse events and product problems

B7. Other relevant history, including preexisting medical conditions continued

socially. No liver/kidney problems. NO major health problems previously. An occasional sinus infection requiring antibiotics.

DSS

NOV 09 201

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::8925114

Individual Case Safety Report

8925114-01-00-01

CDER

...UNTARY reporting of ...nts, product problems and ...roduct use errors

Internet Submission - Page 1/2

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 494483

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 34 Years	☐ Female ☑ Male	190 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
01/10/1977	11/19/2012

5. Describe Event, Problem or Product Use Error

Took Cipro XL 1000mg per day for 2 days. Developed Peripheral neuropathy severe in right quadricep and moderate all over the rest of my body. Ceased treatment after day 2. Severe anxiety and depression, suicidal thoughts -not normal for me- lasted for 3 days after cessation of drug. For the next two months, I had difficulty completing my thoughts and sentences and was extremely sensitive to caffeine and sugar. At the 3 month mark, I developed tendonitis body-wide and popping/cracking sounds in my joints at the wrists, shoulders, knees and ankles. After nine months, this has not improved. Tests show negative for rheumatoid arthritis.

More

6. Relevant Tests/Laboratory Data, Including Dates

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

No previous medical history. Very healthy, athletic 34 year old male.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Ciprofloxacin 1000 mg timed release. Bayer
#2

2.	Dose or Amount	Frequency	Route
#1	1000mg	1 per day	po
#2			

3. Dates of Use *(if unknown, give duration) from/to (or best estimate)*
#1 01/10/2012 -- 01/11/2012
#2 -- --

4. Diagnosis or Reason for Use *(Indication)*
#1 Possible urinary track infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

CTU
NOV 26 2012

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

NOV 26 2012

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

8925114-01-00-02

494483

WATCH

professionals of adverse events and product problems

B5. Describe event or problem continued

Peripheral neuropathy condition has improved as of today, but still noticeable. Tendon and joint pain is worsening still.

DSS

NOV 26 2012

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

U. Individual Case Safety Report

9004685-01-00-01

CDER

TARY reporting of product problems and t use errors

on - Page 1 /2

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 498734

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☑ Female ☐ Male	125 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)* ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
10/01/2012	01/02/2013

5. Describe Event, Problem or Product Use Error

Took one dose of Levaquin TAB-500mg- for diangnosis of Bronchitis. Woke up in middle of night with severe pain in right calf. Called PCP the next morning and was issued a different antibiotic. Ended up at PCP on 10/23/12 because of continued pain in calf. Had MRI on leg and was found that had a muscle strain and sent me to Orthopedic specialist. Gave me 6 weeks of PT and ask that I return after that if not completely cleared up. Since October things have only gotten worse. Muscle aches in feet, legs and arms. All previous activies have been effected. Cannot drive or walk anything but short distances. Was previously healthy, active

More

6. Relevant Tests/Laboratory Data, Including Dates

10/1/12 Prescribed and took one dose of 500MG of Levaquin 10/2/12 Was woke in early morning hours with SEVERE oain in right leg. 10/23/12 saw PCP Had MRI on right leg 11/7/12 Saw orthopedic specialist and was put on 6 weeks of Physical therapy

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Have never smoked and drink socially. Was healthy and active before taking Levaquin. No heatlh issues previously.

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Leviquin 500 MG Ortho-McNeil-Janssen Pharmaceutica
#2

2.	Dose or Amount	Frequency	Route
#1	500MG tablet	once	po
#2			

3. Dates of Use *(if unknown, give duration)* from/to (or best estimate)
#1 10/01/2012 -- 10/01/2012
#2 -- --

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

4. Diagnosis or Reason for Use *(Indication)*
#1 Bronchitis
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID
unknown

E. SUSPECT MEDICAL DEVICE

1. Brand Name
Levaquin

2. Common Device Name
?

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
	?	☐ Health Professional
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. If Implanted, Give Date *(mm/dd/yyyy)*

7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

CTU
JAN 0 3 2013

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

JAN 03 2

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report



9004685-01-00-02

498734

ATCH

for VOLUNTARY reporting by health professionals of adverse events and product problems

B5. Describe event or problem continued

and had no health issues. Now trying to do everyday chores, etc take three times as long and are painful. At first Advil or Aleve seemed to help dull the aches and pain and have tried heat therapy as well. It is near impossible to sleep at night...cannot get comfortable to rest and fall asleep and now I wake up every night and takes me an hour to an hour and a half to fall back asleep. This medication is EVIL and should be taken off the market. I have told everyone I know to NEVER take this or any form of this mediacation. Always wondering if the damage caused by Leviquin is permament. My quality of like is gone! Always tired and in pain. Always wondering if one of my tendons is going to pop. My husband and I used to walk, garden,do yard work, bike ride, and I used to use my treadmill. I can no longer to these activities.

DS

JAN 03

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9145237

Individual Case Safety Report

9145237-01-00-01

CDER

/OLUNTARY reporting of events, product problems and product use errors

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 503890

The FDA Safety Information and Adverse Event Reporting Program

Internet Submission - Page 1/2

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 57 Years	☑ Female ☐ Male	140 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
07/26/2012	02/23/2013

5. Describe Event, Problem or Product Use Error

After taking levaquin for a total of 6 doses-taken at 11pm- for 6 night, my joints, knees, tendons and muscles began hurting. Mri's show minicus tears on both knees, not Present before. Joint stiffnesss and tendon pain in legs and arms and hands. Just recently 6 months later had tendon pops in both hands. Mind you these all occurred while i was sleeping, not active and pops were loud enough for someone to hear. As of today I still have problems which also includes 30 pound weight gain, very sore muscles very bad joint pain stomach and

More

6. Relevant Tests/Laboratory Data, Including Dates

M R I S

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 LEVAQUIN 500MGS
#2

2.	Dose or Amount	Frequency	Route
#1	1 PILL	1 A DAY	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 07/21/2012 -- 6 DOSES 6 DAYS 07/27/2012
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 URINARY TRACT INFECTION
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

GTU
FEB 26 2013

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DSS
FEB 26 2013

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

9145237-01-00-02

MEDWATCH

503890

For VOLUNTARY reporting by health professionals of adverse events and product problems

B5. Describe event or problem continued

intestinal distress. This drug may be good for others but all this drug did was incapacitate me. Take this and cipro off the market they are killing people.

DSS

FEB 26 2013

CaseID::9193328

Individual Case Safety Report

9193328-01-00-01

CDER

)LUNTARY reporting of
vents, product problems and
product use errors

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 506817

The FDA Safety Information and
Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 37 Years	☑ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
07/24/2012	03/23/2013

5. Describe Event, Problem or Product Use Error

Muscle waste Muscle weakness Muscle spasms/twitching Tendon pain Hip joint pain Jaw inflammation Elbow joint pain Flank pain Shoulder pain Neuropathy -random burning throughout body- Anxiety Heart palpations Digestive problems- not absorbing nutrients from foods Food sensitivities to gluten, soy, pork and sugar. Hair loss Weight loss of 21 lbs ear grit sore throat

CTU
MAR 25 2013

More

6. Relevant Tests/Laboratory Data, Including Dates

x-ray 07/2012 cat scan 08/2012 blood work 12/12

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

no preexisting medical conditions

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Cipro
#2

2.	Dose or Amount	Frequency	Route
#1	500 MG	2 times a day	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 07/17/2012 -- 07/18/2012
#2 --

4. Diagnosis or Reason for Use *(indication)*
#1 UTI that came back negative
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

MAR 25 201

Phone # (b) (6) E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Consumer/Non-Health	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9264824

Individual Case Safety Report

9264824-01-00-01

VOLUNTARY reporting of events, product problems and product use errors

CDER

Page 1 of 1

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse

FDA USE ONLY
Triage unit sequence # 510714

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	~~80~~ 79	☒ Female ☐ Male	150 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☒ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
7/7/12	4/23/13

5. Describe Event, Problem or Product Use Error

Doctor prescribed Levoquen, I was given the generic Levofloxacin 250 Mg Tablets, 1 Tablet by mouth once daily for 7 days.

Experienced swelling in my stomach and from rectum from constant diarrhea: On August I started experiencing hip pains eventually it went to other joints in my body; now I can't hardly walk

6. Relevant Tests/Laboratory Data, Including Dates

X-Rays 9/13/12 of Hip

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

allergies, asthmatic allergic to most antibiotics

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☒ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 LEVOFLAXIN, 250 Mg.

~~#1~~ (1) LEVOFLOXACIN

2. Dose or Amount	Frequency	Route
#1 250 Mg.	1 Tablet a day	# 2780
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 7/7/12 - 7/14/12
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

4. Diagnosis or Reason for Use *(Indication)*
#1 Bronchitis
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2 ☐ Yes ☐ No ☒ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

CTU
APR 30 2013

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

DRG

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

USA APR 30 20

Phone #	E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☒

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9292906

Individual Case Safety Report

9292906-01-00-01

'DER

OLUNTARY reporting of
events, product problems and
product use errors

Internet Submission - Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 512247

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☑ Female ☐ Male	200 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☑ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
11/22/2011	05/14/2013

5. Describe Event, Problem or Product Use Error

I was prescribed Levaquin for a mild urinary tract infection at 500mg - 1x per day dosages. I was given one pill after leaving the emergency room and the rest by prescription. By (b) (6) I began feeling light headed, loss of appetite, delerium, dehydrated, hallucinatory, slurred speech, rapid heart beat, anxiousness, and paranoia. After walking around like this all day, I was eventually taken back to this hospital later in the evening. Because I was still non coherent, they kept me in the psychiatric ward because they assumed I would be a threat to someone else or myself. While admitted, the hospital ran no blood tests or other

More

6. Relevant Tests/Laboratory Data, Including Dates

X-Rays taken on October 29, 2012.

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

African American female with one child. Allergies- iodine, Claritin allergy medicine, tomatoes and other fruits and vegetables with a high acidic

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Levaquin 500mg
#2

2.	Dose or Amount	Frequency	Route
#1	500mg	1xday	po
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 11/20/2011 -- 11/22/2011
#2 -- --

4. Diagnosis or Reason for Use *(Indication)*
#1 urinary tract infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Event Reappeared After Reintroduction?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name CTU
2. Common Device Name
3. Manufacturer Name, City and State MAY 15 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor DSS
MAY 15 2013

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

FORM FDA 3500 (8/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

9292906-01-00-02

512247

MedWatch

...health professionals of adverse events and product problems

B5. Describe event or problem continued

diagnostics to determine if any further damage had been done by the medicine. Instead they diagnosed me with psychological conditions and continued to give me psychotropic drugs of varying sorts. After being released on (b) (6) I did not notice any joint damage. However, the months ahead brought about joint pain in my knees. It worstened very quickly. On October 29, 2012, I was diagnosed with osteoarthritis. I am now suffering with this in my right hip and right shoulder as well.

DSS

MAY 15 2013

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

9292906-01-00-03

5122477

MEDWATCH

...th professionals of adverse events and product problems

B7. Other relevant history, including preexisting medical conditions continued

content. Previous smoker- 486 days of cessation. Alcohol use is minimal. Previous polynephritis diagnosis -one occasion-. I was treated and released in the ER.

DSS

MAY 15 2013

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9470480

Individual Case Safety Report

9470480-01-00-01

Consumer Report

VOLUNTARY reporting of events, product problems and product use errors

Page ~~1 of 2~~ CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 521320

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	31 Years (b) (6)	☑ Female ☐ Male	158 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/07/2012	08/19/2013

5. Describe Event, Problem or Product Use Error

I was prescribed ciprofloxacin twice, once in January 2012 and again in March 2012. As a result I have tingling, crawling and burning sensations. Additionally, I get sensations that I am shaking and vibrating internally. I also have buzzing, tremors, continuous muscle twitching, fatigue and muscle pain, tendon issues, nerve pain and debilitating burning sensations. I also developed a tremendous amount of anxiety. I STRUGGLE and SUFFER from peripheral neuropathy issues as a result of Cipro, every day of my life! Cipro has ruined my life!

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White Medical Conditions: None aside from Cipro damage Allergies: Important Information: RX Meds: OTC Meds:

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

(1)
#1 Name: ciprofloxacin
Strength: 500 mg
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pill	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 2 courses, totaling 1000 mg/day
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 For Urinary Tract Infections
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

CTU
AUG 20 2013

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
AUG 20 2013

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9486543

Individual Case Safety Report

9486543-01-00-01

Consumer Report

OLUNTARY reporting of vents, product problems and product use errors

CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

1/1

Page ~~1 of 2~~

FDA USE ONLY
Triage unit sequence # 522155

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	23 Years (b) (6)	☑ Female ☐ Male	135 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
05/17/2013	08/26/2013

5. Describe Event, Problem or Product Use Error

I took two 500mg ciprofloxacins. One May 17 at night then one the following morning. Talked to my doctor and was advised to stop the medicine. I have been experiencing joint popping, tendon pain, headaches, nausea, eye dryness, mouth dryness, muscle pain, fatigue, and depression since taking the medicine. I have limited moblility now that started upon taking the ciprofloxacin.

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:Black/African American Medical Conditions: Depression, fibroid breast tumours, costochrodritis Allergies: Anti inflammatory drugs. Important Information: RX Meds: OTC Meds: Food Based Mutivitamin prenatal One by rainbow light. Probiotics.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

(1)
#1 Name: Ciprofloxacin Antibiotic
Strength: Ciprofloxacin
Manufacturer: 500mg

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 tablet	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 05/17/2013 - 05/18/2013
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary Tract infection.
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1 05/04/2014	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU

3. Manufacturer Name, City and State

AUG 27 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
AUG 27 2013

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9496893

Individual Case Safety Report

9496893-01-00-01

...OLUNTARY reporting of ...ents, product problems and ...product use errors

Page 1 of 1

CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY

Triage unit sequence # 522664

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	75 Years (b) (6)	☑ Female ☐ Male	190 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
10/13/2010	09/03/2013

5. Describe Event, Problem or Product Use Error

On 10/12/2010 I was prescribed Avolex for bronchitis, I started having trouble walking, AN MRI showed shredded tendons. I had special orthotics put in my shoes and an ankle brace to walk. Now 08/31/13, my feet are numb, tingling and they burn and hurt. I have very little feeling in my toes. It appears that it is getting worse.

