**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

# Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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| **Product Name:** | Levaquin® (levofloxacin) |
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| **Application Type/Number:** | NDA 020634 |
| **Applicant/Sponsor:** | Janssen Pharmaceuticals, Inc. |
| **OSE RCM #:** | 2014-574 |

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## EXECUTIVE SUMMARY

In accordance with the FDAAA Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports of adverse events and drug utilization data for levofloxacin in pediatric patients.

Levofloxacin was first approved in 1998 and is indicated for pneumonia, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, skin and skin structure infections, chronic bacterial prostatitis, urinary tract infections, acute pyelonephritis, inhalational anthrax, and plague. The approved pediatric labeling is for inhalational anthrax and plague in patients 6 months of age and older.

We identified 32 pediatric cases of levofloxacin associated adverse events in the FDA Adverse Event Reporting System (FAERS) database received by the FDA from April 1, 2011, to March 31, 2014. As seen in previous reviews, musculoskeletal events continue to be one of the most frequently reported adverse events in pediatric patients. Additionally, hypersensitivity reactions (particularly allergic skin reactions) were also commonly noted in this review. Musculoskeletal events, hypersensitivity reactions, central nervous system (CNS) events, and hepatotoxicity are well characterized in the levofloxacin labeling under WARNINGS AND PRECAUTIONS.

This review did not identify any unlabeled, drug-related safety concerns that are clearly causally related to levofloxacin. The unlabeled events include single reports of cerebral edema, intestinal obstruction, and Raynaud's phenomenon. The extent of levofloxacin's contribution to cerebral edema and Raynaud's phenomenon cannot be assessed in light of the limited information provided in the case reports. Intestinal obstruction appears to be a complication of chemotherapy and not a levofloxacin-induced adverse event.

The pediatric death cases are confounded by patients who were administered levofloxacin to treat life-threatening diseases (i.e., CNS tuberculosis and meningitis), as well as multiple use of concomitant medications, making it challenging to assess the role of levofloxacin on the outcome of death. These patients were severely ill prior to receiving the first dose of levofloxacin.

Pediatric patients aged 0-16 years old accounted for less than 1% (nearly 69,000 patients) of the total 17.6 million patients who received a dispensed prescription for oral levofloxacin tablets from U.S. outpatient retail pharmacies during the cumulative time period from April 2011 through March 2014. In the same time period, pediatric patients aged 0-16 years old accounted for 30% (nearly 9,900 patients) of the total 32,000 patients who received a dispensed prescription for oral levofloxacin solution from U.S. outpatient retail pharmacies. In the same time period, pediatric patients aged 0-16 years old accounted for less than 1% (nearly 19,000 patients) of the total 6.6 million patients who had a hospital billing for injectable levofloxacin from U.S. non-federal hospitals (inpatient and outpatient ER).

No new safety concerns in pediatric patients were identified in this review of FAERS post-marketing reports of levofloxacin. At this time, levofloxacin is adequately labeled with safety information for pediatric use.

The Division of Pharmacovigilance II (DPVII) will continue to monitor for adverse events associated with the use of levofloxacin in pediatric patients.

# 1 INTRODUCTION

## 1.1 PEDIATRIC REGULATORY HISTORY

- Product Information and Dosing[1]
  Levofloxacin (Levaquin®) is a fluoroquinolone antimicrobial that inhibits DNA-gyrase in susceptible organisms thereby inhibiting relaxation of supercoiled DNA and promoting breakage of DNA strands. DNA gyrase (topoisomerase II) is an essential bacterial enzyme that maintains the superhelical structure of DNA and is required for DNA replication, transcription, repair, recombination, and transposition.

  The usual levofloxacin adult dose is 250-750 mg every 24 hours, as indicated by infection and renal function. For pediatric patients ≥ 6 months of age the dosage is based on indication and body weight.

  Table 1.1.1 provides additional pediatric dosing recommendations (adapted from the product package insert):[1]

  **Table 1.1.1. Recommended dosage of levofloxacin in pediatric patients ≥ 6 months of age**

| Type of Infection | Dose | Frequency Once every | Duration |
|---|---|---|---|
| Inhalational Anthrax (post-exposure) | | | |
| Pediatric patients > 50 kg | 500 mg | 24 hr | 60 days |
| Pediatric patients < 50 kg and ≥ 6 months of age | 8 mg/kg (not to exceed 250 mg per dose) | 12 hr | 60 days |
| Plague | | | |
| Pediatric patients > 50 kg | 500 mg | 24 hr | 10 - 14 days |
| Pediatric patients < 50 kg and ≥ 6 months of age | 8 mg/kg (not to exceed 250 mg per dose) | 12 hr | 10 - 14 days |

- Approved Indication for Use

  Levofloxacin is indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible isolates of the designated microorganisms in the conditions listed below:
  - Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*.
  - Community-acquired pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae* (including multidrug-resistant *Streptococcus pneumoniae* [MDRSP]), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae* (7-14 day regimen);

community-acquired pneumonia due to *Streptococcus pneumoniae* (excluding multi-drug-resistant isolates [MDRSP]), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae (*5-day regimen).

- Acute bacterial sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis.*
- Acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.
- Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes,* or *Proteus mirabilis.*
- Uncomplicated skin and skin structure infections (mild to moderate) due to methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes.*
- Chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or methicillin-susceptible *Staphylococcus epidermidis.*
- Complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis*, *Enterobacter cloacae*, or *Pseudomonas aeruginosa*.
- Acute pyelonephritis caused by *Escherichia coli*, including cases with concurrent bacteremia.
- Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus.*

Levofloxacin is indicated for the treatment of adults (≥18 years of age) and pediatric patients (6 months of age and older) in the conditions listed below:

- Inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.
- Plague treatment, including pneumotic and septicemic plague, due to *Yersinia pestis* and prophylaxis for plague.

- Formulations
  Levofloxacin is available as oral, intravenous, and ophthalmic formulations as described in Table 1.1.2.

**Table 1.1.2. Levofloxacin formulations and how supplied**

| Levofloxacin formulation | How supplied |
|---|---|
| Oral tablets | 250 mg, 500 mg, 750 mg |
| Oral solution | 25 mg/mL |
| Intravenous solutions | Single use vials: 25 mg/mL<br>Pre-mixed solution: 5 mg/mL |
| Topical ophthalmic solution | 0.5% (2.5 mL and 5 mL) |

- Safety Data from Pediatric Clinical Trials

Inhalational Anthrax (Post-Exposure)
The effectiveness of levofloxacin for this indication is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. Levofloxacin has not been tested in humans for the post-exposure prevention of inhalation anthrax. The mean plasma concentrations of levofloxacin associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens. The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been studied. An increased incidence of musculoskeletal adverse events (arthralgia, arthritis, tendinopathy, gait abnormality) compared to controls has been observed in clinical studies with treatment duration of up to 14 days. Long-term safety data, including effects on cartilage, following the administration of levofloxacin to pediatric patients is limited.

Plague

Efficacy studies of levofloxacin could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals. The mean plasma concentrations of LEVAQUIN® associated with a statistically significant improvement in survival over placebo in an African green monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens. The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate. Safety and effectiveness in pediatric patients below the age of six months have not been established.

## 1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

On September 29, 2008, DPVII completed a detailed pediatric review of levofloxacin postmarketing adverse drug events.[2] At that time, DPVII concluded that the overall safety profile of levofloxacin in pediatrics appeared similar to adults without new serious unlabeled adverse events. Musculoskeletal events, primarily arthralgia, were the most frequently reported events and represented the predominant adverse events reported among pediatric users. Central nervous system events were also reported in pediatric cases and were most often seizure, abnormal behavior, confusion, hallucination, and panic attack.

