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Subject:	Pediatric Exclusivity Postmarketing Adverse Event Review
Drug Name(s):	Levaquin® (Levofloxacin) Tablets (20-634) Levaquin® (Levofloxacin) Oral Solution (21-721) Levaquin® (Levofloxacin) Injection for Intravenous Use (20-635)
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Applicant/sponsor:	Ortho McNeil Raritan, New Jersey 08869
OSE RCM #:	2008-834

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EXECUTIVE SUMMARY

In accordance with the Best Pharmaceuticals for Children Act (BPCA), the Division of Pharmacovigilance II (DPV II) was asked to summarize post-marketing reports of adverse events associated with the use of levofloxacin in pediatric patients. The main focus of this review is pediatric reports of deaths and reports of serious adverse events with levofloxacin following the granting of pediatric exclusivity on March 14, 2007 and the approval of pediatric labeling. Specifically, we were asked to focus on the musculoskeletal (MS) and central nervous system (CNS) effects in pediatric patients. In order to provide a more complete review, a dataset containing all pediatric adverse event reports (n=116) were reviewed, versus reviewing only those in the exclusivity period.

According to the May 2008 levofloxacin label, the drug has multiple indications in adults (see Section 1 of the label). The drug's sole pediatric indication is in the treatment of inhalational anthrax (post exposure) in children greater than 6 months of age.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) up to the data lock date of August 27, 2008. AERS contained 10,166 reports for levofloxacin. Pediatric reports represent approximately 1.1 % of the total (116/10,166). While pediatric reports in AERS represented approximately 1% of all reports for levofloxacin, pediatric prescriptions were low representing approximately 1% of total U.S. prescriptions dispensed for the drug in the years 2006-2008. Overall, the use of levofloxacin in the pediatric population is low, and the frequency of AERS reports is proportional to its use.

The overall safety profile of levofloxacin in pediatrics appears to be similar to adults without new serious unlabeled adverse events. Musculoskeletal events, primarily arthralgia, is the most frequently reported event and represents the predominant adverse event reported among pediatric users. The most prevalent central nervous system event reported in the pediatric case series was seizure, followed by abnormal behavior or confusion, hallucinations and panic attacks.

The Division of Special Pathogens and Transplant Products is currently working with sponsors to update all fluoroquinolone labeling to reflect a Black Box warning with regard to tendinopathy and tendon rupture in patients of all ages. In the opinion of the reviewer, with the addition of this Black Box and the current labeled CNS warnings (convulsions and toxic psychosis), levofloxacin will be adequately labeled to warn prescribers of potential musculoskeletal and central nervous events in users of all ages. DPV II will continue to monitor the AERS database for adverse events associated with the use of levofloxacin in pediatric patients.

BACKGROUND

Levofloxacin, a fluoroquinolone antibacterial agent (marketed as Levaquin® by Ortho McNeil), was first approved in the United States on December 20, 1996. Pediatric exclusivity was granted on March 14, 2007 based on a final amended "Written Request" for pediatric studies for levofloxacin issued by the agency on June 16, 2006. The agency requested that the sponsor conduct studies in pediatric subjects (≥ 6 months to 17 years of age) with bacterial infections, evaluating the safety profile, antibacterial activity and the pharmacokinetics of the drug with special attention to short and long term safety of musculoskeletal adverse events. The sponsor responded by submitting Phase III studies during which study drug was administered in both active-controlled (community acquired pneumonia and acute otitis media (clinical outcome)) and uncontrolled acute otitis media (bacteriologic outcome). There were no significant differences observed between levofloxacin users and the comparators in these studies with respect to musculoskeletal and central nervous system events.[1]

The sponsor also conducted a long-term surveillance study in which the primary objective was to evaluate and compare the overall incidence of musculoskeletal disorders in pediatric subjects after the first dose of levofloxacin with that of standard non-fluoroquinolone therapy. In this study, pediatric patients treated with levofloxacin for an acute bacterial infection showed a significantly higher incidence of musculoskeletal disorders (tendinopathy, arthritis, arthralgia, gait abnormality) compared to "standard" non-fluoroquinolone therapy (p=0.038). The review of this study, resulted in additional safety information added to the levofloxacin label in September 2007. The sponsor did not request additional indications for pediatrics based on the Phase III studies, but rather, added the musculoskeletal findings from the long-term surveillance study to the **USE IN SPECIAL POPULATIONS** section (section 8.4 Pediatric Use) of the levofloxacin label. The safety observations in this surveillance study are not unlike those seen in adults in postmarketing reports.

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Levofloxacin is available in the following three formulations:

- Oral Tablet- FDA approved December 20, 1996 and is available in 250mg, 500mg and 750mg tablets.
- Oral Solution- FDA approved October 21, 2004 and is available as 250mg/10ml solution.
- Injectable- FDA approved December 20, 1996 and is available as a premixed intravenous solution in D5W (250mg/50ml, 500mg/100ml and 750mg/150ml). The drug is also available in more concentrated intravenous solution (500mg/20ml, 750mg/30ml).

A fourth formulation, levofloxacin ophthalmic drops (0.5% and 1.5%), manufactured by Santen Inc., is approved but was not a subject of this review.

Levofloxacin is indicated for the following conditions in **adults**:

Levofloxacin is a quinolone antibacterial indicated in adults (≥ 18 years of age) with infections caused by designated, susceptible bacteria to include the following:

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[1] Medical Officer Review of Pediatric sNDAs located in DFS and signed 6/21/2007. Kassa Ayalew M.D.