6. Relevant Tests/Laboratory Data, Including Dates

Beside the MRI, (11/24/2010) My Doctor has used a pin to test the nerves, there are some areas that I have no feeling at all. Not to much interest shown, I was told probably restless leg syndrome, no-one wants to hear AVOLEX caused this.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White Medical Conditions: Borderline Blood Pressure Allergies: Sulfa, IVP Dyes, MSG, artificial sweeteners, Avolex, Cipro, Important Information: Non smoker, non drinker RX Meds: AVAPRO 75mg OTC Meds: Vitamin d, 1000mg, CoQ10, 100mg, Lutein 20mg 3xwk,

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: AVELOX
Strength: 400mg
Manufacturer: Bayer/Schering

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 tablet	Once daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 10/12/2010 - 10/19/2010
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Bronchitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	00085-1733-01
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU

3. Manufacturer Name, City and State

SEP – 3 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS

State: (b) (6)

SEP 03 2013

Phone #	E-mail
(b) (6)	

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☑ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9517815

Individual Case Safety Report

9517815-01-00-01

(b) (6)

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523364

HUMAN SERVICES

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CDER

Form Approved: OMB No. 0910-0291
Expiration Date: 6/30/2015
(See PRA Statement on preceding general information page)

MedWatch Consumer Voluntary Reporting (FORM FDA 3500B)

Section A – About the Problem

What kind of problem was it? *(Check all that apply)*

- [X] Were hurt or had a bad side effect *(including new or worsening symptoms)*
- [ ] Used a product incorrectly which could have or led to a problem
- [ ] Noticed a problem with the quality of the product
- [ ] Had problems after switching from one product maker to another maker

Did any of the following happen? *(Check all that apply)*

- [ ] Hospitalization – admitted or stayed longer
- [ ] Required help to prevent permanent harm *(for medical devices only)*
- [X] Disability or health problem
- [ ] Birth defect
- [ ] Life-threatening
- [ ] Death *(Include date)*: SEP 10 2013
- [ ] Other serious/important medical incident *(Please describe below)*

CTU

Date the problem occurred *(mm/dd/yyyy)*

12/03/2012

Tell us what happened and how it happened. *(Include as many details as possible)*

I took one tablet at about 3pm for a urinary tract infection. Within one hour I felt my both feet tingling/burning. Then a few hours later I noticed that both my legs felt very warm and tender. At the time I just thought the antibiotic must be working. After going to

Continuation Page

List any relevant tests or laboratory data if you know them. *(Include dates)*

Continuation Page

For a problem with a product, including

- prescription or over-the-counter medicine
- biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies
- nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods
- cosmetics or make-up products
- foods (including beverages and ingredients added to foods)

Go to Section B

For a problem with a medical device, including

- any health-related test, tool, or piece of equipment
- health-related kits, such as glucose monitoring kits or blood pressure cuffs
- implants, such as breast implants, pacemakers, or catheters
- other consumer health products, such as contact lenses, hearing aids, and breast pumps

Go to Section C (Skip Section B)

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SEP 10 20

For more information, visit *http://www.fda.gov/MedWatch*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

(b) (6)

003

9517815-01-00-02

5233364

Section B – About the Products

(1)

Name of the product as it appears on the box, bottle, or package *(include as many names as you see)*
Levofloxacin

Name of the company that makes the product
Dr. Reddy's Lab

Expiration date *(mm/dd/yyyy)*	Lot number	NDC number
		55111028050

Strength *(for example, 250 mg per 500 mL or 1 g)*	Quantity *(for example, 2 pills, 2 puffs, or 1 teaspoon, etc.)*	Frequency *(for example, twice daily or at bedtime)*	How was it taken or used *(for example, by mouth, by injection, or on the skin)*?
		once daily	by mouth

Date the person first started taking or using the product *(mm/dd/yyyy)*: 12/03/2012

Date the person stopped taking or using the product *(mm/dd/yyyy)*: 12/03/2012

Why was the person using the product *(such as, what condition was it supposed to treat?)*
It was ordered by urologist for a urinary tract infection.

Did the problem stop after the person reduced the dose or stopped taking or using the product? ☐ Yes ☒ No

Did the problem return if the person started taking or using the product again? ☐ Yes ☐ No ☒ Didn't restart

Do you still have the product in case we need to evaluate it? *(Do not send the product to FDA. We will contact you directly if we need it.)* ☐ Yes ☒ No

☐ **Go to Section D (Skip Section C)**

Section C – About the Medical Device

Name of medical device

Name of the company that makes the medical device

Other identifying information *(The model, catalog, lot, serial, or UDI number, and the expiration date, if you can locate them)*

Was someone operating the medical device when the problem occurred?
☐ Yes
☐ No

If yes, who was using it?
☐ The person who had the problem
☐ A health professional *(such as a doctor, nurse, or aide)*
☐ Someone else *(Please explain who)*

For implanted medical devices ONLY *(such as pacemakers, breast implants, etc.)*

Date the implant was put in *(mm/dd/yyyy)*	Date the implant was taken out *(if relevant) (mm/dd/yyyy)*

☐ **Go to Section D**

DSS
SEP 10 201

Individual Case Safety Report (b) (6) 004

9517815-01-00-03

5233364

About the Person Who Had the Problem

Person's Initials	Sex	Age (at time the problem occurred) or Birth Date	Weight (Specify lbs or kg)	Race
(b) (6)	☒ Female ☐ Male	65	158	Caucasian

List known medical conditions *(such as diabetes, high blood pressure, cancer, heart disease, or others)*

high blood pressure, arthritis, history of thyroid cancer and glaucoma

Please list all allergies *(such as to drugs, foods, pollen, or others)*.

only levofloxacin

List any other important information about the person *(such as smoking, pregnancy, alcohol use, etc.)*

List all current prescription medications and medical devices being used.

Synthroid, Lisinipril, Vagifem, Timolol eye drops

Continuation Page

List all over-the-counter medications and any vitamins, minerals, supplements, and herbal remedies being used.

Calcium, baby aspirin, flexamin

Continuation Page

☐ *Go to Section E*

Section E – About the Person Filling Out This Form

We will contact you only if we need additional information. Your name will not be given out to the public.

Last name	First name
(b) (6)	(b) (6)

Number/Street	City and State/Province
(b) (6)	(b) (6)

Country	ZIP or Postal code
(b) (6)	(b) (6)

Telephone number	Email address	Today's date *(mm/dd/yyyy)*
(b) (6)	(b) (6)	09/09/2013

Did you report this problem to the company that makes the product (the manufacturer)?

☐ Yes ☒ No

May we give your name and contact information to the company that makes the product (manufacturer) to help them evaluate the product? ☒ Yes ☐ No

Send This Report by Mail or Fax

Keep the product in case the FDA wants to contact you for more information. Please do not send products to the FDA. Mail or fax the form to:

Mail:	Fax:
MedWatch Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857	1-800-332-0178 (toll-free)

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Thank you for helping us protect the public health.

For more information, visit *http://www.fda.gov/MedWatch*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

(b) (6)

002

9517815-01-00-04

523364

Continued Entries

CONTINUED ENTRY FOR: Tell us what happened and how it happened. *(Include as many details as possible)*

bed, I was awakened in the middle of the night with SEVERE legs cramps in both calves. The pain was so severe I couldn't move for a little while because my legs were rigid. It would let up and then reoccur. This went on for about 2 hours. I then jumped out of bed and tried to walk. This seemed to help a little, but my legs and body in general were still aching. First thing in the morning, I called the pharmacist, my urologist, and my primary to report what had happened. I only took one tablet when the reaction had occurred. But today (September 9, 2013), I still have burning sensation in both feet periodically, as well as discomfort in both calves, as well as my both shoulders. This mainly occurs in the afternoon and at night, when I feel it most.

Back to Form

CONTINUED ENTRY FOR: List any relevant tests or laboratory data if you know them. *(Include dates)*

Back to Form

CONTINUED ENTRY FOR: List all current prescription medications and medical devices being used.

Back to Form

CONTINUED ENTRY FOR: List all over-the-counter medications and any vitamins, minerals, and herbal remedies being used.

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SEP 10 20

Back to Form

CaseID::9563865

Individual Case Safety Report

9563865-01-00-01

Report

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 525601

Adverse Event Reporting Program

1/1 Page ~~1 of 2~~ CDER

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	62 Years (b) (6)	☑ Female ☐ Male	____ lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
02/01/2013	09/25/2013

5. Describe Event, Problem or Product Use Error
I had diareha for 3months.. 10 times a day! back in 2010.. 2013.. I have pain in arm.. hands thumb.. numbness, etc Protrusion in my lower lumbar L1

6. Relevant Tests/Laboratory Data, Including Dates
MRI cervical and lumbar 2013

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
Race:White Medical Conditions: Allergies: Wheat and Gluten Important Information: RX Meds: Armour Thyroid 60mg a day OTC Meds: Multiple.. Vit d3 Magnisium, Gaba

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: Cipro
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1	--	--
#2		

3. Dates of Use *(if unknown, give duration) from/to (or best estimate)*
#1 01/01/2010 - 12/30/2010
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Sinus problems.. bronchitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name CTU

3. Manufacturer Name, City and State SEP 26 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)
(b) (6)

DSS SEP 26 2013

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9586187

Individual Case Safety Report

9586187-01-00-01

Report

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 52L0211

The FDA Safety Information and Adverse Event Reporting Program

Page 1 of 2 CDER

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	37 Years (b) (6)	☑ Female ☐ Male	135 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
01/31/2008	10/01/2013

5. **Describe Event, Problem or Product Use Error**

I was first prescribed Levoquin (not the generic) 11/24/2006, 500mg and had dizziness, joint pain, fatigue, shortness of breath and a thyroid condition (graves disease) flared up after finishing the course. On 09/08/2007, I was prescribed Levoquin (again, not the generic), 750. Had dizziness, joint pain, weakness, tingling, shortness of breath. My legs buckled a couple times. On 1/31/2008, I was again prescribed 750 (not generic). The side effects were so unbearable this time, I begged my doctor to let me stop the course after several days (4?). I got psoriasis shortly afterwards, something I ...

6. **Relevant Tests/Laboratory Data, Including Dates**

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White Medical Conditions: Hypothyroidism Allergies: Levoquin Important Information: I was a smoker at the time RX Meds: Naturethroid, Cytomel OTC Meds: vitamin c, multi vitamin, fish oil

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

(1)
#1 Name: Levoquin
Strength: 500mg
Manufacturer:

LEVAQUIN

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 per day	Once daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 11/24/2006 - 11/30/2006
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Bronchitus
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

CTU

2. **Common Device Name**

OCT - 2 2013

3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)* 7. **If Explanted, Give Date** *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**

(b) (6)

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Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☑

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

9586187-01-00-02

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The FDA Safety Information and
Adverse Event Reporting Program

B.5. **Describe Event or Problem** *(continued)*

... hadn't had in over 30 years. The tingling in my arms and frequent numbness in one hand has never gone away, has gotten worse. I'm not able to crochet anymore and have constant discomfort in my arms, shortness of breath and weakness. All of this was ten times worse when I became pregnant later in the year (2008), my arms were constantly numb or tingling. My thyroid condition was never able to be treated again and I ended up having to have a thyroidectomy. They psoriasis persists and also didn't respond to treatment.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event) (continued)*

DSS
OCT 22

CaseID::9625932

Individual Case Safety Report

9625932-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and Adverse Event Reporting Program

Page 1 of 2

FDA USE ONLY
Triage unit sequence # 527308

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	57 Years (b) (6)	☑ Female ☐ Male	168 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
06/14/2013	10/11/2013

5. Describe Event, Problem or Product Use Error

Was prescribed Levoquin for Bronchitis. Took "one" tablet, woke up in the middle of the night from a terrible nightmare, screaming headache, all joints locked up in fetal position. With massage was able to open arms, walking has and still is strenuous, I ache constantly, headaches are terribly, joint pain, muscle pain is never ending, tendons tend to tear or feel as though they are. Depression sets in, I fight it off as best as I can, as I must continue on. I am trying not to let this get to me, but Ladies and Gentlemen, there are day's that I just can' t function. To go to the restroom is an ...

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White Medical Conditions: HEART ATTACK (3 STINTS IN AUG 2010. FISTULA BETWEEN BLADDER AND BOWEL, TO BE REPAIRED SOON. OTHER THAN WHAT I AM GOING THRU FROM THIS DRUG I AM HEALTHY OR WAS Allergies: POLLEN, FURINOL, GREEN PEPPERS Important Information: NO SMOKING
NO DRUGS
ONE FULL PREGNANCY ...

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: LEVOFLOXACIN
Strength: 500MG TAB WOCK
Manufacturer: ? NABP: 413978 ? H7EDEWR

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 10	Once daily	--
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 06/14/2013 -
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 ASTHMA ATTACK, BRONCHITIS
#2

6. Lot #	7. Expiration Date
#1 UNKNOWN	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID
64679-0545-02

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name CTU

3. Manufacturer Name, City and State OCT 15 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

DSS OCT 15 2013

Phone #	E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

9625932-01-00-02

527308

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RY reporting of
product problems

The FDA Safety Information and
Adverse Event Reporting Program

B.5. **Describe Event or Problem** *(continued)*

... enormous chore in and of itself. To bend your legs, arms, head in any fashion is near to impossible. I live with Freeze creams, heating ointments in hopes that they will help. Some days they do, some days it makes it worse! AT 58 I am scared that a life as most know is over. I was once healthy, hiked mountains, rode bikes on trails, worked out daily. All dreams of what was right now. I still work daily as I have to maintain my life, but I pay for it dearly at the end of each day! I want you to know that there are millions of us out here that have been floxed. This drug is a nightmare waiting to jump onto a new victim!

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... 1980 - HEALTHY RX Meds: ABIEN FOR SLEEP OTC Meds: DAILY VITAMIN, .81 BABY ASPRIN, OMEGA 3 GUMMY VITA, SUPER B COMPLEX, VITAMIN C, TIGER BALM, FREEZE MAX, ICE PACKS, HEATING PADS

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event) (continued)*

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OCT 15 2013

CaseID::9631942

Individual Case Safety Report

9631942-01-00-01

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See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 527634

...Safety Information and
Adverse Event Reporting Program

Page 1 of ~~2~~ 1

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	23 Years (b) (6)	☑ Female ☐ Male	113 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
09/05/2013	10/16/2013

5. **Describe Event, Problem or Product Use Error**

I took 5000 mg of Ciprofloxacin (500 mg twice a day for 5 days), and started experiencing numbness in my big toe on my left foot two days into the medication. After a month, the peripheral neuropathy started spreading to my other foot, calves and fingers. Currently, I have twitching and numbness in my legs, stiff and numb fingers/hands, and stiff forearms. My brain also feels foggy and I am having difficulty coming up with terms for certain words. The numbness and stiffness continues to spread. I am certain it is the Cipro since the numbness started briefly after I took the medication.

6. **Relevant Tests/Laboratory Data, Including Dates**

MRI, blood tests, and ultrasound were all normal

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:Asian Medical Conditions: Asthma, Graves Disease Allergies: Dust mites, furry animals Important Information: N/A RX Meds: N/A OTC Meds: B12 and Super B complex

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: Ciprofloxacin
Strength: 500 mg
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pill	Twice daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 09/03/2013 - 09/07/2013
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Urinary Tract Infection
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name**

3. **Manufacturer Name, City and State**

CTU
OCT 17 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**

(b) (6)

DSS
OCT 17 2013

(b) (6)

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::9639830

Individual Case Safety Report

9639830-01-00-01

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CDER Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 527957

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6)	57 Years (b) (6)	☑ Female ☐ Male	140 lb or kg
In confidence			

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☑ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
09/19/2013	10/18/2013

5. **Describe Event, Problem or Product Use Error**

I had a UTI that was treated with Macrobid first and when the symptoms persisted I was given Cipro. I became very sick on the Cipro with diarrhea and extreme fatigue. On the last day of the seven day course of Cipro, I developed a pain in my left calf muscle. The next day the pain was so bad that my whole leg hurt. I took a nap when I arrived home and when I woke up I developed numbness in my left arm and hand, the left side of my neck and face. It seemed to get better so I did not go to the doctor. Two days later it returned as pain and numbness on my left side again. I went to see a doctor ...

6. **Relevant Tests/Laboratory Data, Including Dates**

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White Medical Conditions: diabetes type 2
Allergies: Demerol, Statins Important Information:
RX Meds: Vivelle Dot OTC Meds: Fish oil

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: ciprofloxacin hcl
Strength: 250 mg
Manufacturer: ndc 16571-411-10 pack p

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 tablet by mouth two times da	Twice daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 09/10/2013 - 09/16/2013
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Urinary tract infection
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1 09/10/2014	ndc 16571-411-10
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name** CTU

3. **Manufacturer Name, City and State** OCT 21 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)* 7. **If Explanted, Give Date** *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
(b) (6)

DSS
OCT 21 2013

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

9639830-01-00-02

527957

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Adverse Event Reporting Program

B.5. **Describe Event or Problem** *(continued)*

... and was sent to the emergency room to be checked for a heart attack or stroke. After all the tests, my heart was declared to be fine but no cause for my pain was addressed. I have recurring pain, numbness, and severe fatigue. I was forced to check out of school by my physical condition. I believe that I have had a toxic reaction to Cipro that is still affecting my health.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event) (continued)*

DSS
OCT 21 2013

CaseID::9648927

Individual Case Safety Report

9648927-01-00-01

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Page 1 of 1

Form Approved: OMB No. 0910-0291, Expires: 12/31
See OMB statement on re

FDA USE ONLY
Triage unit sequence # 52861 2

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
In confidence	41	☑ Female ☐ Male	116 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
9/5/2013	9/27/2013

5. **Describe Event, Problem or Product Use Error**

While taking Cipro I actually felt worst. my body ached (especially back) still my back, neck, wrist, shoulder and ankles started making popping sounds. my back has sensations of burning (rear spine) my knees feel weak when I bend them forgetfulness, moody. And none of this is getting better.