On July 13, 2011, DPV II completed an updated review of levofloxacin postmarketing adverse events in accordance with the Pediatric Research Equity Act (PREA).[3] The focus of this review was reports of pediatric death and serious unlabeled adverse events with levofloxacin. The review concluded that the adverse events reported in children were similar to those reported in adults, primarily describing musculoskeletal and central nervous system events, both of which were adequately reflected in labeling. No new or significant adverse events in pediatric patients exposed to levofloxacin were identified.

## 1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

- CONTRAINDICATIONS
  - Levofloxacin is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterials.
- WARNINGS AND PRECAUTIONS
  - Risk of tendinitis and tendon rupture is increased in all ages. The risk 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. Discontinue if pain or inflammation in a tendon occurs.
  - May exacerbate muscle weakness in persons with myasthenia gravis. Avoid levofloxacin in patients with a known history of myasthenia gravis.
  - Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose.
  - Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses.
  - Hypersensitivity reactions including severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome), interstitial nephritis, allergic pneumonitis
  - Severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur.
  - Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia may occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold. Increased intracranial pressure (pseudotumor cerebri) has been reported.
  - *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including levofloxacin, and may range in severity from mild diarrhea to fatal colitis.
  - Peripheral neuropathy . Cases of sensory or sensimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dyasthesias, and weakness have been reported in patients receiving fluoroquinolones, including levofloxacin. Levofloxacin should be discontinued immediately if the patient experiences symptoms of neuropathy.
  - Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval.
  - An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving levofloxacin.
  - Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with levofloxacin, usually in diabetic patients.
  - Moderate to severe photosensitivity/phototoxicity reactions can be associated with the use of fluoroquinolones after sun or UV light exposure.

- ADVERSE REACTIONS
    - The most common adverse reactions (≥ 3%) were nausea, headache, diarrhea, insomnia, constipation and dizziness.
- DRUG INTERACTIONS
    - Multivalent cation-containing products including antacids, metal cations or didanosine: absorption of levofloxacin is decreased when the tablet or oral solution formulation is taken within 2 hours of these products. Do not co-administer the intravenous formulation in the same IV line with a multivalent cation.
    - Warfarin: effect may be enhanced. Monitor prothrombin time, INR, and watch for bleeding
    - Antidiabetic agents: carefully monitor blood glucose
- USE IN SPECIFIC POPULATIONS
    - Geriatrics: severe hepatotoxicity has been reported. The majority of reports describe patients 65 years of age or older. May have increased risk of tendinopathy (including rupture), especially with concomitant corticosteroid use. May be more susceptible to prolongation of the QT interval.
    - Pediatrics: musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) seen in more levofloxacin-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals. Safety in pediatric patients treated for more than 14 days has not been studied. Risk-benefit appropriate only for the treatment of inhalational anthrax (post-exposure) and plague.

# 2 DRUG UTILIZATION DATA

## 2.1 METHODS AND MATERIALS

### 2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for levofloxacin (oral and injectable). Approximately 82% of oral levofloxacin was distributed to outpatient retail pharmacies, while nearly 100% of levofloxacin vials for injectable use were distributed to non-retail settings (primarily non-federal hospitals)[1]. As a result, outpatient retail pharmacy drug utilization patterns were examined for oral levofloxacin and inpatient drug utilization patterns (non-federal inpatient and outpatient ER) were examined for injectable levofloxacin. Mail-order/specialty pharmacy data were not included in this analysis.

### 2.1.2 Data Sources Used

Proprietary drug utilization databases were used to conduct this analysis. ***(See Appendix A for full database descriptions).***

[1] IMS Health, IMS National Sales Perspectives™, Extracted May 2014. File:NSPC 2014-574 Levaquin by formulation BPCA 6.4.2014.xlsx

The IMS, Total Patient Tracker (TPT) database was used to obtain the nationally estimated number of patients receiving a dispensed retail prescription for oral levofloxacin in the U.S., stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17 years and older), from April 2011 through March 2014.
The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of dispensed retail prescriptions for oral levofloxacin in the U.S., stratified by prescriber specialty, for the cumulative time period from April 2011 through March 2014.
Encuity Research, LLC., Treatment Answers™ was used to obtain the diagnoses, as reported by office-based physician surveys, associated with the use of oral levofloxacin for the cumulative time period from April 2011 through March 2014.
The IMS Health, Inpatient HealthCare Utilization System database (IHCarUS) was used to obtain the nationally estimated number of patients who were billed for injectable levofloxacin in a hospital setting (non-federal inpatient and outpatient ER) in the U.S., stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17 years and older), from April 2011 through March 2014.

## 2.2 RESULTS

### 2.2.1 U.S. Outpatient Pharmacy Drug Utilization Patterns for Oral Levofloxacin

#### *2.2.1.1. Unique Patient Data for Oral Levofloxacin*

Table 1 below shows the nationally estimated number of patients, stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17 years and older), receiving a dispensed prescription for oral levofloxacin tablets from U.S. outpatient retail pharmacies, from April 2011 through March 2014. During the entire time period examined, less than 1% (about 69,000 patients) of the total use for oral levofloxacin tablets was in the pediatric population aged 0-16 years old, while patients aged 17 years and older accounted for more than 99% (about 17.6 million patients). Among pediatric patients aged 0-16 years, patients aged 12-16 years old accounted for 86% (about 59,000 patients), and patients aged 6-11 years accounted for about 11% (about 7,900 patients) of the total pediatric patients.

Overall, the total number of patients receiving a dispensed prescription for oral levofloxacin tablets from U.S. outpatient retail pharmacies increased from about 5.2 million patients during the 12-month period ending March 2012 to about 7.8 million patients during the 12-month period ending March 2014. In the same time period, the use in pediatric patients aged 0-16 years increased by 51% from about 17,800 patients to about 26,800 patients. Among pediatric patients, patients aged 12-16 years accounted for the majority of use and increased by about 50% over the same time period from about 15,300 to 22,900 patients. The use in patients aged 6-11 years increased by about 58% over the same time period from about 2,000 to 3,200 patients, and use increased nearly 70% over the same time period in patients aged 2-5 years from about 260 to 440 patients. The use of oral levofloxacin tablets among patients aged 0-1 year old remained relatively steady across the same time period ranging between 210 - 260 patients.

Table 1.