- Pneumonia: nosocomial and community acquired
- Acute bacterial sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Skin and skin structure infections both complicated and uncomplicated
- Chronic bacterial prostatitis
- Urinary tract infections both complicated and uncomplicated
- Acute pyelonephritis
- Inhalational anthrax (post exposure)

Levofloxacin is indicated for the following condition in **pediatrics:**

- Inhalational anthrax (post exposure)

1.2 PEDIATRIC LABELING

As of August 29, 2008, the most recent levofloxacin labeling change issued in May 2008, reflected updated pediatric information. Below are sections of the label that contained pediatric labeling.

1 INDICATIONS AND USAGE

1.13 Inhalational Anthrax (Post-exposure): reflects that levofloxacin may be used for this indication in pediatric patients (≥6months) although safe use beyond 14 days for this population has not been evaluated.

2 DOSAGE AND ADMINISTRATION

2.2 Dosage in Pediatric Patients: provides dosage recommendations for the only pediatric indication for levofloxacin (inhalational anthrax-post exposure).

5 WARNINGS AND PRECAUTIONS

5.9 Musculoskeletal Disorders in Pediatric Patients and Arthopathic Effects in Animals

"LEVAQUIN® is indicated in pediatric patients (≥6 months of age) only for the prevention of inhalational anthrax (post-exposure). An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy and gait abnormality) compared to controls has been observed in pediatric patients receiving LEVAQUIN®.

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in weight-bearing joints and other signs of arthropathy in immature animals of various species."

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use: Provides inhalational anthrax post-exposure dosing recommendations, adverse events including the incidence of musculoskeletal disorders in a pediatric clinical trial. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. Additional details from this section of the label may be found in the Appendix as Figure 5.

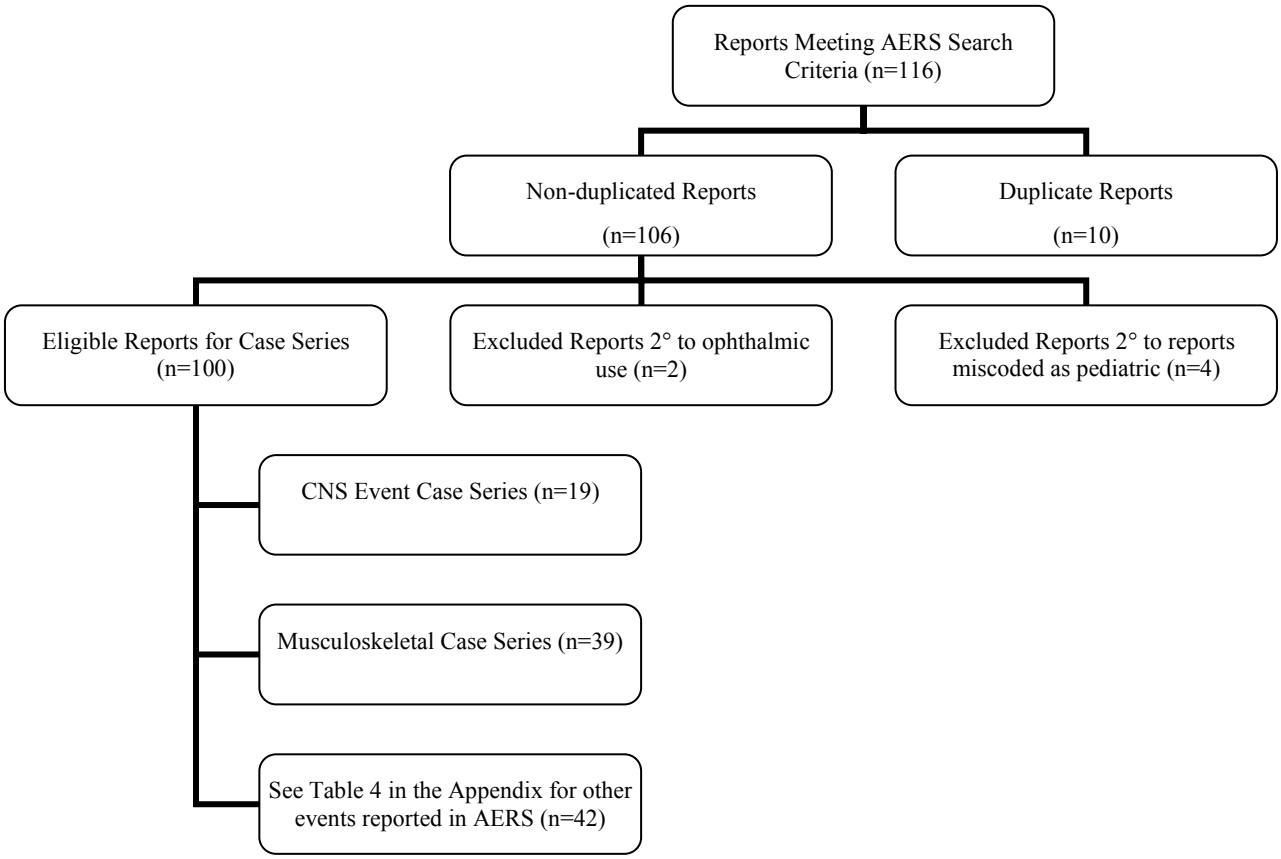
2 METHODS AND MATERIALS

2.1 AERS SEARCH CRITERIA

AERS was searched on August 27, 2008 for all reports in the database of pediatrics (age 0-16 years) and adults (17 years and greater) associated with levofloxacin use (see Table 1 in Section 3.1).