6. **Relevant Tests/Laboratory Data, Including Dates**

none- I just know my body.

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

allergic to amox + pen. asthmatic-NO asthma Symptoms for 3 years. (no meds)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*
#1 Cipro 500mgs
#2

2. Dose or Amount	Frequency	Route
#1 500mgs	2X	Oral
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 9/01/13 – 9/07/13
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Urinary Tract Infection
#2

5. **Event Abated After Use Stopped or Dose Reduced**
#1 ☐ Yes ☑ No ☐ Do Ap
#2 ☐ Yes ☐ No ☐ Do Ap

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Do Ap
#2 ☐ Yes ☐ No ☐ Do Ap

6. **Lot #**
#1
#2

7. **Expiration Date**
#1
#2

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

1. **Brand Name** CTU
2. **Common Device Name**
3. **Manufacturer Name, City and State** OCT 25 2013

4. Model #	Lot #	5. Operator of Devi
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Profess ☐ Lay User/Patie
Serial #	Other #	☐ Other:

6. **If Implanted, Give Date** *(mm/dd/yyyy)*
7. **If Explanted, Give Date** *(mm/dd/yyyy)*
8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?** ☐ Yes ☐ No
9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

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OCT 252

G. REPORTER *(See confidentiality section on back)*

(b) (6)

Phone # (b) (6) E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No	Unemployed Home maker	☐ Manufacturer ☐ User Facility ☐ Distributor/Impo

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

CaseID::9690626

Individual Case Safety Report

9690626-01-00-01

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See OMB statement on reverse.

Adverse Event Reporting Program

2

FDA USE ONLY
Triage unit sequence # 530739

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	40 Years (b) (6)	☑ Female ☐ Male	150 lb or kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
08/29/2006	11/13/2013

5. Describe Event, Problem or Product Use Error

I began taking a 10 day course of the antibiotic Cipro on 8/23/06 and on 8/29/06 I began experiencing small fiber neuropathy symptoms of numbness, tingling, burning pain, decreased sensation in my legs, feet, hands and arms. I was diagnosed with a skin biopsy at the (b) (6) with moderately severe small fiber neuropathy on 12/7/08. At the time, we didn't associate the symptoms with the Cipro. Recent information published by the FDA brought this to my attention and I was able to secure my records from CVS to confirm that I was taking Cipro when this started. Over the last couple years I ...

6. Relevant Tests/Laboratory Data, Including Dates

12/7/08 Skin Biopsy at (b) (6) in (b) (6) (b) (6) positive for moderately severe, length dependent small fiber neuropathy. It should be noted that I had numerous tests that were normal, including diabetes testing, and tests for autoimmune diseases. All negative.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White Medical Conditions: Mild Asthma under good control without meds. Occasionally albuterol as needed when around an allergen. Allergies: dogs, cats, dust, horses Important Information: None. RX Meds: Currently, I am taking Estrodial and Progesterone for hot flashes. OTC Meds: Currently, I ...

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Ciprofloxacin
Strength: 250 mg
Manufacturer: Bayer

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 Ciprofloxacin	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 08/23/2006 - 09/01/2006
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary Tract Infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU

3. Manufacturer Name, City and State

NOV 14 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
NOV 14 2013

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

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The FDA Safety Information and
Adverse Event Reporting Program

B.5. **Describe Event or Problem** *(continued)*

... have developed new troubling symptoms that include tinnitus, hyperacusis and central nervous system damage. I am currently unable to work do to the illness created by the toxicity of this adverse reaction.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... am taking vitamins and supplements to restore my body back to health. Multivitamin, B complex, Provex CV from Mellaleuca, Kavinace for sleeping.

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event) (continued)*

DSS
NOV 14 2013

CaseID::9695879

Individual Case Safety Report

9695879-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

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FDA USE ONLY
Triage unit sequence # 53173

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	43 Years (b) (6)	☑ Female ☐ Male	160 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☑ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/07/2012	11/15/2013

5. Describe Event, Problem or Product Use Error

In early March 2012, I was prescribed Levaquin for a UTI. Within a week of finishing the drug, my ankle began to swell and I endured debilitating pain. Within 2 weeks, my other ankle was in the same condition. From March - July, I had several tests performed and many visits to my PCP, the ER, Urgent Care, a Neurologist, an Orthopedist, and a Physical Therapist. I was diagnosed with an adverse/allergic reaction to Levaquin, Tendonitis, Tendon Tear, Plantar Fasciitis, and Peripheral Neuropathy. In mid-July 2012, I went to my PCP because I was severely depressed due to my condition. She suggested ...

6. Relevant Tests/Laboratory Data, Including Dates

Many, many. I will gladly turn over my medical records!!!

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White Medical Conditions: Back issues (MRI's, CT Scans available), conditions listed in description associated with Levaquin Poisoning. Allergies: Fluoroquinolones. Important Information: None. RX Meds: Hydrocodone/Acetaminophen 10/325 as needed for back condition and pain associated with ...

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Levaquin
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 10 pills	Once daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 03/07/2012 - 03/16/2012
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary Tract Infection. Lot #, strength, Manufacturer/
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU

3. Manufacturer Name, City and State

NOV 18 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
NOV 18 20

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

531193

Individual Case Safety Report

9695879-01-00-02

PAGE)
reporting of
duct problems

Adverse Event Reporting Program

B.5. **Describe Event or Problem** *(continued)*

... antidepressants. In tears, I begged her to treat the PAIN instead. She prescribed 1,000 mg/day of Naproxin, along with 10/325 vicodin. Within two weeks, I was no longer wearing the boots during the day or the splints at night. I am neither pain-free, nor am I cured; but, my pain is reduced enough that I can function almost normally. I still take the pain medication as needed. I consider myself a success story compared to others I have read about. This drug is a KILLER! If not for my 4 children and the support of my husband & family, I surly would not be here today. The depression, caused by the pain from fluoroquinolones, is enough to end one's life. I read that 83 people were known to be disabled due to Peripheral Neuropathy associated with this family of drugs. I am not included in that number, which tells me this "study" is BS. I continue to work, but I certainly, absolutely positively, have been DISABLED by this drug. The quality of my life has been forever changed because of 10 poisonous pills. It may not seem that way on the outside because I am a strong person, but I have the medical records to prove it. Of all the doctors who treated me, only ONE was familiar with the Levaquin poisoning. Why is that? This family of drugs should be pulled from the market. It has already ruined thousands of lives.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)* *(continued)*

... Levaquin Poisoning. OTC Meds: Ibuprofen - as needed.

F. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)* *(continued)*

DSS
NOV 18 2013

CaseID::9723049

Individual Case Safety Report

9723049-01-00-01

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Y reporting of ...ict problems and product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 53227

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	33 Years (b) (6)	☑ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☑ Disability or Permanent Damage
☐ Life-threatening
☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
05/07/2013	11/26/2013

5. Describe Event, Problem or Product Use Error

I took a short three day course of Cipro for a urinary track infection. While taking the Cipro I had nausea, weakness, joint pain and headaches. A week later I tore my left achilles and peroneal tendon turning in the shower. There was no acute precipitating event, and I am an extremely healthy and fit 34 year old. I went to the orthopaedist who said that in addition to the damage to my left ankle, my right ankle also showed small tears in the achilles tendon. After the course of Cipro the full body joint pain continued, including carpal tunnel pain and nerve pain in my elbows, neither of which ...

6. Relevant Tests/Laboratory Data, Including Dates

MRI on Tuesday May 21st 2013
MRI and Ultrasound Tuesday September 24th 2013

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: None.

Allergies: Ragweed, dairy.

Important Information: I am an extremely fit and active person. I have NO history of tendon problems.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: CIPRO® (ciprofloxacin hydrochlo
Strength: 250 mg
Manufacturer: Bayer Healthcare Pharmaceuticals

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1	q 12 h	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 04/20/2013 - 04/22/2013
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary tract infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name
CTU

3. Manufacturer Name, City and State
NOV 27 2013

4. Model #	Lot #	5. Operator of Device
		☐ Health Professional
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Lay User/Patient
		☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)
DSS
NOV 27 2

Phone #	E-mail
(b) (6)	

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

53227

B.5. Describe Event or Problem *(continued)*

... I had before the Cipro. I wore an 'air-cast' for my torn left ankle tendons, and despite extensive physical therapy, the healing has been extremely slow. It is now more than six months since the Cipro, and I am only now able to walk without the brace and extreme pain. I have taken Cipro on a number of occasions previous to this without visible tendon damage and suspect that there is some type of 'lifetime load' at work, because this course was extremely short but completely devastating to my system. I continue to experience joint pain and have not yet been able to return to my formerly active lifestyle before the Cipro which included yoga, rock climbing, running, etc. -- for many months I've barely been able to walk!

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NOV 27 20

CaseID::9725540

Individual Case Safety Report

9725540-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

FDA USE ONLY	
Triage unit sequence #	032547

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	42 Years (b) (6)	☐ Female ☑ Male	175 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
06/17/2013	12/01/2013

5. **Describe Event, Problem or Product Use Error**

After taking a 6 day course of 500mg 2/day of Ciprofloxacin for a suspected UTI, I have developed tendon and body pain, peripheral neuropathies, insomnia (at times only being able to sleep for 3 hours a night), skin rashes, fatigue, urinary incontinence, sensitivity to medicines (corticosteroids, NSAIDs, & Clindamycin antibiotic), decreased sweating, difficulty regulating body temperature, and painful erections. I did not experience any side effects while taking the drug. The first effects began 2 days after the prescription ended. It has been 5 months since my last pill and I still have body ...

6. **Relevant Tests/Laboratory Data, Including Dates**

I have had scores of bllod tests in the last 5 months. The only irregularities have been a low vitamin B12 (I tested in the high normal range prior to the Cipro, and I am a meat eater), a high B6 after taking a B complex (based on the B12 results), and a low normal vitamin D. I have had these ...

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: Asthma as a younger person. I have not taken medications or had an incident in a decade.

Allergies: dogs, cats, jellyfish

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: Ciprofloxacin
Strength: 500mg
Manufacturer: Bayer

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pill	Twice daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 06/17/2013 - 06/22/2013
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Suspected Urinary Tract Infection
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name**

3. **Manufacturer Name, City and State**

CTU
DEC - 2 2013

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)* 7. **If Explanted, Give Date** *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**

(b) (6)

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2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☑

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

532547

B.5. **Describe Event or Problem** *(continued)*

... pains, a rash, and neuropathies. I have been to my Primary Care Physician on at least 6 occasions, as well as a podiatrist, rheumatologist, neurologist, nutritionist, dermatologist, and therapist. The doctors do not disagree that the Cipro caused my symptoms, but they have not been able to successfully treat me.

Individual Case Safety Report

9725540-01-00-02

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5302547

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

... levels checked regularly for the last 5 months.

Individual Case Safety Report

9725540-01-00-03

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532547

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... vitamin D, vitamin B12, melatonin, probiotics, vitamin C

Individual Case Safety Report



9725540-01-00-04

DSS
DEC 02

CaseID::9782749

Individual Case Safety Report

9782749-01-00-01

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r Report

reporting of
problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and
Adverse Event Reporting Program

1/3

FDA USE ONLY
Triage unit sequence # 534721

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	51 Years (b) (6)	☑ Female ☐ Male	175 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
12/06/2013	12/23/2013

5. Describe Event, Problem or Product Use Error

In (b) (6) I had experienced a headache for about 2 weeks. I had taken Aleve (1 per day and 2 on a couple of days during that time). After about 2 weeks I had 3 nosebleeds in one afternoon/evening. I had never experienced nosebleeds in my life and that coupled with the ongoing headache scared me since my mother had a brain aneurysm. I went to the ER where the Dr. diagnosed me with sinusitis which caused the headache & the Aleve had triggered the nosebleed. He prescribed Levaquin 500 mg, 1 tablet per day. About 3 days into the Rx I felt changes in my body including stiffness, sore muscles ...

6. Relevant Tests/Laboratory Data, Including Dates

I have had xrays twice and my dad has undergone xrays, CT scan, and numerous blood tests

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: None

Allergies: No known allergies to drugs prior to this time. Allergic to dust, mold, certain trees, certain cleaning supplies
---

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Levaquin
Strength: 500
Manufacturer: Dr. Reddy's Lab

#2 Name:
Strength:
Manufacturer:

(1)

2. Dose or Amount	Frequency	Route
#1 1 pill	Once daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*	5. Event Abated After Use Stopped or Dose Reduced?
#1 01/30/2012 - 02/06/2012	#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply
4. Diagnosis or Reason for Use *(Indication)*	8. Event Reappeared After Reintroduction?
#1 Prescribed at the ER for Sinusitis	#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1 01/29/2013	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name: CTU

2. Common Device Name: DEC 24 2013

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
DEC 24 20

Phone #	E-mail
(b) (6)	

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

534721

B.5. **Describe Event or Problem** *(continued)*

... and joints, unusual tiredness and the tendons in the backs of my heels hurt very bad when going downstairs. I felt like I had aged 15 years. I could not figure out what was wrong and started to analyze it in my head. This was 6 days into the Rx. The only thing different was the Levaquin, which I had never even heard of before that time. I got on my computer and sure enough I found all kinds of information from people who had the same symptoms that I was having and that some had permanent damage. I immediately discontinued use and reported it to my Dr. I was in perfect health to that time. Since taking Levaquin I have experienced ongoing pain in my joints and tendons, most pronounced in my ankles, knees and hips with pain also in my shoulders arms and hands, specifically fingers. I was in school at the time and maintaining a 3.86 GPA. After taking the Levaquin and experiencing the body aches and extreme tiredness, it felt like I could not focus on my studies or much of anything else. The final quarter that I was enrolled in school, I failed, which is not like me at all. I am a super achiever. I have had ongoing lethargy since that time. I also developed serious stomach & bowel problems after never having had any type of stomach problem in my life up to that point. I have had added to my medical records that I cannot take Levaquin, that I have severe adverse reactions to it. I feel 100% sure that the Levaquin is behind my medical issues and I have not felt the same since taking it. Just this week my father was hospitalized with Acute Renal Failure after having been prescribed Levaquin for an upper respiratory illness. He has bone cancer and has been doing prefectly well with it being in remission. Within 4 days of beginning his 750 mg Rx of Levaquin, he could not walk and had to start using a walker. He continued to deteriorate and was hospitalized with Acute Renal Failure. He has been told by 3 doctors that the Levaquin is the cause of his serious medical condition. One doctor had said he took it for one day himself and he could feel a change and immediately stopped taking it. Two of the doctors said they will not ever prescribe it again. They are continuing to run tests on my dad and he could well have permanent damage caused by the Levaquin. He is experiencing a tremendous amount of pain in his joints, rib cage and chest area and his back in addition to the pain in his legs which led to his not being able to walk without a walker. He was getting outside every day and tending to his chickens which they rely upon for eggs and income. He was physically active and easily able to motivate on his own without any assistance until he had been on the Levaquin for 4 days. I am convinced that we both had serious side effects and lasting damage related to the use of Levaquin for only a few days each.