**Nationally estimated number of patients, stratified by patient age 0-1, 2-5, 6-11, 12-16, and 17 years and older, receiving a prescription for oral levofloxacin tablets from an outpatient U.S. retail pharmacy, April 2011 through March 2014,**

| | Apr 2011- Mar 2012 | | Apr 2012-Mar 2013 | | Apr 2013-Mar 2014 | | Cumulative April 2011-March 2014 | |
|---|---|---|---|---|---|---|---|---|
| | Patients (N) | *Share %* | Patients (N) | *Share %* | Patients (N) | *Share %* | Patients (N) | *Share %* |
| **Total** | **5,182,216** | ***100%*** | **7,664,699** | ***100%*** | **7,824,636** | ***100%*** | **17,637,819** | ***100%*** |
| **0 - 16 years old** | **17,760** | ***0.34%*** | **27,538** | ***0.36%*** | **26,793** | ***0.34%*** | **68,664** | ***0.39%*** |
| **0 - 1 year old** | **206** | *1.16%* | **233** | *0.85%* | **261** | *0.97%* | **678** | *0.99%* |
| **2 - 5 years old** | **256** | *1.44%* | **430** | *1.56%* | **436** | *1.63%* | **1,076** | *1.57%* |
| **6 - 11 years old** | **2,034** | *11.45%* | **3,145** | *11.42%* | **3,208** | *11.97%* | **7,887** | *11.49%* |
| **12 - 16 years old** | **15,285** | *86.06%* | **23,785** | *86.37%* | **22,935** | *85.60%* | **59,353** | *86.44%* |
| **17 years and older** | **5,164,412** | ***99.66%*** | **7,637,153** | ***99.64%*** | **7,795,207** | ***99.62%*** | **17,568,456** | ***99.61%*** |
| **UNKNOWN AGE** | **141** | *<0.01%* | **214** | *<0.01%* | **4,198** | *0.05%* | **4,525** | *0.03%* |

*Source: IMS Health, Total Patient Tracker, April 2011-March 2014, extracted JUN2014, source file: TPT 2014-574 MAT BPCA 0-1, 2-5, 6-11, 12-16, and 17 + 6.4.2014; TPT 2014-574 levaquin BPCA 0-1,2-5,6-11,12-16,17+ Apr2011 to Mar2014 6.9.2014.xls*

Table 2 below shows the nationally estimated number of patients, stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17 years and older), receiving a dispensed prescription for oral levofloxacin solution from U.S. outpatient retail pharmacies, from April 2011 through March 2014. During the entire time period examined, pediatric population aged 0-16 years old accounted for 30% (nearly 9,900 patients) , while patients aged 17 years and older accounted for 70% (nearly 22,700 patients) of the total patients. Among pediatric patients aged 0-16 years, patients aged 12-16 years accounted for 11% (nearly 1,100 patients), patients aged 6-11 years accounted for 33% (nearly 3,200 patients), patients aged 2-5 years accounted for 38% (about 3800 patients), and patients aged 0-1 year accounted for 18% (nearly 1,800 patients).

Overall, the total number of patients receiving a dispensed prescription for oral levofloxacin solution from U.S. outpatient retail pharmacies increased by more than two-fold from about 5,800 patients during the 12-month period ending March 2012 to about 14,700 patients during the 12-month period ending March 2014. In the same time period, pediatric patients aged 0-16 years increased by more than two-fold from about 1,700 patients to about 4,700 patients. Among pediatric patients, patients aged 2-5 years accounted for the majority of use and increased by nearly three-fold from about 600 to 1,900 patients, while pediatric patients aged 6-11 years increased by almost three-fold from about 560 to 1,500 patients. Following this, use in patients aged 0-1 year increased by nearly three-fold during the same time period from about 300 to 830 patients, while use in patients aged 12-16 years increased by more than two-fold from about 200 to 500 patients.

Table 2

| Nationally estimated number of patients receiving a dispensed prescription for levofloxacin oral solution (25mg/ml) from outpatient U.S. retail pharmacies, stratified by patient age, 0-1, 2-5, 6-11, 12-16, and 17 years and older, April 2011-March 2014 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Apr 2011- Mar 2012 | | Apr 2012-Mar 2013 | | Apr 2013-Mar 2014 | | Cumulative April 2011-March 2014 | |
| | Patients (N) | *Share %* | Patients (N) | *Share %* | Patients (N) | *Share %* | Patients (N) | *Share %* |
| **Grand Total** | **5,792** | ***100%*** | **14,048** | ***100%*** | **14,719** | ***100%*** | **32,419** | ***100%*** |
| **0 - 16 years old** | **1,672** | ***29%*** | **4,141** | ***29%*** | **4,691** | ***32%*** | **9,883** | ***30%*** |
| **0 - 1 year old** | **307** | *18%* | **685** | *17%* | **827** | *18%* | **1,756** | *18%* |
| **2 - 5 years old** | **590** | *35%* | **1,594** | *38%* | **1,850** | *39%* | **3,796** | *38%* |
| **6 - 11 years old** | **564** | *34%* | **1,404** | *34%* | **1,505** | *32%* | **3,244** | *33%* |
| **12 - 16 years old** | **211** | *13%* | **458** | *11%* | **509** | *11%* | **1,087** | *11%* |
| **17 years and older** | **4,132** | ***71%*** | **9,964** | ***71%*** | **10,084** | ***69%*** | **22,742** | ***70%*** |
| **UNKNOWN AGE** | **2** | ***0.03%*** | **1** | ***0.01%*** | **5** | ***0.03%*** | **8** | ***0.02%*** |
| Source: IMS Health, Total Patient Tracker, April 2011-March 2014, Data Extracted Jul2014, Source File: TPT 2014-574 Levofloxacin 25mg/ml oral solution BPCA | | | | | | | | |

### *2.2.1.2. Dispensed Prescriptions for Oral Levofloxacin by Prescriber Specialty*

Table 3 below shows the estimated number of oral levofloxacin prescriptions dispensed through U.S. outpatient retail pharmacies, stratified by prescriber specialty, for the cumulative time period from April 2011 through March. Approximately 29 million oral levofloxacin prescriptions were dispensed through U.S. outpatient retail pharmacies for the examined time period. Internal Medicine was the top prescribing specialty accounting for approximately 24% (about 7.1 million prescriptions) of total prescriptions dispensed, followed by Family Practice and Osteopathic Medicine with approximately 22% (about 6.7 million prescriptions) and 10% (about 3 million prescriptions) of the total, respectively. Prescriptions dispensed by pediatric specialty accounted for about 1% of the total (approximately 297,000 prescriptions).

Table 3

| Nationally estimated number of prescriptions dispensed for oral levofloxacin, stratified by prescriber specialty, from April 2011 - March 2014, cumulative | | |
|---|---|---|
| | TRx | *Share %* |
| Total Prescriptions for Oral Levofloxacin | 29,895,175 | ***100%*** |
| Internal Medicine | 7,132,461 | ***24%*** |
| Family Practice | 6,655,865 | ***22%*** |
| Osteopathic Medicine | 3,011,977 | ***10%*** |
| Nurse Practitioner | 2,188,527 | ***7%*** |
| Physician Assistant | 1,854,656 | ***6%*** |
| Emergency Medicine | 1,265,533 | ***4%*** |
| Urology | 908,468 | ***3%*** |
| Specialty Unspecified | 766,142 | ***3%*** |
| Otolaryngology | 697,120 | ***2%*** |
| Pulmonary Diseases | 626,588 | ***2%*** |
| Pediatrics | 296,547 | ***1%*** |
| All Other Specialties | 4,491,291 | ***15%*** |
| Source: IMS National Prescription Audit (NPA), Apr2011-Mar2014, Extracted Jun 2014, Source File: NPA 2014-574 Levofloxacin by Specialty April 2011-March 2014.xlsx | | |

### *2.2.1.3. Diagnoses Associated with Use of Oral Levofloxacin*

Table 4 below shows the diagnoses (in terms of drug use mentions)[2], associated with the use of oral levofloxacin, stratified by patient age, as reported by office-based physician practices for the cumulative time period from April 2011 through March 2014. Diagnoses were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates.