A detailed (case by case) review of all AERS reports (n=116) with levofloxacin as the suspect drug was conducted. Figure 1 below is a schematic which shows duplicate and miscoded reports as well as reports for ophthalmic levofloxacin administration. After removing these reports, this subset constituted the eligible reports for case series (n=100) which was used to characterize the post-marketing adverse events associated with pediatric use of levofloxacin.

Figure 1. Flow Diagram of Case Selection for Levofloxacin Pediatric Use (12/20/1996 -8/27/2008)



In order to better focus this pediatric review, a data mining algorithm was used to identify disproportionately reported preferred terms as areas to review in more detail. Using these data coupled with the specific request from the Office of Pediatric Therapeutics (OPT) and Pediatric and Maternal Health Staff (PMHS), this review focuses on musculoskeletal and central nervous system events in pediatric patients associated with levofloxacin use. Additional rationale for choosing these events is based on an OSE review of levofloxacin pediatric adverse events from 8/10/2004 (ODS PID# D040411), in which the most frequently reported events involved these two body systems.

3 AERS RESULTS FOR LEVOFLOXACIN

3.1 CRUDE COUNTS OF ALL AERS REPORTS: TABLE 1

Table 1: Crude counts[1] of AERS Reports for All Sources from Marketing Approval Date (12/20/1996) through 8/27/2008

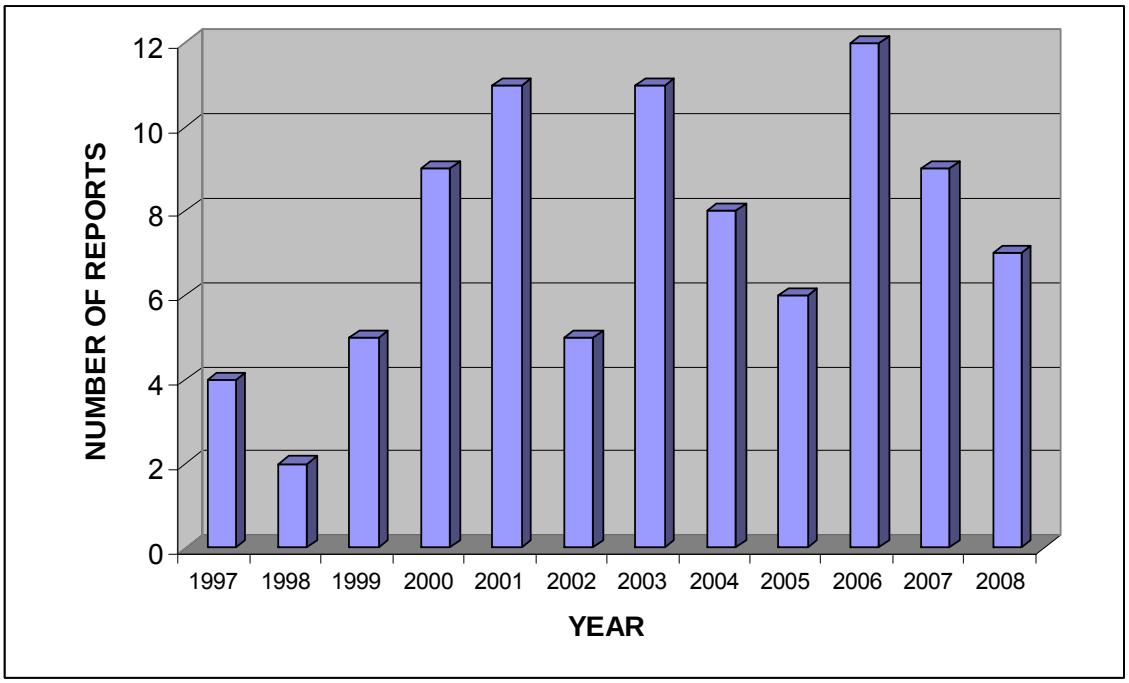
	All reports (US)[2]	Serious[3] (US)	Death (US)
Adults (≥ 17 yrs.)	8321 (6367)	7100 (5176)	774 (317)
Pediatrics (0-16 yrs.)	116 (89)	100 (77)	3 (0)
Age unknown (Null values)	1729 (1594)	1362 (1229)	147 (107)
Total	10166 (8050)	8562 (6482)	924 (424)

[1] May include duplicates

[2] US Counts in parentheses

[3] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

Figure 2: Crude reporting trend for pediatric domestic reports (n=89) from approval date