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B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... controlled with allergy medicines and an inhaler on as needed basis
---
RX Meds: Loratidine 10 mg

OTC Meds:

Individual Case Safety Report



9782749-01-00-03

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DEC 24

CaseID::9803231

Individual Case Safety Report

9803231-01-00-01

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LUNTARY reporting of
nts, product problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 535644

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	53 Years (b) (6)	☑ Female ☐ Male	220 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
08/08/2013	01/06/2014

5. Describe Event, Problem or Product Use Error

This past summer I took Levofloxacin for a bladder and brochitis infection on a Friday. I woke up Saturday completely engulfed in pain. Every single part of my body hurt to move. I could hardly walk. The previous day I was completely pain free...had nothing wrong in my body to cause this pain what so ever. My doctor took me off it within 24 hours...yet the pain persisted. It was so awful I could not function. It hurt to lift or move or walk on my feet. I could not type. My hands experienced numbness. The pain was excrutiating. In the end, my doctor sent me to a rhuematologist, who put me on ...

6. Relevant Tests/Laboratory Data, Including Dates

what kind of tests and results? we just have the results from getting sick initally.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: (b) (6) diabetes, high blood pressure, DCIS survivor, stent in heart
daughter (b) (6) information: (b) (6) is 9 her date of birth. She started Levofloacin on 8/11/2013,
---

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Levofloxacin
Strength: 500 mg
Manufacturer: walmart

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 500 mg	Once daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 06/21/2013 - 06/22/2013
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 bladder infection and bronchitis
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

JAN - 7 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

Phone #	E-mail
(b) (6)	

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

5356414

B.5. **Describe Event or Problem** *(continued)*

... steroids. gradually I felt relief. But when I went off the steroids the pain came back. To this day, I am off the steroids (which made me gain 10 pounds) and suffer ongoing pains in areas of my body I never had before. My wrists and knees are especially affected. I cannot get up from sitting or lying down without crippling pain that makes me hobble until I walk for a while. After a while, as long as I keep moving I do not stiffen up. My vision also has been effected. From the time I took that medicine it felt as if my eyes were bulging out. I have trouble focusing now and cannot tolerate bright light. In the beginning I also experience a strange kind of dizziness. I would be walking and I felt like I was unstable. To this day, 7 months later I am still not pain free. I still cannot get up without stiffness, pain and discomfort. I still experience eye problems and weird unstability. I am under treatment with a rhuematologist, and trying to stay off of steroids. This Levofloxacin is a horrible medicine. On 8/11/2013, my 26 year old daughter was put on it for a bladder infection. She was in the hospital because the infection became toxic, and they had to do heavy duty treatment. She is handicapped and on four medicines and a VNS Siezure implant device to stop seizures. Once she went on Levofloxacin, it produced terrible, unusual siezures that had her throwing herself from the bed or couch. She had prolonged seizures lasting on and off for 1/2 an hour. Strange seizures we had never seen up to this point in time. We discontinued use of the Levofloxacin. To this day, the seizures are not completely gone, like they were prior to Levofloxacin. To combat her seizures, she was put on ONFI...but that caused an awful rash around her mouth. We were fearful it was eating away her skin. She was taken off of that, as well. I do not know if Levofloxacin reactions are hereditary...but it adversely affected both of us.

Individual Case Safety Report



9803231-01-00-02

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5356644

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... ampicillian (b) (6): None

Important Information: Never smoked, don't drink for both of us
---
RX Meds: (b) (6): simvastatin, carvidolol, plavix, ranexa, losartin, janumet, pantoprozole, meloxican (b) (6): lamictal, clonazepam, vimpat, lamictal, pantoprozole, glycolax
---
OTC Meds: (b) (6): black cohash, vitamin D, fish oil, CoQ Max, Cinnamon, Vitamin B complex, (b) (6): vitamin D,

Individual Case Safety Report

9803231-01-00-03

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CaseID::9870433

Individual Case Safety Report

9870433-01-00-01

...iet Consumer Report

CDER

...LUNTARY reporting of ...nts, product problems and product use errors

1/3

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 538545

The FDA Safety Information and Adverse Event Reporting Program

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	34 Years (b) (6)	☑ Female ☐ Male	112 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
07/22/2013	02/03/2014

5. **Describe Event, Problem or Product Use Error**

I was prescribed Ciprofloxacin on July 22, 2013 for a mild UTI. I took (3) 500 mg pills. This first pill I took was in the evening and had slightly disrupted sleep. I took the second pill the next morning, I felt jittery and anxious. I took the third pill that night and was not able to fall asleep until 5:30 am. I slept for one hour. This did not seem right to me along with other side effects I was experiencing, so I stopped taking the pills and contacted the physician who prescribed the medication. I was not able to sleep again for 48 hours after stopping the pills. The other side effects I ...

6. **Relevant Tests/Laboratory Data, Including Dates**

My doctor did not do any lab work.

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: Since taking Cipro I am still experiencing anxiety, insomnia, and chest pressure.

Allergies: Azithromycin (2011), Lexipro (2011), Claritin D (2010)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: Ciprofloxacin
Strength: 500 mg
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pill	Twice daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 07/22/2013 – 07/27/2013
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Urinary tract infection
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**
2. **Common Device Name**
3. **Manufacturer Name, City and State**

CTU
FEB – 4 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
Name: (b) (6)
Address:
City: State: US ZIP:

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FEB 04 20

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☑

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

538545

B.5. **Describe Event or Problem** *(continued)*

... experienced were: Serve anxiety, insomnia, suicidal thoughts, chest pressure, wrist/elbow/heel/calf pain & cramping, shaking, chills, sweats, nervousness, diarrhea, dry mouth, felt like my skin was crawling, tingling feeling in lips, nausea, no appetite, yeast infection, hair loss, twitching when trying to sleep, loss of period and very distant mood. I also felt burning sensation in my wrists. I lost 12 pounds in 3 weeks. The majority of the symptoms subsided after 3-4 months, however I am still experiencing anxiety, insomnia and chest pressure 6 months after taking medication. The anxiety is almost constant.

Individual Case Safety Report



9870433-01-00-02

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5385415

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... times per week and eat a very health diet (mostly organic).

RX Meds: None

OTC Meds: B-12 vitamin, Min Chex, Cultrelle probotic

Individual Case Safety Report



9870433-01-00-03

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FEB 04

CaseID::9908057

Individual Case Safety Report

9908057-01-00-01

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et Consumer Report

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nts, product problems and
product use errors

1/3

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 539537

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	30 Years (b) (6)	☑ Female ☐ Male	120 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/15/2013	02/11/2014

5. Describe Event, Problem or Product Use Error

I was prescribed a course of Cipro for a suspected urinary tract infection in March 2013. I only took 3 days worth, so 6 pills. Come to find out there was never bacteria present to begin with from the culture results. I have suffered since then, so the last 11 months, with bilateral achilles tendonosis, burning and shooting peripheral neuropathy in every area of my body, joint pains, plantar fascitis, and numerous back and neck problems and tinnitus. I did not have any of these issues prior to taking Cipro. I have lost my life as I knew it from this drug. It has affected my personal life, my ...

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: Stomach ulcers

Allergies: Nothing prior to this

Important Information:

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Ciprofloxacin
Strength: 250 mg
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 2 pills	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*	5. Event Abated After Use Stopped or Dose Reduced?
#1 03/12/2013 - 03/14/2013	#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

4. Diagnosis or Reason for Use *(Indication)*	8. Event Reappeared After Reintroduction?
#1 Suspected urinary tract infection	#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1 03/31/2015	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

CTU

2. Common Device Name

FEB 1 2 2014

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
Name: (b) (6)
Address:
City: State: ZIP:

DSS
7
FEB 1 2 20

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

B.5. **Describe Event or Problem** *(continued)*

5:39537

... work and my family. I had only been married for 6 months (I'm only 30 years old) when this happened and we were starting to try for a family. That is now on hold indefinitely while I try to heal from the horrible, life altering affects of this drug and who knows if or when that will evern happen. My life dreams have been shattered for three days of an antibiotic I was told was safe. In addition, when I first realized I was having a reaction I saw numerous doctors, not a one knows how to help someone who has been injured by these drugs. There is ZERO recourse for us and we are left trying to heal ourselves because no doctor can. These drugs are the farthest thing from safe that I can possibly think of!!!!!! In my personal opinion, and I'm sure the opinion of all the other people who have been life-alteringly harmed from these drugs, all Fluoroquinolones need to be removed from the market and FAST!!!

Individual Case Safety Report

9908057-01-00-02

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539537

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... nightmare

Individual Case Safety Report

9908057-01-00-03

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FEB 12

CaseID::9924828

Individual Case Safety Report

9924828-01-00-01

ernet Consumer Report

VOLUNTARY reporting of events, product problems and product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/20
See OMB statement on revers

FDA USE ONLY
Triage unit sequence # 541015

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	42 Years (b) (6)	☑ Female ☐ Male	125 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
11/25/2013	02/21/2014

5. Describe Event, Problem or Product Use Error

I was on a 10 day dose of Levawuin for persistAnt bronchitis. I have been on Levaquin quite a few times in the past 3-4 years. About day 7 I started to feel this vibration in my back with every movement and a bit of vertigo. It has persisted since. Muscle weakness in my legs and arms. Tiredness.

6. Relevant Tests/Laboratory Data, Including Dates

I have seen two chiropractors , at least 12 visits. Chest x-ray, blood work, full spine MRI, EKG. Everyone says it's that I need to relax. I started seeing an Acupuncurist 3 weeks ago. I have had 3 good days since and the level of vibration is down by at to east half overall. I am also taking ...

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: None

Allergies: Grass and mold

Important Information: Wine every night, intense exercise every day, never smoked, eats an amazing die

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Levaquin
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1	Once daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 11/21/2013 - 11/30/2013
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Bronchitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn Apply
#2 ☐ Yes ☐ No ☐ Doesn Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn Apply
#2 ☐ Yes ☐ No ☐ Doesn Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

CTU
FEB 24 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professiona ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

DS
FEB 24

Phone #	E-mail
(b) (6)	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☑ Manufacturer ☐ User Facility ☐ Distributor/Importe

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

... milk thistle to cleanse my liver.

541015

Individual Case Safety Report



9924828-01-00-02

DS
FEB 24

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

541015

... Spironlactone for skin, synthroid

OTC Meds: 3,0000/day d, milk thistle, multi vitamin

Individual Case Safety Report

9924828-01-00-03

DSS
FEB 24

CaseID::9971310

Individual Case Safety Report

9971310-01-00-01

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vents, product problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 541933

1/1

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	35 Years (b) (6)	☐ Female ☐ Male	180 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
01/22/2014	03/02/2014

5. **Describe Event, Problem or Product Use Error**

I was prescribed Levaquin for sinusitis on 1/22/14. I took a single 500 mg dose that night and had severe insomnia with rapid heartbeat. I discontinued using the drug, having taken only one pill. It is over 5 weeks later and I am still having trouble sleeping. 3-4 days after taking the drug I had pain in my calves and wrists. 5 weeks out I have moderate tendonitis in my right achilles. I am unable to hike or run, which were regular activities prior to taking the drug.

6. **Relevant Tests/Laboratory Data, Including Dates**

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: Iritis, History of Retinal Detachment

Allergies: No known drug allergies prior to incident.

Important Information:

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: Levofloxacin
Strength: 500 mg
Manufacturer: Teva

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 Tablet	Once daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 01/22/2014 – 01/22/2014
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Sinusitis
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1 0403380	#1 01/22/2015
#2	#2

9. **NDC # or Unique ID**
09566

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name**
CTD

3. **Manufacturer Name, City and State**
MAR – 5 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
(b) (6)
MAR – 5 2014

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☑

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID::10029666

Individual Case Safety Report

10029666-01-00-01

...et Consumer Report

...UNTARY reporting of ...ts, product problems and product use errors

CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse

Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 544097

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	51 Years (b) (6)	☐ Female ☑ Male	215 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/17/2014	03/20/2014

5. Describe Event, Problem or Product Use Error

In March 2011 I was prescribed Levaquin and Avelox with prednisone (contraindicated) for a sinus infection. In November 2011 I suffered a third tear to my right rotator cuff and a suspected tear to my right hip labrum which occured when I shifted the weight on my leg - nothing more. The last tear to my rotator cuff occurred as a result of picking up a 10 lb bag of groceries. The tear to my right rotator cuff was repaired in (b) (6). I tolerated the pain in my hip for more than two years with various diagnosis from different doctors, only one suspected a tendon tear, others suspected lower ...

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: High Blood Pressure, Atrial Fibrilation (developed after FQ prescriptions), Ulcerative Colitis, Peripheral Neuropathy.

Allergies: Augmentin - causes severe vommitting. All Floroquinolone Antibiotics, Biaxcin (severe diarrhea)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Levaquin
Strength:
Manufacturer: Johnson & Johnson

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pill	Three times daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 1 month
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Sinusitis. Levaquin prescribed by PCP, ENT prescribed Avelox
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

CTU
MAR 21 2014

4. Model #	Lot #	5. Operator of Device
		☐ Health Professional
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Lay User/Patient
		☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
MAR 21

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

544097

B.5. **Describe Event or Problem** *(continued)*

... back problems. On (b) (6) I had arthroscopic surgery on my right hip to try and reduce the amount of pain I was suffering. The surgeon discovered and repaired a torn hip labrum. This is the 6th tendon tear I have suffered as a result of Levaquin and Avelox. All have been reported along with the other events such as the development of Ulcerative Colitis and peripheral neuropathy. I suspect that these drugs played a role in the development of Atrial Fibrillation in 2012.

Individual Case Safety Report



10029666-01-00-02

DS

MAR 2

5/4/09

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... skin rash.

Important Information: occassional drinker. approximately 1 - 2 drinks daily (sometimes none).

RX Meds: Flecainide, Metoprolol, and Lialda. Daily aspirin.

OTC Meds: Aspirin, tylenol, ibuprofen as needed.

Individual Case Safety Report

10029666-01-00-03

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MAR 2 1

CaseID::10061618

Individual Case Safety Report

10061618-01-00-01

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...Y reporting of
...uct problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 545699

The FDA Safety Information and Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	35 Years (b) (6)	☑ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
08/01/2013	04/03/2014

5. **Describe Event, Problem or Product Use Error**

I am writing this for my daughter that had taken CIPRO for a urinary tract infection. The drug has affected her neurological system. She's in severe pain and cannot use her arms and she can barely walk. She has disorientation, blurred vision, peripheral neuropathy, tendon pain, depression, gut problems, and she continues to acquire more health problems as time passes. She has lost her job because she is disabled and cannot work any longer. I am writing this for her because she is unable to type or focus.

6. **Relevant Tests/Laboratory Data, Including Dates**

In the last 6 months she as been tested for autoimmune disease, rheumatoid arthritis, lupus. She has had so many blood tests I cannot count. She has also had x-rays and other such testing.

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: none before taking Cipro

Allergies: Fluoroquinolones, Seroids, NSAIDs.

Important Information: Ocassionally drank alcohol before Cipro---now, can't drink at all. She was

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name: cipro
Strength: unkown
Manufacturer: unknown

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1	Three times daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 1 day
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Urinary tract infection
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1 unknown	#1 08/01/2013
#2	#2

9. **NDC # or Unique ID**
unknown

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**
2. **Common Device Name**
3. **Manufacturer Name, City and State**

CTU
APR - 4 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)*
7. **If Explanted, Give Date** *(mm/dd/yyyy)*
8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?** ☐ Yes ☐ No
9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
(b) (6)
(b) (6)

DS
APR 04

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

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B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... None

OTC Meds: Mulitiple Vitamins, minerals, probiotics, fish oil, adrenal support.