The pediatric patients aged 0-16 years comprised less than 1% of the total drug use mentions. Among pediatric patients, there were no drug use mentions captured for pediatric patients aged 0-1 year old. "Asthma Not Otherwise Specified" (ICD-9 code 493.9) was the only diagnosis captured among pediatric patients aged 2-5 years. "Cellulitis Not Otherwise Specified" (ICD-9 code 682.9) was the top diagnosis associated with the use of oral levofloxacin among pediatric patients aged 6-11 years followed by "Cellulitis Of Finger" (ICD-9 code 681.0). "Urinary Tract Infection Not Otherwise Specified" (ICD-9 code 599.0) was the top diagnosis associated with the use of oral levofloxacin among pediatric patients aged 12-16 years followed by "Cellulitis Not Otherwise Specified" (ICD-9 code 682.9). *Of note, the number of drug use mentions as reported by office-based physician surveys for pediatric patients aged 2-5, 6-11, and 12-16 years was below the acceptable count allowable to provide a reliable estimate of national use*

Table 4

**Diagnoses associated with oral levofloxacin as reported by office-based physician surveys, stratified by paitent age, from April 2011 through March 2014, cumulative**

| | Uses (000) | *Share %* | 95% C.I. (000) |
|---|---|---|---|
| **Oral levofloxacin** | **22,426** | ***100%*** | **21,699 - 23,153** |
| **0-16 years old** | **114** | ***0.5%*** | **62 - 166** |
| **2-5 years old** | **6** | ***5.3%*** | **<0.5 - 18** |
| **4939 ASTHMA NOS** | 6 | *100%* | <0.5 - 18 |
| **6-11 years old** | **37** | ***32.5%*** | **7 - 66** |
| **6829 CELLULITIS NOS** | 21 | *56.8%* | <0.5 - 43 |
| **6810 CELLULITIS OF FINGER** | 16 | *43.2%* | <0.5 - 36 |
| **12-16 years old** | **71** | ***62.3%*** | **30 - 112** |
| **5990 URIN TRACT INFECTION NOS** | 19 | *26.8%* | <0.5 - 39 |
| **6829 CELLULITIS NOS** | 15 | *21.1%* | <0.5 - 33 |
| **4900 BRONCHITIS NOS** | 11 | *15.5%* | <0.5 - 27 |
| **4739 CHRONIC SINUSITIS NOS** | 10 | *14.1%* | <0.5 - 25 |
| **4860 PNEUMONIA, ORGANISM NOS** | 7 | *9.9%* | <0.5 - 21 |
| **4630 ACUTE TONSILLITIS** | 6 | *8.5%* | <0.5 - 19 |
| **6811 CELLULITIS OF TOE** | 3 | *4.2%* | <0.5 - 11 |
| **17 years and older** | **21,197** | ***94.5%*** | **20,490 - 21,904** |
| **4860 PNEUMONIA, ORGANISM NOS** | 4,626 | *21.8%* | 4,296 - 4,957 |
| **5990 URIN TRACT INFECTION NOS** | 2,872 | *13.5%* | 2,612 - 3,132 |
| **4900 BRONCHITIS NOS** | 2,107 | *9.9%* | 1,884 - 2,330 |
| **4660 ACUTE BRONCHITIS** | 1,546 | *7.3%* | 1,355 - 1,737 |
| **4619 ACUTE SINUSITIS NOS** | 1,517 | *7.2%* | 1,328 - 1,706 |
| **All Others** | 8,529 | *40.2%* | 8,081 - 8,978 |
| **UNSPEC** | **1,115** | ***5%*** | **953 - 1,277** |

*Source: Encuity TreatmentAnswersTM, Apr2011-Mar2014, Extracted Jun2014, Source File: PDDA 2014-574 levaquin Dx4 0-16, 17+ xlsx*

[2] "Drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. 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 prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit

### *2.2.2. Unique Patient Data for Injectable Levofloxacin*

Table 5 below displays the nationally estimated number of patients, stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17 years and older), with a hospital billing for injectable levofloxacin from non-federal U.S. hospitals (inpatient and outpatient ER) from April 2011 through March 2014. During the entire time period examined, less than 1% (about 19,000 patients) of the total use for injectable levofloxacin was in the pediatric population aged 0-16 years old, while patients aged 17 years and older accounted for more than 99% (about 6.6 million patients) of the total patients with a hospital billing for injectable levofloxacin. Among pediatric patients aged 0-16 years, patients aged 12-16 years accounted for majority of the patients (about 68% or 13,000 patients), followed by patients aged 6-11 years (16% or 3,100 patients), patients aged 2-5 years ( 9% or 1,700 patients), and patients aged 0-1 year (about 7% or 1,400 patients).

Overall, the total number of patients with a hospital billing for injectable levofloxacin from non-federal U.S. hospitals (inpatient and outpatient ER) decreased from about 2.3 million patients during the 12-month period ending March 2012 to about 2.2 million patients during the 12-month period ending March 2014. In the same time period, the use in pediatric patients aged 0-16 years decreased by nearly 18% from about 6,700 patients to about 5,500 patients. Among pediatric patients, patients aged 12-16 years old accounted for the majority of use and decreased by nearly 25% from about 4,600 to 3,500 patients during the same time period. The second highest use among pediatric patients was in patients aged 6-11 years and increased by approximately 21% from nearly 930 to 1,100 patients. For patients aged 2-5 years, use did not change across the same time period with nearly 600 patients, while use in patients aged 0-1 year decreased by nearly 40% from about 560 to 340 patients

Table 5

**Nationally estimated number of patients with a hospital billing for injectable levofloxacin from non-federal U.S. hospitals (inpatient and outpatient ER), stratified by patient age, 0-1, 2-5, 6-11, 12-16, and 17 years and older, April 2011-March 2014**

| | Apr 2011- Mar 2012 | | Apr 2012-Mar 2013 | | Apr 2013-Mar 2014 | | Cumulative April 2011-March 2014 | |
|---|---|---|---|---|---|---|---|---|
| | Patients (N) | Share % | Patients (N) | Share % | Patients (N) | Share % | Patients (N) | Share % |
| Grand Total | 2,312,418 | 100% | 2,420,879 | 100% | 2,196,895 | 100% | 6,625,877 | 100% |
| 0 - 16 years old | 6,699 | 0.29% | 6,981 | 0.29% | 5,506 | 6.23% | 19,034 | 0.29% |
| 0 - 1 year old | 556 | 8.30% | 508 | 7.27% | 343 | 6.23% | 1,402 | 7.36% |
| 2 - 5 years old | 618 | 9.22% | 558 | 7.99% | 606 | 11.01% | 1,731 | 9.09% |
| 6 - 11 years old | 934 | 13.95% | 1,056 | 15.12% | 1,133 | 20.57% | 3,101 | 16.29% |
| 12 - 16 years old | 4,596 | 68.61% | 4,870 | 69.76% | 3,450 | 62.66% | 12,864 | 67.58% |
| 17 years and older | 2,305,649 | 99.71% | 2,413,555 | 99.70% | 2,190,051 | 99.69% | 6,605,125 | 99.69% |
| UNKNOWN AGE | 88 | <.01% | 366 | 0.02% | 1,505 | 0.07% | 1,949 | 0.03% |

*Source: IMS Health, IHCarUS, April 2011-March 2014, Data Extracted Jun2014, Source File: IHCarUS 2014-574 Levaquin BPCA JUN2014.xls*

# 3 POSTMARKET ADVERSE EVENT REPORTS

## 3.1 METHODS AND MATERIALS

### 3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The FAERS database was searched with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

| ***Table 3.1.1 FAERS Search Strategy*** | |
|---|---|
| Date of search | March 31, 2014 |
| Time period of search | April 1, 2011* - March 31, 2014 |
| Product Name(s) | Levofloxacin, Levaquin |
| Search Parameters | All ages, all outcomes, worldwide |