****Approved 12/20/1996**

3.2 CASE CHARACTERISTICS FROM PEDIATRIC EXCLUSIVITY REVIEW

Table 2: Characteristics of all AERS Pediatric Musculoskeletal Cases through August 27, 2008 (n=39)		
Gender [n=39]	Male: 12 Female: 25 Unknown: 2	
Age [n=39]	0- <1 month 0 1 month <2 yrs 1 2-5 yrs 1 6-11 yrs 5 12-16 yrs 32 Mean : 13.1 years Median: 14 years Range: (0.33-16.5 years)	
Percent of total levofloxacin reports in AERS for a pediatric patient (0-16) with a musculoskeletal adverse event	39% (39 levofloxacin pediatric reports/100 levofloxacin reports)	
Origin [n=39]	US: (35) Foreign: Japan (4)	
Daily dose [n=29]	Mean: 548.3 mg Median: 500 mg Range: 250-1000 mg	
Days of therapy leading up to event [n=31]	Mean: 7.9 days (See Figure 3 Appendix for Histogram) Median: 7 days Range: 1-25 days	
Indications [n= 39]	Sinusitis (14) Unknown (4) Bronchitis/Pneumonia/Lung infection (3) Cystic fibrosis related infection (2) Prophylaxis (2) Otitis Media (2) Acne vulgaris (2) Nasopharygitis (1) Cellulitis (1)	Dental abscess (1) Diverticulitus (1) Glomerulonephritis (1) Laminectomy (1) Scalp infection (1) Sinus surgery (1) Urinary tract infection (1) Skin papilloma (1)
Outcomes [n=36]	Death: 0 Disabling: 7 Hospitalization: 8 Required Intervention: 3 Other: 21 Outcome Unknown: 3	

Table 3: Characteristics of all AERS Pediatric Central Nervous System (CNS) Cases through August 27, 2008 (n=19)		
Gender [n=19]	Male: 12 Female: 6 Unknown: 1	
Age [n=19]	0- <1 month 1 1 month <2 yrs 1 2-5 yrs 1 6-11 yrs 1 12-16 yrs 15 Mean : 11.8 years Median: 13 years Range: (0.01-16 years)	
Percent of total levofloxacin reports in AERS for a pediatric patient (0-16) with a CNS adverse event	19% (19 levofloxacin pediatric reports/100 levofloxacin reports)	
Origin [n=19]	US: 14 Foreign: Japan (4), Germany (1)	
Daily dose [n=15]	Mean: 414.7 mg Median: 500 mg Range: 200-500 mg	
Days of therapy leading up to event [n=16]	Mean: 10 days (See Figure 4 Appendix for Histogram) Median: 3.5 days Range: 1-90 days	
Indications [n=19]	Sinusitis (4) Unknown (4) Pulmonary infection (2) Infected foot or toenail (2) Pharyngitis (1) Pancreatitis (1)	Gastroenteritis (1) Gum abscess (1) Infection (1) Staphylococcus aureus infection (1) Urinary respiratory infection (1)
Outcomes [n=19]	Death: 0 Disabling: 3 Hospitalization: 6 Required Intervention: 1 Other: 9 Outcome Unknown: 2	

4 DISCUSSION/SUMMARY OF CASES

4.1 PEDIATRIC DEATHS (N= 3)

All three pediatric death cases are either confounded by use of concomitant medications or concurrent disease. These cases were also not associated with a musculoskeletal or central nervous system event.

Case #3431736 (ISR 3461848-3)

Report originating from Japan of a13 year old boy with a history of spastic tetraparesis due to perinatal anoxia, mental retardation, frequent convulsive seizures, esophageal atresia and recurrent bronchopulmonary infection. He received levofloxacin (dose, route and therapy dates not specified) for bronchopneumonia and died on an unspecified date of unknown cause, while on levofloxacin. He was concomitantly receiving sodium valproate, cisapride and lansoprazole.

Case #3442674 (ISR 3547845-8)

Physician report originating from Japan of a 12 year old boy, with a history of asthma and allergies,was prescribed levofloxacin 500 mg oral and benzydamine HCl (anti-inflammatory agent) spray (twice daily) for treatment of acute pharyngitis. Several minutes after taking the first tablet of levofloxacin, he took benzydamine HCl followed by coromoglicate Na (mast cell stabilizer). Approximately 6 - 10 minutes after taking levofloxacin he experienced dyspnea and developed anaphylactic shock. The parents describe life saving measures were attempted but were only partially successful. Cromoglicate Na had been previously well tolerated by this child. He was resuscitated and admitted to the intensive care unit. The patient went into a coma immediately after the event and was declared clinically dead two days after the event. He subsequently died eight days after the event. The hospital physicians deny a causal relationship between the anaphylactic shock and the intake of levofloxacin because of the short time of onset of the event. The reporting physician commented that the use of benzydamine HCl as an inhaler could induce larygeo-bronchospasm which is speculated as the cause of the death.

Case #6392468 (ISR 5787641-4)

Report originating from Health Authority for Great Britain of a 12 month old male with a medical history of colectomy (three months previously), ulcerative colitis, ileostomy (3 months previously), pelvic collection, sepsis (secondary to pelvic collection) and rheumatoid arthritis was treated with levofloxacin (unspecified, unknown) and metronidazole (unspecified, unknown) initiated on an unknown date for an unknown indication. The patient was also treated with paracetamol (acetaminophen) for analgesia. Concomitant medications included: clavulin (amoxicillin/clavulanate K), gentamicin and vancomycin for unknown indications as well as diclofenac, metoclopramide and omeprazole. The patient developed high-anion gap metabolic acidosis secondary to pyroglutamic aciduria following the administration of paracetamol as an analgesic. Following the drainage of the abscess, the patient was treated with the antibiotics listed above, and was commenced on total parenteral nutrition after three weeks. One week later the patient's condition deteriorated and, on an unknown date, the patient experienced disorientation. Examination of the urine revealed the presence of pyroglutamic acid. Paracetamol and the antibiotic drugs were discontinued, but the patient further deteriorated and died secondary to a myocardial infarction after a non-specified time period. The reporters noted that paracetamol and antibiotics are known risk factors for pyroglutamic aciduria.