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APR 0

CaseID::10061762

Individual Case Safety Report

10061762-01-00-01

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t problems and
errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 546676

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	46 Years (b) (6)	☑ Female ☐ Male	126 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
02/26/2007	04/03/2014

5. Describe Event, Problem or Product Use Error

In Feb of 2007 I took 4 pills of ciprofloxacin and I am now on disability due to the severe damage this antibiotic caused. I have suffered almost every single side effect listed. My most debilitating side effects are neurological damage, tendon/ligament damage and joint pain/stiffness. My digestive tract was badly damaged and I have problems with balance/coordination. Prior to this I was in the best physical shape of my life. I exercised regularly and could ski all day with my husband/children. The reaction I had was severe which is why I only took 2 days of a 10 day rx. Even after stopping ...

6. Relevant Tests/Laboratory Data, Including Dates

MRI's '09, '11, '13. EMGs '09, '13. Blood work ups, spinal, hip arthroscopy for a labral tear which occurred during a non weight bearing movement. Colonoscopy, Xrays, numerous rounds of physical therapy.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: Allergies, Von Willebrand's disease

Allergies: Sulfa antibiotics, Contrast dyes, Cipro/ Fluoroquinolones Mold, tree pollens, Sage, Dogs/cats
---

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: ciprofloxacin
Strength: 500 mgs
Manufacturer: generic

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pills	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 02/26/2007 – 02/28/2007
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Sinusitis
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU

3. Manufacturer Name, City and State

APR – 4 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*

7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

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PR 042

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

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B.5. Describe Event or Problem *(continued)*

... the medication i kept getting new and worsening symptoms during the days, weeks, months and years following use. Diagnosis of possible PLS in Nov of 2012 (after over 3 yrs and seeing 5 different neurologists/specialists in difficult to diagnose cases) although I am missing 2 key markers for this disease. The reason is because I suffered a medication toxicity/fluoroquinolone toxicity syndrome.

Individual Case Safety Report



10061762-01-00-02

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APR 04 2

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B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

... healthy children, Social drinker (wine and sometimes beer/ 3-5 drinks per week) before floxing, non drinker now.

RX Meds: Cane for walking No medications as I can't tolerate medications that I could before floxing due to cyp450 pathway damage to my liver
---
OTC Meds: Nasacort as needed. Also take vitamins (Bs, C, D, K2, CoQ10) krill oil, digestive enzymes, etc

Individual Case Safety Report

10061762-01-00-03

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APR 04 2

04/22/2014 10:27 (b) (6)
Individual Case Safety Report



10101517-01-00-01

(b) (6)

PAGE 01/0

547708

IVICES CDER

Form Approved: OMB No. 0910-0291
Expiration Date: 6/30/2015
(See PRA Statement on preceding general information page

MEDWATCH Consumer Voluntary Reporting (FORM FDA 3500B)

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Section A – About the Problem

What kind of problem was it? *(Check all that apply)*

- [X] Were hurt or had a bad side effect *(including new or worsening symptoms)*
- [ ] Used a product incorrectly which could have or led to a problem
- [ ] Noticed a problem with the quality of the product
- [ ] Had problems after switching from one product maker to another maker

Did any of the following happen? *(Check all that apply)*

- [ ] Hospitalization – admitted or stayed longer
- [ ] Required help to prevent permanent harm *(for medical devices only)*
- [X] Disability or health problem
- [ ] Birth defect
- [ ] Life-threatening
- [ ] Death *(include date)*: _____
- [X] Other serious/important medical incident *(Please describe below)*

CTU

APR 23 2014

Besides the severe and excruciating joint pain I am experiencing, my thyroid levels elevated off the charts. I take synthroid and ~~my levels have been steady for 2 years. Since taking levaquin~~ my thyroid levels are way off. My Dr. is very concerned.

Date the problem occurred *(mm/dd/yyyy)*

03/01/14

Tell us what happened and how it happened. *(Include as many details as possible)*

On March 1, 2014 (eight days into a ten day prescription of Levofloxacin 500 MG) I noticed that my right knee was starting to hurt. March 9, I went to ER because knee was so swollen. 35 cc's of fluid was removed from knee. Gout and bacteria tests were negative. ~~Over the next week the knee swelled up again and other joints began to hurt. Went to Orthopedic Surgeon – Dr.~~ (b) (6) ~~on March~~

Continuation Page

List any relevant tests or laboratory data if you know them. *(Include dates)*

Gout / Bacteria-Negative
Lyme Disease - Negative
~~Rheumatoid Arthritis – Negative (2 x)~~

Continuation Page

For a problem with a product, including

- prescription or over-the-counter medicine
- biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies
- nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods
- cosmetics or make-up products
- foods (including beverages and ingredients added to foods)

Go to Section B

For a problem with a medical device, including

- any health-related test, tool, or piece of equipment
- health-related kits, such as glucose monitoring kits or blood pressure cuffs
- implants, such as breast implants, pacemakers, or catheters
- other consumer health products, such as contact lenses, hearing aids, and breast pumps

DSS

Go to Section C (Skip Section B)

ADD 23 2

For more information, visit *http://www.fda.gov/MedWatch*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.



10101517-01-00-02

(b) (6)

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he Products

...ame of the product as it appears on the box, bottle, or package *(include as many names as you see)*

Levofloxacin

Name of the company that makes the product

Dr. Reddy's Lab

Expiration date *(mm/dd/yyyy)*	Lot number	NDC number
2/21/15	N/A	55111028050

Strength *(for example, 250 mg per 500 mL or 1 g)*	Quantity *(for example, 2 pills, 2 puffs, or 1 teaspoon, etc.)*	Frequency *(for example, twice daily or at bedtime)*	How was it taken or used *(for example, by mouth, by injection, or on the skin)*?
500 mg	10	one per day for 10 days	by mouth

Date the person first started taking or using the product *(mm/dd/yyyy)*: 2/21/14

Date the person stopped taking or using the product *(mm/dd/yyyy)*: 3/2/14

Why was the person using the product *(such as, what condition was it supposed to treat?)*

Bronchitis which persisted after a round of Zithromax (didn't go away so levaquin was prescribed)

Did the problem stop after the person reduced the dose or stopped taking or using the product? ☐ Yes ☒ No

Did the problem return if the person started taking or using the product again? ☐ Yes ☐ No ☒ Didn't restart

Do you still have the product in case we need to evaluate it? *(Do not send the product to FDA. We will contact you directly if we need it.)* ☐ Yes ☒ No

☐ *Go to Section D (Skip Section C)*

Section C – About the Medical Device

Name of medical device

Name of the company that makes the medical device

Other identifying information *(The model, catalog, lot, serial, or UDI number, and the expiration date, if you can locate them)*

Was someone operating the medical device when the problem occurred? ☐ Yes ☐ No

If yes, who was using it?

☐ The person who had the problem

☐ A health professional *(such as a doctor, nurse, or aide)*

☐ Someone else *(Please explain who)*

For implanted medical devices ONLY *(such as pacemakers, breast implants, etc.)*

DSS

Date the implant was put in *(mm/dd/yyyy)*	Date the implant was taken out *(if relevant)* *(mm/dd/yyyy)*
	APR 23

☐ *Go to Section D*

10101517-01-00-03

(b) (6)

on Who Had the Problem

(b) (6)	☐ Female ☒ Male	Age (at time the problem occurred) or Birth Date: 50 yrs. (b) (6)	Weight (Specify lbs or kg): 200 lbs.	Race: Caucasian

List known medical conditions (such as diabetes, high blood pressure, cancer, heart disease, or others)

High blood pressure
Hypothyroid

Please list all allergies (such as to drugs, foods, pollen, or others).

Naproxen

List any other important information about the person (such as smoking, pregnancy, alcohol use, etc.)

none

List all current prescription medications and medical devices being used.

Lisinopril, Levothyroxine, Otux-E Foam, (since ADR I have been using Ibuprofin-600mg, Gabapatin, percoset, vicodin). Continuation Page

List all over-the-counter medications and any vitamins, minerals, supplements, and herbal remedies being used.

CoQ-10, Magnesium 250mg., Intramax liquid vitamin supplement-started all of these after I realized my symptoms were f Continuation Page

☐ Go to Section E

Section E – About the Person Filling Out This Form

We will contact you only if we need additional information. Your name will not be given out to the public.

Last name: (b) (6)	First name: (b) (6)
Number/Street: (b) (6)	City and State/Province: (b) (6)
Country: United States	ZIP or Postal code: (b) (6)

Telephone number: (b) (6)	Email address: (b) (6)	Today's date (mm/dd/yyyy): 04/21/14

Did you report this problem to the company that makes the product (the manufacturer)?
☐ Yes ☒ No

May we give your name and contact information to the company that makes the product (manufacturer) to help them evaluate the product? ☒ Yes ☐ No

Send This Report by Mail or Fax

Keep the product in case the FDA wants to contact you for more information. Please do not send products to the FDA. Mail or fax the form to:

Mail:	Fax:
MedWatch Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857	1-800-332-0178 (toll-free)

DSS
APR 23 2

Thank you for helping us protect the public health.

For more information, visit http://www.fda.gov/MedWatch

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

10101517-01-00-04

(b) (6)

Entries

CONTINUED ENTRY FOR: Tell us what happened and how it happened. *(Include as many details as possible)*

March 14, MRI and x-ray showed nothing structurally wrong with the knee. At this time, I didn't associate my knee problem with Levofloxacin. I called my Family Practioner - Dr. (b) (6) and he ordered a blood test for Lyme and Rheumatoid Arthritis (March 24th). March 28th I went back to the Family Practioner - Dr. (b) (6) and he told me that both the Lyme and RA were negative. By this time my joints in both knees, both ankles, and both hips were so painful I had to walk with a walker. On March 28 a good friend came to visit me (he is a dentist). We were discussing my joint pain and he asked me if I had taken any medications lately, I told him I was prescribed Levofloxacin for Bronchitis at the end of February. He looked very concerned and told me that he had three patients who were severely effected by Levofloxacin, one of them is now in a wheelchair. We immediately began to research the drug and found that thousands of people have been injured by the Adverse Drug Reaction to Levofloxacin. Each day, pain has fluctuated in intensity and has now become very intense in both of my shoulders. I began to experience Peripheral Neuropathy in my right hand. On April 17th during the night my right hand swelled up to twice the size of my left hand I was in such intense pain, even pain medication didn't aleviate the excruciating burning, stabbing pain in my hand and shoulder. On April 19, Dr. (b) (6) put me on Gabapentin for the Peripheral Neuropathy. He set up an appointment with a Rheumatologist for April 21. We will see what happens from here.

Back to For

CONTINUED ENTRY FOR: List any relevant tests or laboratory data if you know them. *(Include dates)*

Back to For

CONTINUED ENTRY FOR: List all current prescription medications and medical devices being used.

Back to For

CONTINUED ENTRY FOR: List all over-the-counter medications and any vitamins, minerals, and herbal remedies being used.

DSS

APR 23 201

Back to For

CaseID::10101699

Individual Case Safety Report

10101699-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 547674

Adverse Event Reporting Program

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	52 Years (b) (6)	☑ Female ☐ Male	125 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
02/17/2010	04/22/2014

5. Describe Event, Problem or Product Use Error

I was prescribed ciprofloxacin for a simple UTI at an urgent care facility. 1000mg daily for ten days. Not having a UTI before, I wasn't surprised by the dosage or the duration of the recommended course of antibiotic. Within several weeks, I was having body wide muscular pains, nerve pain in my hands and feet, allodynia, insomnia, and fatigue. Prior to the course of antibiotics, I ran daily, hiked, skied, played tennis and golf, etc. Never had an ache or pain, was in great physical health. I was seen at (b) (6) within eight weeks of taking cipro. A definitive diagnosis wasn't made. Since ...

6. Relevant Tests/Laboratory Data, Including Dates

(b) (6): CBC: Iron deficiency. Scan of kidneys: kidney stones. MRI: normal. Lab work: normal. Thyroid tests: normal. Tests done in 2010.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

Medical Conditions: None previously. Now suffer from chronic wide spread muscle aches, nerve pain and other central nervous system problems.

Allergies: Ciprofloxacin

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Ciprofloxacin
Strength: Ciprofloxacin
Manufacturer: 500mg

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 500 mg twice daily	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 02/17/2010 - 02/26/2010
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary tract infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU
APR 23 2014

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*

7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
APR 23

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

s417674

B.5. **Describe Event or Problem** *(continued)*

... then, I've continued to regress, spend many days in bed, walk when I can, and try to maintain some semblance of a life. It's beyond my comprehension how a drug that is designed to improve a simple medical condition, can destroy a life. Since I've been sick, two other women who I personally know have had severe and debilitating reactions to ciprofloxacin, and one younger woman is recovering after tendon ruptures and six months on crutches. I got sick when I was 52. I'm currently 56.

Individual Case Safety Report



10101699-01-00-02

DSS
APR 23



10101699-01-00-03

547674

B.7. **Other Relevant History, Including Pre** *renal dysfunction, etc.) (continued)*

... Clonazepam as needed

OTC Meds: Magnesium Multi vitamin Cal/mag Probiotics

DSS
APR 23 201

CaseID::10264214

Individual Case Safety Report

10264214-01-00-01

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reporting of
t problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

1/3

Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 554920

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	29 Years (b) (6)	☑ Female ☐ Male	135 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
06/22/2013	06/23/2014

5. Describe Event, Problem or Product Use Error
I was taking cipro for a simple uti when I ruptured my Achilles I had to have surgery. I have since still suffered a year later with tendon and joint pain, headaches, buzzing/twitching in my legs and arms and fatigue. This drug is a poison.

6. Relevant Tests/Laboratory Data, Including Dates
Ruptured Achilles ...

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
Race:White

For additional information see B7 below.

DSS
JUN 24 2014

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: Antibiotic
Strength: Ciprofluxocin
Manufacturer: 500 mg

CTU
JUN 24 2014

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 30	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 06/09/2013 - 06/19/2013
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary tract infection
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
Name: (b) (6)
Address:
City: State: (b) ZIP: (b) (6)

USA

Phone #	E-mail
(b) (6)	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☑ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

554920

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

... June 22, 2013 I had surgery for it (b) (6)

Individual Case Safety Report



10264214-01-00-02

DSS

JUN 24 2014

544920

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Medical Conditions:

Allergies: Pollen, dust, mold, grass, cats,

Important Information:

RX Meds:

OTC Meds:

Individual Case Safety Report



10264214-01-00-03

DSS
JUN 24 2014

CaseID::10264284

Individual Case Safety Report

10264284-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

1/3

...FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 554929

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	52 Years (b) (6)	☑ Female ☐ Male	99 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/01/2011	06/23/2014

5. Describe Event, Problem or Product Use Error

Multiple Rx 500 mg Cirpo resulted in long term sever SVT (what ER diagnosed the heart issue as). Then took Levaquin, 500 mg/10 days and immediately neck sounded like cellophane crumpling, then knees then shoulders all make the same sound along with advancing pain. I had semi psychotic episodes for 6 months post Levaquin. Extreme mental 'fog' resulting in inability to work at all. Lost word recall. Extreme fatigue set in. Began blacking out for no reason. Have lost weight, down to 99 lbs at 5' 6 1/2". Lost muscle control and tone and use. Am unable to hold a small coffee mug without dropping ...

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

For additional information see B7 below.