** Prior pediatric review for levofloxacin summarized data up until March 31, 2011*

## 3.2 RESULTS

### 3.2.1 Total number of FAERS cases by Age

***Table 3.2.1 Total Adult and pediatric FAERS cases* (April 1, 2011 - March 31, 2014 ) with levofloxacin***

| | **All reports (US)** | **Serious† (US)** | **Death (US)** |
|---|---|---|---|
| **Adults (≥ 17 years)** | 4320 (2684) | 3940 (2316) | 227 (65) |
| **Pediatrics (0 - <17 years)** | 65 (25) | **59‡ (20)** | 5§ (1) |

**** May include duplicates and transplacental exposures, and have not been assessed for causality***

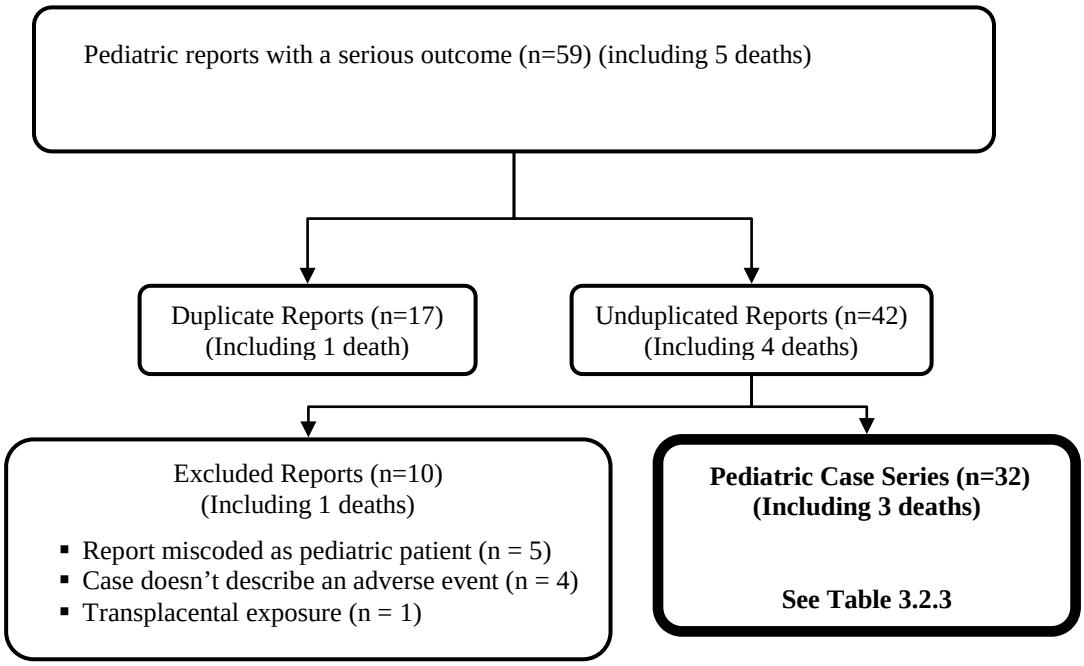
*† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.*

*‡See Figure 3.2.2*

### 3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 59 pediatric reports with a serious outcome (See Table 3.2.1). **Figure 3.2.2** below summarizes the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

***Figure 3.2.2 Selection of Serious Pediatric Cases with Levofloxacin***




### *3.2.3 Characteristics of Pediatric Case Series*

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

***Table 3.2.3 Characteristics of Pediatric Case Series with Levofloxacin (N=32)***

| | | |
|---|---|---|
| Age (n=32) | 0 - <6 months | 1 |
| | 6 months - <2 years | 2 |
| | 2- < 6 years | 5 |
| | 6- <12 years | 8 |
| | 12- < 17 years | 16 |
| Sex | Male | 12 |
| | Female | 20 |
| Daily Dose (n=22) | Mean | 537 mg/day |
| | Median (Range) | 500 (250-1000) mg/day |
| Country of Reporter | United States | 11 |
| | Foreign | 21 |

| | | |
|---|---|---|
| Frequently Reported Indication | Tuberculosis | 6 |
| | Respiratory infection | 5 |
| | Sinusitis | 4 |
| | Bronchitis | 3 |
| Serious Outcome* | Death | 3 |
| | Life-threatening | 1 |
| | Hospitalized | 14 |
| | Disability | 1 |
| | Congenital anomaly | 0 |
| | Other serious | 13 |

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

## 3.3 SUMMARY OF SERIOUS ADVERSE EVENT REPORTS (N=32)

### *3.3.1 Labeled Event: Hypersensitivity reactions (N=12)*

Anaphylaxis, allergic skin reactions and severe dermatologic reactions are labeled in the *Warnings and Precautions* sections *5.3 Hypersensitivity Reactions* and *5.4 Other Serious and Sometimes Fatal Reactions* (e.g., TEN, SJS). Of the 12 cases reviewed, the events reported were consistent with the known risk in the labeling and no increased severity was observed in these reports. Three cases reported anaphylaxis and nine cases reported skin reactions. Of the nine skin cases, most were of rash and urticaria, however, 2 cases reported SJS or TEN. Below is a summary of the cases.

***Anaphylaxis (N=3)***

Case# 8020834 describes a 16-year-old female who experienced anaphylactic shock after one dose of oral levofloxacin. The patient was admitted to the intensive care unit and received treatment with epinephrine, hydrocortisone, and dexchlorpheniramine. The patient's condition resolved within 48 hours. Anaphylactic reactions (occasionally fatal) are labeled in the *Warnings and Precautions* section of the levofloxacin label.

Case# 7902058 describes a 15-year-old female who experienced pharyngeal edema, urticaria, swollen extremities and difficulty breathing 90 minutes after treatment with oral levofloxacin and tranexamic acid. The patient improved after administration of epinephrine and methylprednisolone and was discharged from the hospital the same day. Of note, this case was confounded by the concomitant use of tranexamic acid which is labeled for allergic reactions.

Case# 8306301 reported an anaphylactic reaction following the use of a levofloxacin ophthalmic solution; however, based on the information provided it appears to be a local allergic reaction. This case describes an 8 year old male who was treated with levofloxacin ophthalmic solution for conjunctival hyperemia after excoriation on the left eyelid. Immediately after administration, the patient complained of intense pain. Eyewash was performed and betamethasone ophthalmic solution was instilled for treatment of chemosis and hyperemia. Eye pain and chemosis were worsening so loratadine and

betamethasone/dexchlorpheniramine were administered. The swollen eyelid persisted but chemosis resolved. A scratch test was performed with 11 different drugs and levofloxacin was the only drug that the patient had a positive reaction to with an urticarial lesion and redness. Two days after the "anaphylactic reaction," the event was almost resolved. The physician reporter assessed the event as probably related to levofloxacin. Of note, the patient was exposed to ophthalmic levofloxacin six months prior and sensitization may have occurred at that time according to the reporter. Ocular reactions including chemosis, hyperemia, transient ocular burning, ocular pain, and/or allergic reactions are labeled in the levofloxacin ophthalmic product labels.