4.2 NON-FATAL SERIOUS MUSCULOSKELETAL (N=39) AND CNS (N=19) ADVERSE EVENT REPORTS

The cases included in this section were chosen based on discussions during the May 23, 2008 meeting with OPT and PMHS. These discussions were primarily focused on musculoskeletal events, based on data mining scores which demonstrated disproportionate reporting of musculoskeletal events in pediatric levofloxacin users. In a prior OSE review of levofloxacin pediatric adverse events reports in AERS, which was completed on 8/10/2004 (ODS PID# D040411), the most prevalent events reported in AERS among pediatric users were musculoskeletal events (32%: 19 of 59 total pediatric reports) and central nervous system events (20%: 12 of 59 total pediatric reports). This reporting trend has not changed since the completion of that review.

4.2.1 MUSCULOSKELETAL (N=39) ADVERSE EVENT REPORTS

Fluoroquinolones as a drug class have the ability to accumulate intracellularly[2] and could potentially concentrate in connective tissue.[3] Tendon cells, which are predominantly fibroblasts, are responsible for the maintenance of the extracellular matrix which most likely involves turnover of extracellular components, including collagen cross-linking, breakdown and resysnthesis of tissue in tendons.[4] A key factor in this remodeling process is believed to be mediated by a group of enzymes known as metalloproteinases. Corps et al demonstrated that a change in the expression of metalloproteinases could alter tissue remodeling and therefore increase the likelihood of tendinopathy. While the mechanism of fluoroquinolone induced tendinopathy remains to be fully elucidated, this hypothesis may partially explain this toxicity. To the reviewer's knowledge, there is no evidence that suggests metalloproteinase expression in children differs from that in adults, thereby children may be equally susceptible to this toxicity. Therefore, the reviewer believes a biological basis for the observed tendinopathy with fluoroquinolones may exist for both adult and pediatric patients.

Musculoskeletal adverse events are well documented in the Levaquin® May 2008 revision of the label. Tendon effects are documented in section 5 under the **WARNINGS AND PRECAUTIONS** heading of the label under sub-section 5.4 Tendon Effects and sub-section 5.9 Musculoskeletal Disorders in Pediatric Patients and Arthopathic Effects in Animals. In section 8 under the **USE IN SPECIFIC POPULATIONS** under sub-section 8.4 **Pediatric Use**, the label further describes the results of a long-term surveillance study evaluating musculoskeleal disorders in children on levofloxacin or an non-fluoroquinolone antibiotic. This study suggests that children using levofloxacin are more likely to experience a musculoskeletal event through one year of follow-up (p=0.025). The Division of Special Pathogens and Transplant Products (DSPTP) is also in the process of adding a Black Box warning to all fluoroquinolone products to inform prescribers of tendinopathy and tendon ruptures which have been associated with fluoroquinolone use, including levofloxacin, in patients of all ages.

This review of the post-marketing AERS data noted that 39% (39 out of 100 cases) of levofloxacin cases in pediatrics were submitted to notify the agency of a musculoskeletal event. These events were predominantly reported as joint related symptoms; arthralgia or arthropathy (n=21) with fewer reports of bone or tendon symptoms (n=13) and myalgia or myopathy (n=5). Arthralgia was also the most commonly reported musculoskeletal event among levofloxacin pediatric users in a recent observational study.[5] There were a total of five cases of tendon rupture (see Table 5, Appendix). Qualitatively, most of these patients presented with generalized symptoms of not feeling "normal" with joint edema and pain, significant enough to alter normal daily activities. Among the 39 cases, the recovery outcome was unknown for most (n=17), with

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[2] Pasqual A, Garcia I, Ballesta S, Perea EJ. Uptake and intracellular activity of trovafloxacin in human phagocytes and tissue-cultured epithelial cells. Antimicrob. Agents Chemother. 1997; 41(2):274-277.

[3] Melhus A. Fluoroquinolones and tendon disorders. Expert Opin Drug Saf. 2005; 4(2): 299-309.

[4] Corps An, Harrall RL, Curry VA, Fenwick SA, Hazleman BL, Riley GP. Ciprofloxacin Enhances the Stimulation of Matrix Metalloproteinase 3 Expression by Interleukin-1 in Human Tendon-Derived Cells- A Potential Mechanism of Fluoroquinolone Induced Tendinopathy. Arthritis Rheum. 2002; 46(11): 3034-3040.

[5] Noel GJ, Bradley JS, Kauffman RE, Duffy CM, Gerbino PG, Arguedas A, Bagchi P, Balis DA, Blumer JL. Comparative Safety profile of Levofloxacin in 2523 Children with a focus on four specific musculoskeletal disorders. Ped. Infectious Disease Journal. 2007; 26(10):879-891.

six patients fully recovered and a large number (n=16) not fully recovered based on the last AERS submission. Using the dataset assembled from these 39 cases in AERS, the reviewer was unable to accurately estimate the time to symptom resolution as only three cases had symptom abatement time documented in AERS.