DSS
JUN 24 2014

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Levaquin
Strength: 500 mg
Manufacturer: J&J

CTU
JUN 24 2014

#2 Name:
Strength:
Manufacturer:

2.	Dose or Amount	Frequency	Route
#1	1	Twice daily	Taken by mouth
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 10 days
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 sinusitis
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
Name: (b) (6)
Address:
City: State (b) (6) ZIP:

USA

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

554929

B.5. **Describe Event or Problem** *(continued)*

... it, can't lift anything. Legs are weak and can barely walk most days. I'm now bedridden going on 2 yrs later! I'm not getting any medical help because no one can figure out all the symptoms. These symptoms I just noticed are common to Levaquin and/or Cipro ADR's. My health is still declining with new electric shocks nearly rendering me unconscious, nerve pain so sever I would rather die. Heart goes 170 bpm lasting 12 hours and there is no warning or common denominators. I'm wasting away, screaming in pain, and am ignored by the medical community who do not want to connect the dots to their favorite drugs. I'm getting worse after 2+ yrs not any better. And I self paid for this slow death due to lack of insurance. I have lost my home, my savings, my work. Now I cannot get any medical help because I'm poor. I'm 56 yrs old now. These drugs are dangerous but no one told me. No one. Prior to all this I had a 148 IQ, hiked the (b) (6) on weekends, was at the peak of a consulting career in large scale contracts. Had earned a Ph.D., CHt, Lean Six Sigma Black Belt. Studied Quantum Mechanics. Had been supporting my family since age 16. I was a dedicated, passionate, person who always took pride in being independent; ate clean, was very healthy. Rarely saw a Dr., until CO sinus problems hit me. I'm not able to get out of bed most days and have lost everything, work, assets, mind, body, soul.

Individual Case Safety Report



10264284-01-00-02

DSS

JUN 24 2014

554924

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Medical Conditions: SVT, chronic fatigue syndrome, fibromyalgia, RA, adrenal fatigue (these are all boxes the Dr can put the varied symptoms into), cognitive impairment NOS,
---
Allergies:

Important Information:

RX Meds:

OTC Meds:

Individual Case Safety Report

10264284-01-00-03

DSS
JUN 24 2014

CaseID::10395791

Individual Case Safety Report

10395791-01-00-01

CDER

: Consumer Report

JNTARY reporting of
s, product problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 560895

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	61 Years (b) (6)	☑ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
04/03/2014	08/13/2014

5. Describe Event, Problem or Product Use Error

I am a 62 year old healthy female. I was prescribed a 7 day course of cipro for a uti in March of this year. I experienced a slight rash but did not associate it with the Cipro. A week later, I was still experiencing UTI symptoms and was prescribed another 7 day couse of Cipro. on the second day, I broke out from my ears to my hips in a rash and scabby spots. I also was sore in all my joints. I stopped the medication and the rash subsided, but the soreness remained in my right shoulder. The pain disrupted my sleep as well as my functioning during the day. The pain and soreness have ...

6. Relevant Tests/Laboratory Data, Including Dates

Will have MRI on ...

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

Race:White

For additional information see B7 below.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: ciproflaxin
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 9 days
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary Tract infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU
AUG 15 2014

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS
AUG 15 2014

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

560895

B.5. Describe Event or Problem *(continued)*

... progressively gotten worse. Now, four months later it has progressed to the point of severely limited mobility, inability to sleep without pain and sleep medication, inabilty to drive or do anything requiring the use of that arm. I have been to an internist, chiropractor, naturopath, neuromuscular therapist and orthopedist. I have been treated with ultrasound and cold laser /tens therapy, opiates, nsaids, muscle relaxers and gabapentin. There has been no improvement in either function or pain. I will be getting an MRI tomorrow to check for tendon rupture and rotator cuff damage. My arm has atrophied and has radiating pain to the wrist. My fingers go numb during the night even when sleeping with my arm straight by my side. I have had four months of hell with no relief in sight. I ground my teeth so much at night from the pain that I had to have an emergency root canal. Prior to this, I was on no medication and was a very healthy and active person.

DSS
AUG 15 2014

560895

B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

... 8/14/14.

DSS

AUG 15 2014

2607945

B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Medical Conditions: none

Allergies: penicillin, fabric softener

Important Information: extremely healthy

RX Meds: tramadol, compounded cream (ketoprofin, gabapentin, dicl,bacl,amit)

OTC Meds: naproxin, unisom, ibuprofin

Individual Case Safety Report

10395791-01-00-04

DSS
AUG 15 2014

CaseID::10449524

Individual Case Safety Report

10449524-01-00-01

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)LUNTARY reporting of
ents, product problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 563866

The FDA Safety Information and
Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	30 Years (b) (6)	☐ Female ☑ Male	200 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
09/05/2014	09/10/2014

5. **Describe Event, Problem or Product Use Error**
See page 2 for complete text.

6. **Relevant Tests/Laboratory Data, Including Dates**
See page 3 for complete text.

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 4 for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*
#1 Name: Ciprofloxacin
Strength: Ciprofloxacin
Manufacturer: 500 mg

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pill/2 times a day	Twice daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 02/20/2014 - 03/04/2014
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Urinary tract infection
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**
2. **Common Device Name**
3. **Manufacturer Name, City and State**

CTU
SEP 11 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)* 7. **If Explanted, Give Date** *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
(b) (6)

DSS
SEP 11 201

Phone # (b) (6) **E-mail**

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

5638604

B.5. Describe Event or Problem *(continued)*

Bad reaction to ciproflaxin, vision changes, muscle weakness, joint stiffness, anxiety, panic attacks,sleep deprivation, tired feeling, peripheral neuropathy, nausea, diarrhea, and many other symptoms for over 6 momths.

Individual Case Safety Report



10449524-01-00-02

DSS
SEP 11 2014

5638664

B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

Blood test: positive rheumatoid factor June and September 2014

Individual Case Safety Report



10449524-01-00-03

DSS
SEP 11 2014

5638666

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: High blood pressure

Allergies: None

Important Information:

RX Meds: Escitalopram 10mg propranolol 60mg er

OTC Meds: Fish oil 3000 mg, multivitamin 1 per day, vitamin d 2000 mg, magnesium citrate 1000 mg

Individual Case Safety Report

10449524-01-00-04

DSS
SEP 11 2014

CaseID::10466297

Individual Case Safety Report

10466297-01-00-01

CDER

LUNTARY reporting of
nts, product problems and
roduct use errors

Form Approved: OMB No. 0910-0291, Expires: 6/30/2015
See PRA statement on reverse.

The FDA Safety Information and
Adverse Event Reporting Program

Page 1 of 3

Triage unit sequence # 564935

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
In confidence	51	☒ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT / PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy)
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☒ Disability or Permanent Damage ← muscle loss
☐ Congenital Anomaly/Birth Defect
☒ Other Serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
10-20-2011	9-13-2014

5. Describe Event, Problem or Product Use Error

on 10/20, 21, 22, 23, 25/2011 I took a 500 mg. dosage of Levaquin each of those days and starting 10/21/2011 I took 40 Prednisone 5 mg. tablets over a 9 day period because I had bronchitis the medicine caused immediate pain, burning + weakness in arms + hands, pain in left outside ankle, snapping sounds in shoulders, elbows + wrists and the start of muscle loss in shoulders, deltoids, biceps, elbows, forearms + wrists which has gotten worse since the start of this almost 3 yrs. ago.
on (b) (6) I went to the ER because I almost passed out while on the medicine

6. Relevant Tests/Laboratory Data, Including Dates

3/27/12 - x-rays of shoulders, cervical spine = normal
4/3/12 - NCS/EMG = mild bilateral carpal tunnel syndrome + not supportive of myopathy or C5-T1 radiculopathy on either side
11/21/13 - MRI cervical spine = mild disc space disease C5-6 C6-7
8/13/14 - NCS/EMG = mild carpal tunnel syndrome in wrist, minimal neuropathy in the teres minor muscle, no myopathy

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

blood tests from (b) (6) through 6/30/14 show the CPK with progressive elevated results but still in normal range

Allergic to penicillin + now allergic to Levaquin

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☒ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Name: Levofloxacin
Strength: 500 mg.
Manufacturer: Dr. Reddys Lab
#2 Name: Prednisone
Strength: 5 mg
Manufacturer: Actavis

bought at Rite Aid

2. Dose or Amount	Frequency	Route
#1 500 mg.	1 x daily	next day - 1 pill
#2 5 mg	first 3 days - 8 pills daily next 3 days - 4 pills daily next day - 2 pills	last day - 1 pill

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 10/20, 21, 22, 23, 25/2011
#2 10/21 - 29/2011

4. Diagnosis or Reason for Use (Indication)
#1 bronchitis
#2 bronchitis

6. Lot #	7. Expiration Date
#1 unavailable	#1 le info.
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☒ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction? stopped taking
#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2 ☐ Yes ☐ No ☒ Doesn't Apply

9. NDC # or Unique ID: unavailable

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name: CTU

2b. Procode

3. Manufacturer Name, City and State

SEP 19 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Unique Identifier (UDI) #	

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. CONCOMITANT MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER

1. Name and Address
(b) (6)
DSS

Phone # (b) (6)
E-mail
SEP 19 2014

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☒ No	retired teacher	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (2/13) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

↳ please notify the manufacturer, etc. I don't know how to do this.

CaseID::10472523

10472523-01-00-01

CDER

rnet Consumer Report

OLUNTARY reporting of
.vents, product problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 5652260

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	71 Years (b) (6)	☑ Female ☐ Male	170 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
08/19/2014	09/22/2014

5. Describe Event, Problem or Product Use Error
See page 2 for complete text.

6. Relevant Tests/Laboratory Data, Including Dates
See page 3 for complete text.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 4 for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: Levoflaxin
Strength: 750 mg
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount / Frequency / Route

	Dose or Amount	Frequency	Route
#1	1 pill per day	Once daily	Taken by mouth
#2			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 08/19/2014 - 08/29/2014
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary Tract Infection
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1 09/16/2015	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
CTU
SEP 23 2014

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)
SS
SEP 23 2014

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

5652660

B.5. Describe Event or Problem *(continued)*

I was prescribed the drug Levoflaxin 750 mg. for 10 days, one per day, by a nurse at my physician's office ((b) (6) (b) (6)). This was due to a recurrent UTI. This was done on the basis of a dip stick and not a culture as usual. I took the drug as noted from August 19th-29th. After a few days, I noticed stiffening of my knee joints and pains across my shoulders down to my elbows. I didn't think that it could be this medication. I became in severe pain after the drug was finished. I could not sleep, turn or even get off the toilet or up from a chair without assistance. I never too this medication before. A few days after I went to see an orthopaedist at (b) (6) Orthopaedic Center. I took the bottle with me. He said he needn't look any further than the drug as he had seen patients with this result before. He put me on a prednisone pack for 5 days and most of the symptoms dissipated. He gave me a second prescription to take after if the effects continued. It is Diclofenac sod ec 75 mg tabs to be taken twice daily. Now being afraid of side effects of anything, I just took ibuprofen instead. The shoulders got worse again and several days later, I took the prescribed drug. It has helped but I don't know how long I will have the symptoms after not taking those pills. I consulted a urologist who said they do not dispense Levoflaxin anymore and it would never be in that dosage for 10 days. I cannot tell you how many sleepless nights I spent. My Orthopaedist said there is no arthritis shown in my shoulders...but it might take a long time for the symptoms to go away. I began reading other reports of patients saying "they would rather die than take this drug again". I understand their plight by obviously it has not been reported to the FDA or the drug manufacturer making the side effect percentage highly inaccurate. I am in otherwise excellent health.

Individual Case Safety Report



10472523-01-00-02

DSS

SEP 23 2014

5665260

B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

X-rays of the shoulders September 3rd showed nothing.

Individual Case Safety Report



10472523-01-00-03

DSS
SEP 23 2014

5665260

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: mild-hypertension

Allergies: sulfa products

Important Information: non-smoker, non-drinker, none drug user
---
RX Meds: Levothyroxine Tab 0.05 mg (1x daily), Citalopram Tab 20 mg (1 x daily), Lisinopril-HCTZ Tab 10/12.5 (1 x daily), Simvastatin Tab 40 mg (1 x daily)

OTC Meds: Occasional chlorotrimetron, no vitamins or herbal remedies.

Individual Case Safety Report



10472523-01-00-04

DSS
SEP 23 2014

CaseID::10524464

Individual Case Safety Report

10524464-01-00-01

...umer Report ...RY reporting of ...luct problems and ...product use errors

CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 568082

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	33 Years (b) (6)	☑ Female ☐ Male	130 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
06/01/2014	10/10/2014

5. Describe Event, Problem or Product Use Error
See page 2 for complete text.

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 4 for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: Ciprofloxin (Ciprofloxacin)
Strength: 500mg
Manufacturer: Bayer

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 500mg	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 05/29/2014 - 05/31/2014
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 I was prescribed the cipro for a urinary tract infection.
#2

5. Event Abated After Use Stopped or Dose Reduced?	8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☑ No ☐ Doesn't Apply	#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply	#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

CTU
OCT 15 2014

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)
ZIP: (b) (6)

DSS
OCT 15 2014

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

568082

B.5. Describe Event or Problem *(continued)*

At the end of May, 2014 I took a course of Cipro antibiotics for a urinary tract infection. After taking the medication for approximately 3 days, I began to develop crippling pain in my legs: nerve tingling and shooting pains, sensitivity of my skin (as though it were sunburned, but with no exposure to the sun). I stopped taking the medication, but for weeks I couldn't walk properly. The tendons in my legs, and my Achilles tendons in particular, felt extremely tight. For months I felt as though I had heavily exerted my muscles and had difficulty doing basic tasks, like climbing stairs, despite the fact that I could not exercise. It was as though I had aged 50 years overnight. The symptoms have gradually become less intense, but they re-emerge on occasion, especially after I attempt to resume a normal exercise regimen. The sensitivity in my skin (usually between my lower back and my knees) returns even more frequently, and according to no particular pattern that I can decipher. When my skin is sensitive, even wearing clothes and sitting down in painful.

Individual Case Safety Report



10524464-01-00-02

DSS
OCT 15 2014

568082

B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: None.

Allergies: None

Important Information: At the time of taking this medication i was in excellent health.

RX Meds: None

OTC Meds: I take fish oils.

Individual Case Safety Report



10524464-01-00-03

DSS
OCT 15 2014

Individual Case Safety Report

10589537-02-00-01

Form Approved: OMB No. 0910-0291, Expires: 6/30/2015
See OMB statement on reverse.

...ıser-facilities,
...ors and manufacturers
...TORY reporting

Mfr Report # ZYD-14-AE-353

UF/Importer Report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event:	3. Sex	4. Weight
(b) (6) In confidence	or Date of Birth: (b) (6)	☑ Female ☐ Male	____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: ____ *(mm/dd/yyyy)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
- ☑ Disability or Permanent Damage
- ☐ Congenital Anomaly/Birth Defect
- ☑ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of This Report *(mm/dd/yyyy)*
2013 - 2014	01/08/2015

5. Describe Event or Problem

On 11/07/2014, Zydus Pharmaceuticals was contacted by a currently 30 year-old, female consumer (Initials: (b) (6) DOB: (b) (6)) regarding adverse events she experienced while taking Zydus's levofloxacin 250 mg tablets (Lot # & Expiry: unknown). Her medical history is significant for a urinary tract infection in 2013 and she has no known allergies. Concomitant therapy included: Lo-estrin (strength: unknown), taken daily since ~2010. Current medication therapy includes: Lo-estrin, vitamin D3, magnesium threonate, Co-Q 10, vitamin B complex, vitamin B1, taurine, vitamin C, zinc, ginkgo biloba, garlic, an unknown probiotic and glucosamine. On 05/22/2013, she began therapy with Zydus's levofloxacin 250 mg tablets, one tablet by mouth, daily for ten days, for a urinary tract infection. She discontinued therapy with Zydus's levofloxacin 250 mg tablets on 06/01/2013 after completing the ten day regimen. Approximately two weeks later (~06/05/2013), during a yoga class, she developed excruciating pain in her right ankle. After two days, the pain got worse and it "felt like her heel was detaching from her foot." She was seen by an orthopedic physician who referred her for x-rays. The (continued)

(Continue on page 3)

6. Relevant Tests/Laboratory Data, Including Dates

Relevant laboratory Data:
06/2013: x-rays showing strained Achilles tendon

(Continue on page 3)

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Medical History: urinary tract infection (2013)

Allergies: fluoroquinolones (reaction: strained Achilles tendon)

(Continue on page 3)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. Name *(Give labeled strength & mfr/labeler)*
- #1 levofloxacin 250 mg tablets (Zydus Pharmaceuticals)
- #2

2. Dose, Frequency & Route Used	3. Therapy Dates *(If unknown, give duration) from/to (or best estimate)*
#1 250 mg, Daily, Oral	#1 05/22/2013 - 05/31/2013
#2	#2

4. Diagnosis for Use *(Indication)*
- #1 Urinary tract infection
- #2

5. Event Abated After Use Stopped or Dose Reduced?
- #1 ☐ Yes ☑ No ☐ Doesn't Apply
- #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Exp. Date
#1 Unknown	#1 Unknown
#2	#2

8. Event Reappeared After Reintroduction?
- #1 ☐ Yes ☐ No ☑ Doesn't Apply
- #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# or Unique ID

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

Lo-estrin (Strength: unknown, Dates: ~2010 - ongoing)

(Continue on page 3)

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name	2b. Procode

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Unique Identifier (UDI) #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

(Continue on page 3)

E. INITIAL REPORTER

1. Name and Address

Confidential, USA

DSS
JAN 21 2015

Phone #	Email Address

2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA
☐ Yes ☑ No	NA	☐ Yes ☑ No ☐ Unk.