***Skin reactions (N=9)***

Case# 9813618 is a direct report from a healthcare professional that describes TEN in an 11 year old male who was treated with levofloxacin for antibacterial prophylaxis after bone marrow transplant. The patient developed a skin rash with pruritus on his face, head and neck. The rash progressively worsened with the development of blisters on his cheeks and under his neck (35% of body surface area) and skin biopsy was consistent with TEN. The dermatology and burn team managed his care with dressing changes and debridement procedures. The reporter believes the adverse event was due to levofloxacin since it was the only new drug in the patient's regimen, although the patient was on multiple concomitant medications some of which are associated with SJS/TEN (e.g., fluconazole). The patient required prolonged hospitalization but had clinical resolution of symptoms at discharge.

The other SJS/TEN case is a litigation case confounded by use of concomitant medications also labeled for SJS/TEN (i.e., amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole).

Four cases describe hypersensitivity reactions manifested as rash and itching that occurred after the first dose of levofloxacin. Only one of these cases required hospitalization and symptoms resolved with supportive measures (i.e., antihistamines and steroids). Three cases were confounded by the use of concomitant drugs also labeled for allergic skin reactions (e.g., amoxicillin, ethionamide, pyrazinamide, ethambutol, cloxacillin). In all cases discontinuation of the drug and supportive measures was associated with clinical improvement.

### *3.3.2 Labeled Event: Musculoskeletal adverse events (N=11)*

Musculoskeletal adverse events are labeled in two *Warnings and Precautions* sections. The increased risk of tendinitis and tendon ruptures in all ages is labeled under *5.1 Tendinopathy and Tendon Rupture* while *5.10 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals* cautions about the increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) noted in pediatric patients compared to controls. Of the 11 cases reviewed, the events reported were consistent with the known risk in the labeling and no increased severity was observed in these reports.

The adverse events reported included tendinopathy, myalgia, arthralgia, and polyarthritis with the use of levofloxacin. Six of 11 cases reported resolution of symptoms after levofloxacin discontinuation, 4 cases did not have improvement at the time of the report, and 1 case had an unknown outcome.

A representative case (Case# 8060079) describes a 10-year-old female who received treatment with levofloxacin and metronidazole. After ten days of treatment, the patient experienced diffuse arthralgia, bilateral wrist and thumb pain, and bilateral Achilles tendon pain and tendinopathy. Levofloxacin was discontinued while metronidazole treatment was continued and at the time of the report, the patient was recovering from the adverse events.

Of the 4 cases that reported no improvement at the time of the report, one case also described an outcome of disability (Case# 8784301). These 4 cases are summarized below:

- Case# 8784301 was a direct report describing a 3-year-old female who suffered loss of right and left calves use after taking two doses of levofloxacin. The narrative contains limited information and it's unknown whether the disability was permanent or temporary.
- Case# 7987093 is a direct report that describes a 13-year-old female who developed knee pain that progressed to joint and tendon pain all over the body after seven doses of levofloxacin without any further information.
- Case# 8020836 describes a 14-year-old female who developed balance disorder and muscle atrophy after four days of levofloxacin therapy. However, the case is confounded by a comorbidity of algoneurodystrophy and the use of concomitant medications labeled for musculoskeletal adverse events (i.e., omeprazole, midazolam, betamethasone, meperidine, hyoscine).
- Case# 9226861 describes a 14-year-old male who experienced right knee effusion and tendinopathy after a ten day course of levofloxacin (exact time to event unknown). No other information was provided.

### *3.3.3 Labeled Event: Central nervous system adverse events (N=2)*

Central nervous system adverse events are labeled in *Warnings and Precautions* Section *5.6 Central Nervous System Effects* and include toxic psychoses, tremors, restlessness, confusion, and hallucinations. The two cases report events consistent with the known risk in the labeling and no increased severity was observed in these reports.

Case# 10021274 is a literature report describing a 13-year-old female who was treated with levofloxacin for acute bronchitis. Within 2 hours of the first dose, the patient developed "giddiness and vomiting." She became restless with irrelevant speech and complained of "tremulousness and a vibration like sensation in her body." She had difficulty moving her limbs, confusion, and disorientation with features of delirium. Meningitis, hypoglycemia, ketosis, electrolyte imbalances, and malaria were ruled out. Additionally, her MRI and EEG were normal. Levofloxacin was discontinued and the patient was treated with broad-spectrum antimicrobials and antimalarials. The reporters

diagnosed the patient with levofloxacin-induced neurotoxicity. The patient was discharged after 6 days of hospitalization with no evidence of neurological deficit.

The other case (Case# 9002833) reported hallucinations in a 13-year-old male but the case contains very limited information (i.e., unknown time to event, unknown outcome, unknown treatment).

### *3.3.4 Labeled Event: Hepatotoxicity (N=2)*

Severe hepatotoxicity adverse events are labeled in *Warnings and Precautions* Section *5.5 Hepatotoxicity.* The two cases report events consistent with the known risk in the labeling and no increased severity was observed in these reports.

Case# 9308588 reports a 3-year-old female who was treated with ketoconazole and levofloxacin for unspecified fungal infection and unspecified bacterial infection, respectively. After an unknown duration, the patient experienced elevated aminotransferases. Both drugs were discontinued and ten days later lab values returned to normal. The reporter assessed the causality of the events to be related to ketoconazole but did not comment on the contribution of levofloxacin. This case is confounded by the concomitant use of ketoconazole, which is known to cause hepatotoxicity.

Case #9288456 had an outcome of death and is summarized in Section 3.4 of this review.

### *3.3.5 Labeled Event: Cardiac Arrest (N=2)*

Cardiac arrest is labeled in the *Adverse Reactions* section (both in Section *6.2 Clinical Trial Experience* and Section *6.3 Postmarketing Experience*). Two cases reported cardiac arrest leading to death and are summarized in Section 3.4 of this review.

### *3.3.6 Unlabeled event: Cerebral edema (N=1)*

Case# 8531817 reports an 8-year-old female who was treated with a 7-day course of levofloxacin for sinusitis. Comorbidities are unknown but the patient was concomitantly treated with cyclosporine and danazol. After completion of levofloxacin treatment, the patient developed acute cerebral edema, cephalalgia, and vomiting. The patient was then treated with mannitol and dexamethasone which resulted in clinical improvement. The report states that levofloxacin was re-started at a later date but no other information was provided. The reporter assessed that levofloxacin is the suspect drug. Levofloxacin, cyclosporine, and danazol are not labeled for cerebral edema.

*Reviewer's comment: The limited information in the case (i.e., unknown concomitant disease states, lack of information regarding laboratory or virologic results, diagnostic tests, or other medical evaluations, and lack of information surrounding the rechallenge with levofloxacin) makes it challenging to assess the role of levofloxacin in causing cerebral edema.*

### *3.3.7 Unlabeled event: Enterocolitis and intestinal obstruction (N=1)*

Case# 9498339 reports a 12-year-old male patient who received chemotherapy for acute myeloid leukemia and 3 days later developed neutropenic fever. The patient was empirically treated with cefepime, amikacin, and fluconazole. Fever persisted and 5 days after chemotherapy administration amphotericin-B was added to the regimen. On day 10 after chemotherapy administration, the patient developed abdominal distention and hypokalemia so treatment was changed to meropenem and levofloxacin, while amphotericin-B was continued. Patient was diagnosed with intestinal obstruction and required emergency surgery to relieve obstruction. The reporter assessed the neutropenic enterocolitis to be a complication of aggressive chemotherapy.