Table 2 contains characteristics of the musculoskeletal cases. There were twice as many females reported with musculoskeletal symptoms. Although the reviewer is unaware of any biological reason that would make girls more susceptible to these events, a recent review published of fluoroquinolone associated tendon disorders, suggested that the male to female ratio of musculoskeletal adverse events in adult patients is 2:1 or 3:1, which could be reflected in consumption data.[3] The largest group of children experiencing musculoskeletal events were adolescents (12-16 years), which constituted 82% of the total musculoskeletal report subset. This observation is not surprising, since weight bearing tissues are most often affected by fluoroquinolones. Moreover, this age group, unlike adults and younger children, is often involved in strenuous extracurricular activities, such as sports, which place additional stress on connective tissues. Most of these reports provide doses and days of therapy, which are not unusually high or lengthy, with the median dose leading up to event of 500mg/daily and a duration median of 7 days. Figure 3 in the appendix, contains a histogram with the frequency distribution of days of therapy leading up the musculoskeletal event.

Interestingly, this AERS review demonstrates that levofloxacin was often used to treat a non-complicated infection such as sinusitis (n=14), nasopharygitis (n=1) and otitis media (2). None of the patients reported in AERS cases were being treated for inhalation anthrax post-exposure. There were other cases in which levofloxacin was chosen because of failed attempts with other antibiotics or limited microbial susceptibilities, such as acne vulgaris (n=2), cystic fibrosis related infection (n=2), cellulitis (n=2) or lung infections (n=3). Levofloxacin was chosen in several cases in which the patient had multiple drug allergies and the prescriber had already considered other options that were precluded by pre-existing drug allergy. While it appears there are cases in AERS in which levofloxacin was prescribed as an initial drug choice for an non-complicated infection, when perhaps a safer alternative (ß-lactam or macrolide) may have been chosen, this review also notes that overall levofloxacin use among pediatric patients is low. Based on a recent OSE review, approximately 1% of the total levofloxacin prescriptions written in the United States, had an intended use in patients 0-18 years of age.[6] Despite the off-label use of the drug, the reviewer finds the use data in pediatric patients to be reassuring, in that most prescribers are not treating pediatric patients with levofloxacin, therefore, in the reviewer's opinion, this off-label use does not represent a wide spread public health concern.

Most of the patients in this case series did not have evidence of a significant prior medical history documented in AERS. For the purposes of this review, a history of one or more chronic diseases (i.e. asthma, transplantation, musculoskeletal disorder, chromosomal abnormality, thyroiditis, cystic fibrosis), was deemed significant. Prior to the musculoskeletal event, most (27/39 cases, 70%) of these patients did not have a significant prior medical history. Among the 39 cases, 3 cases (7.7%) either had a history of transplant or chronic corticosteroid use.

The reviewer was also concerned with reporting that could be stimulated by safety information regarding fluoroquinolones released by the FDA or other agencies. When the total number of musculoskeletal reports are stratified by time, in the range of 1997-2008, there is not a year in which reporting for this group of adverse events was predominant (Figure 6-Appendix). The reports were received by the agency evenly distributed over time, making stimulated reporting less likely of a concern. It remains unknown whether children are at higher risk for

[6] Drug Use Review Vicky Borders-Hemphill located in DFS dated 7/14/2008 (RCM 2008-330).

musculoskeletal adverse events than adults, however there are an adequate number of cases in AERS to suggest that pediatric patients experience these events.

4.2.2 CNS (N=19) ADVERSE EVENT REPORTS

Levofloxacin CNS adverse events may be explained by the ability of the fluoroquinolones to modulate γ-aminobutyric acid (GABA) and excitatory amino acid (EAA) neurotransmission.[7] Fluoroquinolones may bind to GABA receptors, thereby blocking the natural ligand GABA and may also serve as agonists for receptors activated by EAA. The end result of this action could result in a stimulated CNS which may explain some of the post-marketing observations with levofloxacin. While this is a working hypothesis, it should be noted, that the underlying mechanism by which fluoroquinolones may induce CNS adverse events is not completely understood. Because CNS adverse events are labeled for levofloxacin, it is not surprising to see spontaneous post-marketing reports of such events submitted to the agency.

Central nervous system (CNS) adverse events are well documented in the Levaquin® May 2008 revision of the label. CNS effects are documented in section 5 **WARNINGS and PRECAUTIONS** under sub-section 5.5 **Central Nervous System Effects** and sub-section 5.7 **Peripheral Neuropathy**. CNS adverse events reported with levofloxacin use include convulsions, toxic psychoses, increased intracranial pressure which can lead to tremor, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and rarely suicidal thoughts or acts. These adverse events may occur following the first dose.[8]

This review of the post-marketing AERS data demonstrate that 19% (19 out of 100 cases) of the pediatric levofloxacin cases in AERS were submitted because of a CNS event. These events were predominantly reported as seizures (n=5), followed by abnormal behavior or confusion (n=4), hallucinations (n=3) and panic attacks (n=2). There were other reported CNS events, however all occurred less frequently than two and were also labeled. The median dose for all of these patients was 500mg for a median therapy duration prior to event of 3.5 days. Figure 4 in the appendix, contains a histogram with a frequency distribution of days of therapy leading up the event. It is notable that while MS events approximate a normal distribution, CNS events are left skewed suggesting a rapid onset with fewer levofloxacin doses. This is consistent with the labeling in that CNS events have been observed after a single dose. Notably, a prior medical history of epilepsy, neuropathy or psychiatric disease was not documented in any of these pediatric cases.