JAN 20 2015

CaseID::10589537

Individual Case Safety Report

10589537-02-00-02

FDA USE ONLY

1. **Check One** ☐ User Facility ☐ Importer

2. **UF/Importer Report Number**

3. **User Facility or Importer Name/Address**

4. **Contact Person**

5. **Phone Number**

6. **Date User Facility or Importer Became Aware of Event** *(mm/dd/yyyy)*

7. **Type of Report** ☐ Initial ☐ Follow-up # _____

8. **Date of This Report** *(mm/dd/yyyy)*

9. **Approximate Age of Device**

10. **Event Problem Codes** *(Refer to coding manual)*
Patient Code _____ - _____ - _____
Device Code _____ - _____ - _____

11. **Report Sent to FDA?** ☐ Yes _____ *(mm/dd/yyyy)* ☐ No

12. **Location Where Event Occurred** ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: _____ *(Specify)*

13. **Report Sent to Manufacturer?** ☐ Yes _____ *(mm/dd/yyyy)* ☐ No

14. **Manufacturer Name/Address**

G. ALL MANUFACTURERS

1. **Contact Office (and Manufacturing Site for Devices)**
Name: Zydus Pharmaceuticals, Inc
Address: 73 Route 31 North
Pennington, NJ 08534-3601
United States
Email Address:

2. **Phone Number** (609) 730-1900

3. **Report Source** *(Check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☑ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other:

4. **Date Received by Manufacturer** *(mm/dd/yyyy)* 01/07/2015

5. (A)NDA # 77-652 IND # _____ BLA # _____ PMA/510(k) # _____ Combination Product ☐ Yes Pre-1938 ☐ Yes OTC Product ☐ Yes

6. **If IND, Give Protocol #**

7. **Type of Report** *(Check all that apply)* ☐ 5-day ☐ 30-day ☐ 7-day ☐ Periodic ☐ 10-day ☐ Initial ☑ 15-day ☑ Follow-up # 1

8. **Adverse Event Term(s)** Tendon injury, Pain in extremity, Neuropathy peripheral, Disability, Anxiety, (continued)

9. **Manufacturer Report Number** ZYD-14-AE-353

H. DEVICE MANUFACTURERS ONLY

1. **Type of Reportable Event** ☐ Death ☐ Serious Injury ☐ Malfunction

2. **If Follow-up, What Type?** ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation

3. **Device Evaluated by Manufacturer?** ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code: _____

4. **Device Manufacture Date** *(mm/yyyy)*

5. **Labeled for Single Use?** ☐ Yes ☐ No

6. **Event Problem and Evaluation Codes** *(Refer to coding manual)*
Patient Code _____ - _____ - _____
Device Code _____ - _____ - _____
Method _____ - _____ - _____ - _____
Results _____ - _____ - _____ - _____
Conclusions _____ - _____ - _____ - _____

7. **If Remedial Action Initiated, Check Type** ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/Adjustment ☐ Other: _____

8. **Usage of Device** ☐ Initial Use of Device ☐ Reuse ☐ Unknown

9. **If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:**

10. ☐ **Additional Manufacturer Narrative** and / or 11. ☐ **Corrected Data**

DSS
JAN 21 2015

This section applies only to requirements of the Paperwork Reduction Act of 1995.
The public reporting burden for this collection of information has been estimated to average 66 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Office of Chief Information Officer
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JAN 20 2015

Individual Case Safety Report

10589537-02-00-03

ATION PAGE)
user-facilities,
ors, and manufacturers
TORY reporting

FORM FDA 3500A (2/13) (continued)

Back to Item B.5

B.5. **Describe Event or Problem** *(continued)*

doctor diagnosed a strained Achilles tendon related to levofloxacin exposure. Over the last year and a half, she has developed peripheral neuropathy in both legs and can barely lift her left foot. She also complains of anxiety, insomnia, dizziness, a loss of balance, a "cognitive haze", and trouble with her gums. Her dentist believes the problem with her gums is related to levofloxacin. She also reports that she is no longer working and that she had to change her college studies from full time to part time. She states that the quality of her life is diminished and that she is limited in her activities. She treats her pain with supplements, acupuncture and is eating the "Paleo" diet. At the time of this report, despite discontinuation of therapy with Zydus's levofloxacin 250 mg tablets in 06/2013, the adverse events are ongoing. No further information was provided.

-Additional information: On 01/07/2015, Zydus Pharmaceuticals was contacted via mail with additional information. She states that she is "now allergic to fluoroquinolones." No further information was provided.

Back to Item B.6

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

Back to Item B.7

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Back to Item C.10 Back to Item D.11

Concomitant Medical Products and Therapy Dates *(Exclude treatment of event) (For continuation of C.10 and/or D.11; please distinguish)*

Other Remarks

G.8. Adverse Event Term(s)
Insomnia, Dizziness, Balance disorder, Feeling abnormal, Gingival pain, Quality of life decreased

DSS
JAN 21 2015

JAN 20 2015

CaseID::10637351

10637351-01-00-01

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RY reporting of
duct problems and
product use errors

CDER

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 574608

The FDA Safety Information and Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	60 Years (b) (6)	☑ Female ☐ Male	192 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
01/21/2014	12/03/2014

5. Describe Event, Problem or Product Use Error
See page 2 for complete text.

6. Relevant Tests/Laboratory Data, Including Dates
See page 3 for complete text.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 4 for complete text.

DSS
DEC 04 2014

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: Levofloxacin
Strength: 750 mg
Manufacturer: Zydus

CTU
DEC 04 2014

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 7 pills	Once daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 01/17/2013 - 01/22/2013
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 sinusitis/bronchitis
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)* 7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

574608

B.5. Describe Event or Problem *(continued)*

In January 2014 I was 4 pills into a Levaquin Rx for sinusitis/bronchitis when I had intense pain and stiffness around all my joints, severe diarrhea, and could barely get out of bed to get to the bathroom--this severe reaction lasted for days. Then my feet started tingling/burning and I had numbness in a couple of fingers in my right hand. I stopped the Levaquin after 4 or 5 pills after researching their side effects. The following week I was mobile enough to make it to the doctor who prescribed pain meds--I was still in significant pain for most of the year Returned to doctor in April 2014 and was prescribed gabapentin for neuropathy. I've been battling tendon pain all year and seen a rheumatologist. He ran a myriad of lab tests that came back normal except for a possible RA marker (very low) that he is watching. My Achilles tendons have been the worst affliction all year. In Sept 2014 left Achilles became very swollen and painful, MRI was ordered but I healed before the MRI was taken so I cancelled it. About 2 weeks ago the left Achilles got bad again, this time an MRI was done and showed a torn tendon. I'm now in a cast. Muscles or tendons around my other joints hurt daily. The neuropathy in my hands and feet is now gone. I had not been doing anything unusual when the tendon tore. I'm retired and my daily activities are normal (cleaning house, shopping, light yard work). I was an active adult until last January when Levaquin wreaked havoc on my body. I try not to be angry but it creeps in since I am now in a cast for a month due to torn tendon. DOCTORS MUST BE TOLD TO LIMIT THE USE OF FLUOROQUINOLONES to life threatening infections!!! CAN'T YOU PEOPLE DO SOMETHING ABOUT THIS! I belong to 4 Facebook support groups with thousands of fluoroquinolone victims, this is just a can of worms that eventually with bust wide open. There must be something you can do to impress upon doctors that this drug is lethal; it has it's place in the severest of infections only!!!!

Individual Case Safety Report



10637351-01-00-02

DSS

DEC 04 2014

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B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

MRI, 11-17-14, showed that left ankle has torn tendons; X-rayed on 12-2-14 at orthopedic's office (he didn't share results, but put me in a cast for 4 weeks, then I will go into a boot for a few more weeks)

Individual Case Safety Report



10637351-01-00-03

DSS
DEC 04 2014

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B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

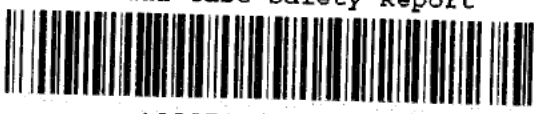
Race:White
Medical Conditions: hypothyroidism; was on medication for high blood pressure, but I lost weight this year due to the fluoroquinolone toxicity and my blood pressure is low enough to discontinue medication.

Allergies: sulfa drugs, pollen allergies

Important Information: non-smoker; occasional drinking

RX Meds: Armour Thyroid; hydrocodone for muscle/tendon pain as needed
---
OTC Meds: One-A-Day Women's Menopause, D3, B-100, MagOx, C

Individual Case Safety Report



10637351-01-00-04

DSS
DEC 04 2014

CaseID::10637469

Individual Case Safety Report

10637469-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 574723

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	25 Years (b) (6)	☐ Female ☑ Male	155 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
10/03/2014	12/04/2014

5. Describe Event, Problem or Product Use Error
See page 2 for complete text.

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 4 for complete text.

DSS
DEC 05 2014

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: Cipro
Strength: 500mg
Manufacturer:

CTU
DEC 05 2014

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 pill	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 09/28/2014 - 12/04/2014
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary Tract Infection
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

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B.5. Describe Event or Problem *(continued)*

I was prescribed Cipro for a UTI. About 5 days into the drug I began hearing voices in my head and was completely unable to sleep and began having burnin/loss of feeling in both my hands and feet. I had to stop the drug immediately. Over the last few months I have been battling tendinitis in both my hands and feet and chronic anxiety.



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DEC 05 2014

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B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: Asthma, IBS

Allergies: Penicillen, Sulfa

Important Information:

RX Meds: Flovent

OTC Meds: Multivitamin

Individual Case Safety Report



10637469-01-00-03

DSS
DEC 05 2014

CaseID::10693032

Individual Case Safety Report

10693032-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 577782

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	52 Years (b) (6)	☐ Female ☑ Male	145 lb or kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/01/2007	01/04/2014

5. Describe Event, Problem or Product Use Error
See page 2 for complete text.

6. Relevant Tests/Laboratory Data, Including Dates
See page 3 for complete text.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 4 for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: avelox
Strength:
Manufacturer:

CTU
JAN 05 2015

#2 Name: levaquin
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1	--	--
#2	--	--

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 03/01/2007 - 03/04/2007
#2 03/01/2009 - 03/07/2009

4. Diagnosis or Reason for Use *(indication)*
#1 sore throat
#2 not sure, flu or sinusitis, or UTI

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☑ No ☐ Doesn't Apply

6. Event Reappeared After Reintroduction?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☑ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

DSS
JAN 05 2015

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☑

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

577782

B.5. Describe Event or Problem *(continued)*

In 2007, I believe I had a strong reaction to being put on avelox by my MD to treat a sore throat. I noticed pretty soon after starting the medication, a heaviness in my feet. I tried to tough it out, but after about three or four days, I was having trouble walking. I called my MD and he told me that I was having peripheral neuropathy, and to immediately stop the medication which I did. My symptoms slowly got better, but never fully went away, which I can only describe as a tingling in my feet, like having novocaine there. In 2009, the same MD put me on levaquin. A little aside, my incomplete medical record also indicates that from 2003 to 2012, I have also been on cipro at least five times, as well as the avelox and levaquin. I have a sister and a cousin with raynaud's phenomena, which is poor microcirculation in the extremities. I am tall and thin, and have always felt that I have a predilection to Raynaud's. In March of 2009, when I was put on levaquin, I had the "normal" cold hands and feet in the winter, and the tingling that I was used to by now, BUT in the spring, as the weather warmed, I noticed that my feet were still really cold, and were actually numb. I am not one to go to doctor's easily, and I ignored this, until the fall of 2009, when I realized that this numbness was worsening and traveling up my legs. I saw this same MD, and told him what was happening, and he told me that he thought I had a B12 deficiency. He gave me a shot of B12, which he said should make me better,and then ran blood tests. The shot did nothing, and the tests came back negative for a B12 deficiency. He then sent me to a neurologist. The neurologist immediately wanted to rule out a brain tumor. Maybe because I wasn't ready to hear that, or maybe because I found this neurologist a little arrogant, and maybe because when I questioned why I had to use only a certain lab for the brain scan, and was told jokingly? by his front desk person "because he owns the lab", I chose not to have the scan. I lived with the progressive numbness for a while, (which was slowly getting worse, and traveling up my shins to my knees), and ultimately decided to see another neurologist. This neurologist did a ton of blood testing from Lyme's disease to diabetes to heavy metal poisoning to raynaud's testing, as well as emg's, etc, all of which came back negative (except for a slightly slower than normal emg transmission rates in my lower legs, which was close to normal and did not concern him. I later went to yet a third neurologist, who also ran a lot of test, including emg' s, HIV, and two spinal mri's and skin graft tests, all of which again were normal. She told me that I did not have MS, which had been a concern of mine. In the meanwhile, my numbness was progressing, and was now affecting my hands slightly as well. (I work with my hands, so I am very fearful that I might not be able to work in the future). I have always been a very fit guy, who eats a healthful diet, who used to go to the gym regularly. These days, I have trouble walking long distances, as my feet give out (they feel heavy, and I tire easily from walking), and I do light gym workouts, as I have less energy, and my legs will cramp up at night sometimes after a workout. Also, after a full day of work at my office, I am left exhausted. I am also sometimes awakened at night by leg cramps, always in the shin areas, and sometimes bilaterally, but much worse than normal "charley horse" type leg cramps, as it feels like bone pain, which can be pretty excrutiating. The incidence of this pain, has thankfully lessened with time, but it is very painful when it happens, which is now maybe once a month. Recent online research led me to discover fluoroquionolone toxocity, my self diagnosis.