*Reviewer's comment: There is a plausible alternate cause of enterocolitis and intestinal obstruction (i.e., chemotherapy).*

### *3.3.8 Unlabeled event: Raynaud's phenomenon (N=1)*

Case# 8399878 reports a 15-year-old female who was treated with azithromycin for pneumonia then switched to levofloxacin for 6 days of treatment. After an unknown period of time, the patient developed Raynaud's phenomenon. Patient's medical history includes developmental delay, hypothyroidism, and Legionnaire's disease.

*Reviewer's comment: The role of levofloxacin in this adverse event is uncertain based on the limited information provided in the FAERS report (time to event unknown, outcome unknown, clinical course unknown).*

## 3.4 SUMMARY OF PEDIATRIC DEATHS (N=3)

The pediatric death cases are confounded by patients who were administered levofloxacin to treat life-threatening diseases (i.e., 2 cases of CNS TB, and one case of meningitis), as well as multiple use of concomitant medications, making it challenging to assess the role of levofloxacin on the outcome of death. These patients were severely ill prior to receiving the first dose of levofloxacin.

**Case #8492697**

Two-month-old male patient weighing 3.2 kg was empirically treated with ampicillin-sulbactam and cefotaxime for meningitis based on cerebral spinal fluid (CSF) findings. Two days later, *C. indologenes* (resistant to cefotaxime) was identified, so ampicillin-sulbactam was continued while cefotaxime was switched to levofloxacin. Growth of *C.indologenes* was not observed in blood culture taken on day 61 of hospital stay. On day 65, the patient's "general condition worsened" and he suffered a cardiopulmonary arrest leading to death.

*Reviewer's comment: The use of levofloxacin to treat a serious infection (cefotaxime resistant C. indologenes meningitis) in this infant makes it unlikely that the cause of death was related to levofloxacin. It is more likely that this patient succumbed to the infection.*

**Case #9288456**
Eighteen-month-old male patient was admitted due to status epilepticus after a 10-day history of presumed viral illness with fever, cough, vomiting, and tonic-clonic seizures. The patient was empirically started on isoniazid, rifampicin, streptomycin, pyrazinamide, levofloxacin, and dexamethasone for suspected central nervous system tuberculosis (CNS TB). After 2 days, multi-drug resistant TB was detected and treatment was modified based on culture sensitivities to isoniazid, levofloxacin, capreomycin, cycloserine, linezolid, and vitamin B6. Culture and polymerase chain reaction (PCR) conversion were achieved 1 month after treatment initiation but the patient remained neurologically unresponsive with spastic quadriparesis, tonic posturing, and ventilation through tracheostomy. The patient had recurrent mild hemorrhagic episodes from the ventricular system, high CSF protein levels, episodes of ventriculitis due to *Acinetobacter baumanii* and *Stenotrophomonas maltophilia*. After 6 months of hospitalization, the patient died due to acute hepatic insufficiency. Etiology of hepatic insufficiency was not identified as HAV, HBV, HCV, and EBV serologies were negative. There were no signs of disseminated TB. Autopsy was not performed.

*Reviewer's comment: The patient's cause of death was multifactorial in light of severe multi-drug resistant TB, and the role of levofloxacin in these events cannot be determined. This patient was severely ill (admitted to intensive care unit) prior to receiving the first dose of levofloxacin and likely on multiple medications for a prolonged period of time, thereby making it difficult to attribute causality to any particular drug.*

**Case #8282500**
Five-year-old female patient was diagnosed with CNS TB and treated with isoniazid, pyrazinamide, streptomycin, and dexamethasone for 2 months. Treatment was then simplified to isoniazid and rifampicin, while dexamethasone was tapered and discontinued. The infection was complicated by hydrocephalus requiring ventriculoperitoneal (VP) shunt insertion. After 4 months of treatment, she deteriorated and was re-started on isoniazid, rifampin, pyrazinamide, and levofloxacin. Four weeks after this change in therapy she developed fever, tonic-clonic seizures of the upper limbs, and redness along VP catheter tunnel. VP catheter was removed and meropenem was administered. Cultures from an external ventricular drainage system grew *Aspergillus fumigatus*; therefore, meropenem was discontinued and liposomal amphotericin B (LAMB) initiated. MRI scan findings were suggestive of ventriculitis so voriconazole was added to the regimen while rifampin was discontinued. Intraventricular amphotericin B deoxycholate (DAMB) was initiated after which fever subsided and CSF analysis was normal. Two months after LAMB and voriconazole therapy initiation, patient developed CNS infections caused by *Stenotrophomonas maltophilia* and multi-drug resistant *Acinetobacter baumannii*; these infections required prolonged treatment with ceftazidime, meropenem, and colistin. One month after discontinuation of voriconazole therapy and while still on meropenem and colistin, she developed abnormal breathing and CT scan revealed hydrocephalus enlargement. The patient had a cardiac arrest and expired.

*Reviewer's comment: The patient's cause of death was multifactorial in light of severe CNS TB, and the role of levofloxacin in these events cannot be determined. The patient received prolonged treatment with various drug combinations prior to receiving the first dose of levofloxacin and throughout levofloxacin therapy, thereby making it difficult to attribute*

*causality to any particular drug. Additionally, the severity of the CNS TB is evident by the complicated hospital course with several episodes of deterioration.*

## 4 DISCUSSION

Of the 32 cases, 21 were foreign reports while 11 were US reports. The low number of pediatric FAERS reports is consistent with the low domestic use in pediatric patients. Limited use of levofloxacin in children is expected as levofloxacin is only indicated for inhalational anthrax (post-exposure) and plague (treatment or prophylaxis) in this population.

Of the 32 pediatric reports reviewed, there were no new safety signals identified, no increased severity of any labeled adverse events and no deaths that can be attributed to levofloxacin use.

As seen in previous DPV reviews (2008[2] and 2011[3]), musculoskeletal events continue to be one of the most frequently reported adverse events in pediatric patients. Additionally, hypersensitivity reactions (particularly allergic skin reactions) were also commonly noted in this review. Musculoskeletal events, hypersensitivity reactions, CNS events, and hepatotoxicity are well characterized in the levofloxacin labeling under Warnings and Precautions.

This review did not identify any unlabeled, drug-related safety concerns that are clearly causally related to levofloxacin. The unlabeled events include single reports of cerebral edema, intestinal obstruction, and Raynaud's phenomenon. The extent of levofloxacin's contribution to cerebral edema and Raynaud's phenomenon cannot be assessed in light of the limited information provided in the case reports. Intestinal obstruction appears to be a complication of chemotherapy and not a levofloxacin-induced adverse event.

The pediatric death cases are confounded by patients who were administered levofloxacin to treat life-threatening diseases (i.e., CNS TB, and meningitis), as well as multiple use of concomitant medications, making it challenging to assess the role of levofloxacin on the outcome of death. These patients were severely ill prior to receiving the first dose of levofloxacin.

## 5 CONCLUSION

No new safety concerns in pediatric patients were identified in this review of FAERS post-marketing reports of levofloxacin. Hypersensitivity reactions and musculoskeletal events are the predominant adverse events reported, both of which are known and reflected in the labeling. At this time, levofloxacin is adequately labeled with safety information for pediatric use.

## 6 RECOMMENDATIONS

DPVII will continue to monitor for adverse events associated with the use of levofloxacin in pediatric patients.

## 7 REFERENCES


1. (Levaquin®) [package insert]. Titusville, NJ 08560: Janssen Pharmaceuticals, Inc.; 2013.
2. Jones SC. Levofloxacin-Pediatric Exclusivity Postmarketing Adverse Event Review (OSE RCM 2008-834) completed September 29, 2008.
3. Jones SC. Levofloxacin PREA Review: Pediatric Postmarketing Adverse Events (OSE RCM 2011-1428) completed July 13, 2011.