Table 3 contains characteristics of the CNS cases. Unlike, musculoskeletal events, there were twice as many males reported with CNS symptoms. Again the reviewer is unaware of any plausible reason that would make one gender more susceptible to these events. Agency drug use data were not stratified by gender, therefore it is unknown if this imbalance reflects usage patterns, chance or a real difference in outcome based on gender. The largest group of children experiencing CNS events were adolescents (12-16 years), which constituted 79% of the total CNS report subset. This observation is consistent with estimated usage patterns of the drug. Based on an OSE drug use review, approximately 92-93% of levofloxacin prescriptions dispensed from U.S. retail pharmacies with intended pediatric use, were intended to be used by patients aged 12-18. Additionally, this age group may be more adept at characterizing an adverse event such that it

[7] De Sarro A and De Sarro G. Adverse Reactions to Fluroquinolones. An Overview on Mechanistic Aspects. Current Medicinal Chemistry. 2001; 8:371-384.

[8] Levaquin (Levofloxacin) May 2008 labeling, Ortho-McNeil Pharmaceuticals.

was reported more often than in younger children. As with musculoskeletal event reporting, the reviewer was concerned with AERS reporting that could have been stimulated by information released regarding fluoroquinolone toxicity. When the number of cases are stratified by time, from 1997-2008, the reports were received by the agency without a surge of reporting in a single year (Figure 7-Appendix). Therefore, the reviewer concludes that stimulated reporting in this situation is less likely. It remains unknown whether children are at higher risk for CNS adverse events than adults, however there are an adequate number of cases in AERS to suggest that pediatric patients experience these events.

5 CONCLUSION

Based on the review of post-marketing reports of levofloxacin pediatric use identified in AERS, it appears the safety profile of the drug is similar in the pediatric population when compared to adults (MS and CNS events) and the proportion of these MS and CNS events reported has not changed since the last OSE pediatric review of the drug in 2004. In the years 2006-2008, levofloxacin use among pediatrics was estimated to be around 1% in the United States and the total number of domestic, pediatric AERS reports for levofloxacin is approximately 1.1% of all domestic AERS reports for levofloxacin in the database. These data suggest that levofloxacin use in pediatrics is low and that it is being appropriately avoided in pediatric patients. Nonetheless, there are some cases in which the drug has been prescribed when perhaps a safer alternative could have been chosen for a non-complicated infection. Levofloxacin currently has one pediatric indication for post-exposure treatment to prevent inhalational anthrax, and none of the AERS cases reviewed indicated the drug was intended to be used for this purpose. The events identified in this review are currently labeled, with specific warnings for musculoskeletal adverse events provided for both pediatric and adult patients as well as warning of potential CNS events in levofloxacin users. In the opinion of the reviewer, the drug is adequately labeled to provide safety information to the prescriber for these events in users of all ages. Therefore, no addition labeling changes are recommended.

6 RECOMMENDATIONS

- Based on the review of the pediatric AERS data for levofloxacin, no labeling updates are recommended at this time.
- Continue monitoring of the AERS database for adverse events associated with the use of levofloxacin in pediatric patients.

7 APPENDIX

Table 4 Summary Characteristics of All Non-Musculoskeletal, Non-Central Nervous System, Non-Death Pediatric Levofloxacin Cases in AERS through August 27, 2008

N=39 Sorted Alphabetically by Adverse Event (U=Unknown, N=42 if death cases included)

ISRNUM	*CSENUM*	*AGE (yrs)*	*GENDER*	*ADVERSE EVENT*	*INDICATION*
3849595-7	3711011	11	U	Acute drug intoxication (valsartan)	U
3507139-3	3481801	16	Female	Agranulocytosis	Bronchitis
3939393-8	3810293	11	Female	Agranulocytosis	Bronchitis
3309596-4	3311670	15	Male	Allergic reactions	U
4140084-1	3966985	0.4	Female	Allergic reactions	Stoma infection
4638832-7	5781158	15	Female	Allergic reactions	Urinary Tract Infection
4981842-0	6035719	9	Male	Allergic reactions	Prophylaxis
5337415-3	6321953	5	Female	Allergic reactions	Staphylococcal infection
5613923-2	6543562	8	Female	Allergic reactions	Cystic Fibrosis
3310040-1	3318902	12	Female	Anaphylactic reaction	Sinusitis
3479046-6	3449418	11	Male	Anaphylactic reaction	Cellulitis
4018600-X	3885666	16	Male	Anaphylactic reaction	CAP
4197087-0	4011603	U	Male	Anaphylactic reaction	Urinary Tract Infection
4854091-4	5953004	13	Male	Anaphylactic reaction	Sinusitis
5628666-9	6562694	16	Female	Anaphylactic reaction	Appendicitis
5272300-7	6267449	16	Male	Asthma	Bronchitis
3187903-3	3242820	16	Female	Autoimmune vasculitis	Urinary Tract Infection
3615232-X	3573508	U	Female	Birth defect, pre-mature birth	Cystitis
3806200-3	3720259	0.2	Male	Bleeding ulcer	Staphylococcal aureus line related bacteremia
3603906-6	3563065	1	U	Breast milk changed color with irritable infant	Otitis media
3869086-7	3763898	16	Female	Brochoconstriction	Pyelonephritis
4163809-8	3985488	10	Female	Bruising unexplained, photosensitivity	Cystic Fibrosis
3816473-9	3718677	4	Female	Deep Vein Thrombosis	Sinusitis
5466578-4	6432652	15	Male	Dispensing error	Sinusitis
3475173-8	3445301	14	Male	Drug interaction	Otitis media and sinusitis
3626132-3	3578462	6	U	Hematuria	Prophylaxis
4351367-4	4013575	12	Male	Hemophagocytic Syndrome-Drug Induced	Prophylaxis
4946386-0	6011138	1.87	Female	LFT increase, skin eruption	Aspiration pneumonia
3479003-X	3448313	6	U	LFT increased	Osteomyelitis
3728807-4	3660031	16	Female	Pancreatitis	Peritonsillar abscess
5259768-7	6261424	13	Male	Postural orthostatic tachycardia syndrome	Septic thrombophlebitis
5683808-4	6597006	U	Male	Premature birth -in utero exposure	U
4852237-5	5942946	11	Male	Pyrexia	Pericarditis
2041244-6	3113171	10	Female	Respiratory distress	Cellulitis