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577782

B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

from 2009 till the present, all normal results: two emg's, skin biopsy, two mri's (spinal, different areas), lyme disease, heavy metals, auto immune diseases like raynaud's and MS, dfiabetes, HIV, B12 deficiency

Individual Case Safety Report



10693032-01-00-03

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B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: none

Allergies: none

Important Information: noine

RX Meds: none

OTC Meds: multi vitamin

Individual Case Safety Report



10693032-01-00-04

DSS
JAN 05 2015

CaseID::10694998

Individual Case Safety Report

10694998-01-00-01

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Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 577937

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	50 Years (b) (6)	☑ Female ☐ Male	271 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
	01/05/2015

5. Describe Event, Problem or Product Use Error
See page 2 for complete text.

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 2 for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name: Levaquin
Strength: 500mg
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1	Twice daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 over 20 years at various times
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 usually for bronchitis, sore throat,etc.
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

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4. Model #	Lot #	5. Operator of Device
		☐ Health Professional
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Lay User/Patient
		☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

DSS
JAN 06 2015

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer
		☐ User Facility
		☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

 Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

577937

B.5. Describe Event or Problem *(continued)*

Not until recently did I realize a lot of my medical problems were stemming from ingestion of Cipro and Levaquin (which I have taken at various intervals over the past 20 years or so,...usually for bronchitis...but also for UTI and other illnesses. My biggest problem and most painful one is the peripheral neuropathy that I have. I have no sensation of feeling in my feet...thus cannot stand or walk and I am always in a wheelchair. I get tingling in my fingers and "crawling" sensations in my arms. I have arthritis and muscle pains, anxiety, insomnia,memory loss, swollen legs, ankles and feet, increase of asthma while on the meds, etc.

Individual Case Safety Report



10694998-01-00-02

DSS
JAN 06 2015

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B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: Diabetes, high blood pressure,aortic aneuryam,low ferrritin
---
Allergies: Benedryl, augment tin, all penicillins, cephalosporins, Darvon, Latex allergy, IV dyes, certain anesthesias (not sure of the name), hazelnuts, crabmeat, swimming fish
---
Important Information: non smoker, no alcohol or drugs

RX Meds: Lopressor, Lasix, Metformin, Virt-Vite,ranitidine,baby aspirins
---
OTC Meds: Vit C,Vit D, Co Q 10,Alpha lipoic acid,

Individual Case Safety Report

10694998-01-00-03

DSS
JAN 06 201

CaseID::10732080

Individual Case Safety Report

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use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence # 579853

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	37 Years (b) (6)	☑ Female ☐ Male	137 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
12/20/2014	01/20/2015

5. **Describe Event, Problem or Product Use Error**
See page 2 for complete text.

6. **Relevant Tests/Laboratory Data, Including Dates**
See page 3 for complete text.

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*
See page 4 for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*
#1 Name: Levofloxacin
Strength: 750mg
Manufacturer: Aurobindo Pharm

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 1 tab	Once daily	Taken by mouth
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1 12/20/2014 - 12/26/2014
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1 Urinary tract infection
#2

6. Lot #	7. Expiration Date
#1	#1 12/19/2015
#2	#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC # or Unique ID**
65862-0538-20

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name**

3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
(b) (6)

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

CTU

JAN 21 2015

DSS

JAN 21 2015

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

579853

B.5. Describe Event or Problem *(continued)*

Prescribed generic Levaquin for UTI, by day 2, I had whole body aches and pains. Took a 7 day Rx of 750mg. Today is one month since my 1st dose and I have experienced the following symptoms: severe muscle weakness, leg & foot cramps, extreme pain in joints of hands, pain in tendons of wrists, swelling from knees down to toes, sharp/ stabbing pain in right side at waistline, electric shock sensation with extension of arm, numbness and tingling in fingers and toes, sharp pains in head behind eye sockets, frequent popping of bones in feet, knee, shoulder and elbow joint popping, constant cold in extremities (except following an episode of leg/foot cramping when within an hour both feet felt very fevered), insomnia, fatigue, inability to focus on thoughts or foggy brain, depression & anxiety due to the pain and not having answers as to why it was happening, lack of stamina/energy for regular day to day activities, lowered blood pressure, infection of skin at inside corner of one eye.

Individual Case Safety Report



10732080-01-00-02

DSS
JAN 21 2015

579853

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

12/30/14 - normal range or negative results for sedimentation rate, ANA screen w/reflex, rheumatoid factor, comprehensive metabolic panel 1/02/15 - Sjögren's syndrome

Individual Case Safety Report



10732080-01-00-03

DSS

JAN 21 2015

5779853

B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: Hashimoto's thyroiditis

Allergies: Sulfa

Important Information:

RX Meds: Synthroid, Vyvanse, Xanax

OTC Meds: N/A

Individual Case Safety Report



10732080-01-00-04

DSS
JAN 21 2015

CaseID::10936278

Individual Case Safety Report

10936278-01-00-01

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se errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #
583394

Adverse Event Reporting Program

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6)	42 Years (b) (6)	☑ Female ☐ Male	140 lb or ____ kg
In confidence			

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
12/05/2010	03/19/2015

5. Describe Event, Problem or Product Use Error

See additional page(s) for complete text.

6. Relevant Tests/Laboratory Data, Including Dates

See additional page(s) for complete text.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

See additional page(s) for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Levaquin
Strength: 500
Manufacturer:

DSS

#2 Name:
Strength:
Manufacturer:

MAR 20 2015

2. Dose or Amount	Frequency	Route
#1 7 pills	Once daily	Taken by mouth
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 5 days
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Bronchitis (first and only occurance)
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU

3. Manufacturer Name, City and State

MAR 20 2015

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

See additional page(s) for complete text.

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.



10936278-01-00-02

588394

I took five Levaquin pills in December of 2010. The antibiotic was prescribed for bronchitis. I could not finish the RX due to severe stomach and leg pain. Within days of stopping the medication I experienced severe muscle and nerve pain, neurapathy, eye pain and vision changes, tendonitis, night sweats, early menopause, and many other severe horomonal and neurological issues. For two years I was in severe pain. Years later I still have issues including chronic pain, severe tendonitis, and neuropathy. Since I have to use my hands for my job (administrative work on a keyboard) I am in pain each day. I am also unable to do many of the things I used to love, such as hiking, dancing, etc. Things have improved but in the over four years since I took the drug I have not gone back to normal. I was extremely healthy before taking this drug and it has absolutely changed my life for the worse.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

I was tested for everything from MS, the Lupus, to Lyme disease. I went to numerous doctors over a period of over a year. No one could find a cause other than the Levaquin.

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race: White

Medical Conditions: Hypothyroidism, Meniere's Disease (hearing loss).

Allergies: Cipro, hayfever, dust allergy.

Important Information: Vegetarian, active, very healthy prior to use.

F. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) *(continued)*

RX Meds: Synthroid, Cytomel, estogen, progesterone

OTC Meds: Vitamin D, biotin, multi-vitamin, DHEA

DSS
MAR 20 2015

CaseID::10997224

Individual Case Safety Report

10997224-01-00-01

CDER 5909G3

RVICES

Form Approved: OMB No. 0910-0291
Expiration Date: 6/30/2015
(See PRA Statement on preceding general information page)

MEDWATCH Consumer Voluntary Reporting (FORM FDA 3500B)

Section A – About the Problem

What kind of problem was it? *(Check all that apply)*

- [X] Were hurt or had a bad side effect *(including new or worsening symptoms)*
- [ ] Used a product incorrectly which could have or led to a problem
- [ ] Noticed a problem with the quality of the product
- [ ] Had problems after switching from one product maker to another maker

Did any of the following happen? *(Check all that apply)*

- [ ] Hospitalization – admitted or stayed longer
- [ ] Required help to prevent permanent harm *(for medical devices only)*
- [X] Disability or health problem
- [ ] Birth defect
- [ ] Life-threatening
- [ ] Death *(Include date)*: _____
- [X] Other serious/important medical incident *(Please describe below)*

SEVERE TENDINITIS IN LEFT FOOT MAKING WALKING IMPOSSIBLE FOR SEVERAL WEEKS. FATIQUE WAS VERY OVERWHELMING

CTU
APR – 7 2015

Date the problem occurred *(mm/dd/yyyy)*

JANUARY 4, 2015

Tell us what happened and how it happened. *(Include as many details as possible)*

SEVERE JOINT PAIN IN BOTH KNEES, HIP, SPINE AND NECK, BACK MUSCLES ACHED. AFTER INGESTING 10 of 14 500MG TABS OF CIPROFLOXACIN I EXPERIENCED DEBILITATING PAIN RENDERING ME BED RIDDEN TO CURRENT DATE OF 3/26/15

Continuation Page

List any relevant tests or laboratory data if you know them. *(Include dates)*

01/02/2015 urinanalysis indicated bacteria in urine.

Continuation Page

For a problem with a product, including

- prescription or over-the-counter medicine
- biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies
- nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods
- cosmetics or make-up products
- foods (including beverages and ingredients added to foods)

Go to Section B

For a problem with a medical device, including

- any health-related test, tool, or piece of equipment
- health-related kits, such as glucose monitoring kits or blood pressure cuffs
- implants, such as breast implants, pacemakers, or catheters
- other consumer health products, such as contact lenses, hearing aids, and breast pumps

Go to Section C (Skip Section B)

DSS
APR – 7 20

For more information, visit *http://www.fda.gov/MedWatch*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

EF



10997224-01-00-02

596963

ut the Products

clude as many names as you see)

(1) CIPROFLOXACIN HCL 500 MG TAB DEA# AR7414864

Name of the company that makes the product

WEST-WARD, INC

Expiration date *(mm/dd/yyyy)*	Lot number	NDC number
01/02/16		

Strength *(for example, 250 mg per 500 mL or 1 g)*	Quantity *(for example, 2 pills, 2 puffs, or 1 teaspoon, etc.)*	Frequency *(for example, twice daily or at bedtime)*	How was it taken or used *(for example, by mouth, by injection, or on the skin)*?
500 MG TAB	14 TABLETS	1 TABLET EVERY 12 HOURS	BY MOUTH

Date the person first started taking or using the product *(mm/dd/yyyy)*: 01/02/2015

Date the person stopped taking or using the product *(mm/dd/yyyy)*: 01/07/2015

Why was the person using the product *(such as, what condition was it supposed to treat?)*

URINARY TRACT INFECTION

Did the problem stop after the person reduced the dose or stopped taking or using the product? ☒ Yes ☐ No

Did the problem return if the person started taking or using the product again? ☐ Yes ☐ No ☒ Didn't restart

Do you still have the product in case we need to evaluate it? *(Do not send the product to FDA. We will contact you directly if we need it.)* ☒ Yes ☐ No

Go to Section D (Skip Section C)

Section C – About the Medical Device

Name of medical device

Name of the company that makes the medical device

Other identifying information *(The model, catalog, lot, serial, or UDI number, and the expiration date, if you can locate them)*

Was someone operating the medical device when the problem occurred? ☐ Yes ☐ No

If yes, who was using it?

☐ The person who had the problem
☐ A health professional *(such as a doctor, nurse, or aide)*
☐ Someone else *(Please explain who)*

For implanted medical devices ONLY *(such as pacemakers, breast implants, etc.)*

Date the implant was put in *(mm/dd/yyyy)*	Date the implant was taken out *(If relevant) (mm/dd/yyyy)*

Go to Section D

DSS
APR -7

...Case Safety Report

10997224-01-00-03

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...rson Who Had the Problem

Person's Initials	Sex	Age (at time the problem occurred) or Birth Date	Weight (Specify lbs or kg)	Race
(b) (6)	☒ Female ☐ Male	64	172 lbs	CAUCASIAN

List known medical conditions *(such as diabetes, high blood pressure, cancer, heart disease, or others)*

HYPOTHYROIDISM - HAYFEVER

OSTEOARTHTIS - PRONE TO CANDIDA ALBICAN INFECTIONS (YEAST)

Please list all allergies *(such as to drugs, foods, pollen, or others)*.

ALLERGIES TO TREE & GRASS POLLENS; RAGWEED; MOLD; DUSTMITES

List any other important information about the person *(such as smoking, pregnancy, alcohol use, etc.)*

NOT A SMOKER, ONLY OCCAISONAL WINE OR BEER

List all current prescription medications and medical devices being used.

NYSTATIN TABS ACETOMINOPHEN AS NEEDED FOR OSTEOARTHTIS

SYNTHROID .05 MG TAB

Continuation Page

List all over-the-counter medications and any vitamins, minerals, supplements, and herbal remedies being used.

-FISH OIL -B12 -GARLIC -CRANBERRY -MAGNESIUM
-TUMERIC -VITAMIN C -RESERVATROL -VITAMIN D -NONI

Continuation Page

➡ **Go to Section E**

Section E – About the Person Filling Out This Form

We will contact you only if we need additional information. Your name will not be given out to the public.

Last name	First name
(b) (6)	(b) (6)

Number/Street	City and State/Province
(b) (6)	(b) (6)

Country	ZIP or Postal code
U.S.A.	(b) (6)

Telephone number	Email address	Today's date *(mm/dd/yyyy)*
(b) (6)	(b) (6)	MARCH 26, 2015

Did you report this problem to the company that makes the product (the manufacturer)?
☐ Yes ☒ No

May we give your name and contact information to the company that makes the product (manufacturer) to help them evaluate the product?
☒ Yes ☐ No

Send This Report by Mail or Fax

Keep the product in case the FDA wants to contact you for more information. Please do not send products to the FDA. Mail or fax the form to:

Mail:	**Fax:**
MedWatch Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857	1-800-332-0178 (toll-free)

DSS
APR - 7 2015

Thank you for helping us protect the public health.

CaseID::10997224

10997224-01-00-04

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ad Entries

CONTINUED ENTRY FOR: Tell us what happened and how it happened. *(Include as many details as possible)*

March 26, 2015: In the last few days I've had severe muscle pain in upper chest, shoulder (right side) and mid-back. I continue to fatigue rapidly and especially after any physical exertion/exercise. I'm taking one 325MG TAB acetaminophen every four hours to alleviate pain. I've continued intake of listed vitamins on pg. 3.
Occasional dizziness occurs.
I'm still depending upon a cane to walk with since my knee joints are sore. I also experience a sharp pain occasionally in my right hip joint. Stiffness in leg muscles continues.
I continue bedrest daily with walking up & down stairs 2-3 times.
Swelling in left foot has subsided.

Back to Form

CONTINUED ENTRY FOR: List any relevant tests or laboratory data if you know them. *(Include dates)*

Back to Form

CONTINUED ENTRY FOR: List all current prescription medications and medical devices being used.

Back to Form

CONTINUED ENTRY FOR: List all over-the-counter medications and any vitamins, minerals, and herbal remedies being used.

OIL OF OREGANO

DSS
APR - 7 20

Back to Form

CaseID::11047971

Individual Case Safety Report

11047971-01-00-01

umer Report

RY reporting of
luct problems and
product use errors

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

The FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY
Triage unit sequence #
592742

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	64 Years (b) (6)	☑ Female ☐ Male	170 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☑ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☑ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
01/17/2015	04/16/2015

5. Describe Event, Problem or Product Use Error

See additional page(s) for complete text.

6. Relevant Tests/Laboratory Data, Including Dates

See additional page(s) for complete text.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

See additional page(s) for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

4. Name, Strength, Manufacturer *(from product label)*

#1 Name: ciprofloxacin
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1 5 pills	Twice daily	--
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 01/12/2015 - 01/15/2015
#2

4. Diagnosis or Reason for Use *(Indication)*
#1 Urinary tract infection
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☑ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU

3. Manufacturer Name, City and State

APR 17 2015

4. Model #	Lot #	5. Operator of Device
		☐ Health Professional
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Lay User/Patient
		☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

See additional page(s) for complete text.

G. REPORTER *(See confidentiality section on back)*

1. Name and Address

(b) (6)

DSS

APR 17 20

Phone #	E-mail
	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.



11047971-01-00-02

592742

Took cipro for uti. Having numbness in face and limbs. Weakness in legs. Stomach problems when eating certain foods. Insomnia. Twitching and burning throughout my body and general weakness. Been happening for three months and it continues.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

Blood work
Appointments with neurological doctor in May.

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race: White

Medical Conditions: High blood pressure. Thyroidcancer

Allergies: None

Important Information:

F. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) *(continued)*

RX Meds: Synthroid
Verapimil

OTC Meds: Vitamins. A. E. C.
Magnesium

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APR 17 2