# 8 APPENDICES

## 8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

***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.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that 82% of oral levofloxacin was distributed to outpatient retail settings; whereas, nearly 100% of levofloxacin for injectable use was distributed to non-retail settings, primarily U.S. non-federal hospitals, based on the IMS Health, IMS National Sales Perspectives™. The data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

The estimates provided are national estimates, but no statistical tests were performed to determine 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.

***IMS Health, National Prescription Audit***

The National Prescription Audit (NPA™) has been the industry standard source of national prescription activity since 1952. NPA measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. 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.

***IMS Vector One®: Total Patient Tracker (TPT)***

The IMS, Vector One®: Total Patient Tracker 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 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

***IMS Inpatient HealthCare Utilization System (IHCarUS)***

The IMS, Inpatient HealthCare Utilization System (IHCarUS) provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from mid-2001, are collected weekly and monthly and are available 25-30 days after the end of each monthly period. This robust data set

includes> 580 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include >16 million patients and >65 million annual hospital encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. IMS' datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

The IMS Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

***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.

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 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.

## 8.2 APPENDIX B FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

**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.

## 8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS

| FAERS Case | Case Version | MCN | Age (years)/ gender | Country | Indication | Adverse event | Time to event | FAERS reported outcome* | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|
| 10021274 | 1 | 2014/014 | 13/F | IND | Acute bronchitis | Delirium with giddiness and vomiting | 2 hours | HO, OT | Recovered |
| 7902058 | 1 | JP-JNJFOC-20110308437 | 15/F | JPN | Acute tonsillitis | Anaphylaxis | Unknown | OT | Recovered |
| 7987093 | 1 | Direct report | 13/F | USA | Strep throat | Tendon rupture | 7 days | OT | Not yet recovered |
| 8020834 | 1 | ES-JNJFOC-20110612452 | 16/F | ESP | Respiratory tract infection | Anaphylaxis | 1 day | HO, LT | Recovered |
| 8020836 | 2 | BE-JNJFOC-20110610952 | 14/F | BEL | Gastrointestinal infection | Balance disorder, muscle atrophy, tingling in hands/feet | Unknown | OT | Not yet recovered |
| 8060079 | 1 | FR-JNJFOC-20110708754 | 10/F | FRA | Brain abscess | Diffuse arthralgia, bilateral pain of both thumbs, bilateral Achilles tendinopathy | 10 days | HO | Recovering |
| 8194629 | 1 | US-RANBAXY-2011RR-49715 | 8/M | USA | Wound infection | SJS | 31 days | HO, OT | Recovered |
| 8194827 | 2 | US-JNJFOC-20111007186 | 7/M | USA | Wound infection | Pain in extremity, diarrhea | Unknown | HO, OT | Recovered |
| 8234782 | 2 | JP-JNJFOC-20111102367 | 16/F | JPN | Acute otitis media | Rash and itching | 15 minutes | HO, OT | Recovered |
| 8337507 | 3 | IT-RANBAXY-2012RR-51782 | 15/F | ITA | Limb injury | Diffuse urticarial eruption, angioedema of the face | 1 day | HO | Recovered |
| 8399878 | 1 | US-JNJFOC-20120203978 | 15/F | USA | Pneumonia | Raynaud's phenomenon | Unknown | OT | Unknown |
| 8445322 | 1 | Direct report | 15/F | USA | Bronchitis | Tendonitis | 2 days | OT | Unknown |
| 8492697 | 2 | PHHY2012TR028080 | 0.17/M | TUR | Meningitis | Cardiopulmonary arrest | 63 days | DE | Death |
| 8531817 | 1 | PHHY2012IT034682 | 8/F | ITA | Sinusitis | Acute cerebral edema, cephalalgia, vomiting | 7 days | HO | Recovered |
| 8573980 | 1 | GER/SPN/12/0024225 | 5/F | ESP | Tuberculosis | Arthralgia | Unknown | OT | Recovered |
| 8742938 | 2 | 2012AP002285 | 3/M | ESP | Tuberculosis | Arthralgia | 2 months | OT | Recovered |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 8784301 | 1 | Direct report | 3.5/ F | USA | Chronic sinusitis | Lower extremity muscle disorder | 2 days | DS | Not yet recovered |
| 8905335 | 2 | IN-RANBAXY-2012RR-61782 | 7/M | IND | Appendicitis | Hypersensitivity reaction | "within seconds" | OT | Recovered |
| 9002833 | 1 | US-009507513-1301USA001838 | 13/M | USA | Sinusitis | Hallucination, crying, chromatopsia | Unknown | HO | Unknown |
| 9057558 | 1 | Direct report | 13/F | USA | Sinus infection | Pain in shoulders, elbows, knees, wrists, hips | 10 days | HO | Recovering |
| 9162424 | 1 | IT-MYLANLABS-2013S1004858 | 16/F | ITA | Tracheobronchitis | Erythema, diffuse edema, urticaria, hives | 1 days | OT | Recovering |
| 9216307 | 1 | 2013/076 | 15/F | FRA | Tuberculosis | Polyarthritis | 30 days | OT | Recovered |
| 9226061 | 1 | IT-TEVA-397149ISR | 8/F | ITA | Tuberculosis | Urticarial rash, vomiting | 20 days | HO | Recovered |
| 9226861 | 1 | US-JNJFOC-20130401561 | 15/M | USA | Pharyngitis | Tendinopathy, muscle atrophy | Unknown | HO | Not yet recovered |
| 9288456 | 1 | GR-PFIZER INC-2013145175 | 1.5/M | GRC | Tuberculosis | Death due to hepatic failure | 6 months | DE | Death |
| 9308588 | 1 | CN-JNJFOC-20130510169 | 3/F | CHN | Bacterial infection | Elevated LFTs, appetite loss, fatigue | Unknown | HO | Recovered |
| 9498339 | 1 | KAD201308-001065 | 12/M | IND | Neutropenic fever | Enterocolitis, intestinal obstruction | 3 days | HO | Recovered |
| 9766445 | 1 | Direct Report | 0.5/F | USA | Unknown | Rash | 1 day | OT | Unknown |
| 9798567 | 2 | AUR-APL-2013-10817 | 16/M | ESP | *Staph. aureus* infection | Generalized macular rash | Unknown | OT | Recovered |
| 9813618 | 1 | Direct report | 11/M | USA | Antibacterial prophylaxis | SJS/TEN | 14 days | HO | Recovered |
| 8282500 | 1 | GR-ROXANE LABORATORIES, INC.-2011-RO-01745RO | 5/F | GRC | Tuberculosis | Tonic clonic seizures of the upper limbs, cardiac arrest | 1 month | DE, LT, OT | Death |
| 8306301 | 1 | JP-SANTEN INC.-INC-11-000172 | 8/M | JPN | Excoriation | Anaphylaxis | "immediate" | OT | Resolved |

*FAERS reported outcome: DE = death, DS = disability, HO = hospitalization, LT = life threatening, OT = other

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/s/

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MIHAELA P JASON
08/18/2014

TRAVIS W READY
08/18/2014

RAJDEEP K GILL
08/18/2014
Drug use data cleared by data vendor

HINA S MEHTA
08/19/2014

KELLY Y CAO
08/19/2014

SCOTT E PROESTEL
08/19/2014