5815021-1	6660255	16	Male	Stevens-Johnson Syndrome	Beta-hemolytic streptococcal infection
3900472-2	3775572	11	Male	Stomatitis,SJS	Pneumonia
5505351-5	6413639	0.01	Male	Tetralogy of Fallot-in utero exposure	U
5557150-6	6465197	4	Female	Tooth enamel destruction	Tuberculosis-resistant
3179300-1	3191439	7	Male	Vomitting	Upper respiratory infection

Table 5 Cases of Tendon Rupture (n=5)

ISR#	Case#	Age/Gender	Narrative
5259532-9	6261438	15/U	Pharmacist reports via a sales representative concerning a 15 year old (gender unknown) who was treated with levofloxacin 500mg daily for an unknown indication. Concomitant medications were also not reported. In May 2006, the patient experienced a tendon rupture at an unknown site.
384416-7	3749068	16/F	Physician reports via a sales representative of a 16.5 year old girl who reportedly was allergic to almost all antibiotics and was given levofloxacin 500mg daily for sinusitis and subsequently experienced an unspecified tendon rupture. Concomitant medications were not reported.
4997871-7	6081604	13/F	Physician reports of a 13 year old girl who was placed on a 14 day course of levofloxacin 500mg daily for diverticulitus (10/14/05 through 10/28/05) who became disabled due to multiple musculoskeletal injuries (February-April 2006) that the physician associated with levofloxacin use. Concomitant mediations included metronidazole 500mg QID stopped 10/12/05 and clindamycin 150mg started QID for 10 days with Darvocet N100 q4h prn. The injuries are listed as follows: (R) Peroneus Longus tear. Peroneus brevis sprain. (L) knee medial meniscus tear. (L) peroneus longus tendonosis + distal tenosynovitis. Peroneus brevis focal longitudinal split tear.
4524480-6	5697553	11/F	Physican reports via a sales representative of an 11 year old girl who was treated levofloxacin 500mg for the treatment of sinusitis who experienced knee and joint pain with a possible tendon tear. No concomitant medications were reported.
4524615-5 3478302-5 3497972-9	3744632 3447759 3471504	16/F	Parent of a 16 year old girl reports that her child was treated with levofloxacin 500mg daily for five days for acute maxillary sinusitis. She was prescribed a 14 day course. Prior to starting the drug, the hearing in her right ear was adversely affected by the infection and it began to improve on the antibiotic. On the fourth day of levofloxacin, the skin on the patient's ears was "itchy and very red". She developed hand tremors and seemed to have difficulty concentrating and her appetite fluctuated wildly. That night, she had bad diarrhea and a severe headache, concentrated around the back of her head. She also felt as if she was going to throw up. On the morning of the fifth day, she could barely get out of bed, but she went to school. When the mother picked her up, she was in tears because she had severe pain in her neck, her middle and upper back, and her right arm, elbow, and hand. The pain in her right arm was intense and it affected every joint. Her joints also felt stiff and swollen. She also kept feeling as if she was going to throw up. I called the physician (specialist) immediately and he said that she was having an allergic reaction to the levofloxacin. He told me to stop all antibiotics for forty-eight hours, to flush her system with as much water as she could keep down, and then, two days later, have her take clarithromycin, as she is allergic to penicillin and sulfa. She has been off the levofloxacin for 24 hours so far, and she is experiencing the following symptoms: trouble concentrating, irritibility, severe headache, severe back and joint pain, itchy, bumpy arms and forehead, trouble sleeping, decreased appetite, nervousness and extreme thirst. The redness of the skin on her outer ear comes and goes with no pattern. In follow-up from the mother, seven weeks after stopping levofloxacin she had multiple tendinopathy and acute tendonitis in Achilles tendon and rotator cuff on right side, extreme light sensitivity, irritability, depression and rash. She was diagnosed with acute adverse drug reaction (ADR) to levofloxacin. She is in a wheel chair because of imminent rupture of the Achilles tendon and her right arm is also immobilized to prevent tendinopathy exacerbation. With the exception of the sinus infection, she was a perfectly healthy 16 year old girl and all physicians have agreed that she has experienced an ADR to levofloxacin.

Figure 3. Days of Levofloxacin Therapy Prior to Musculoskeletal Event

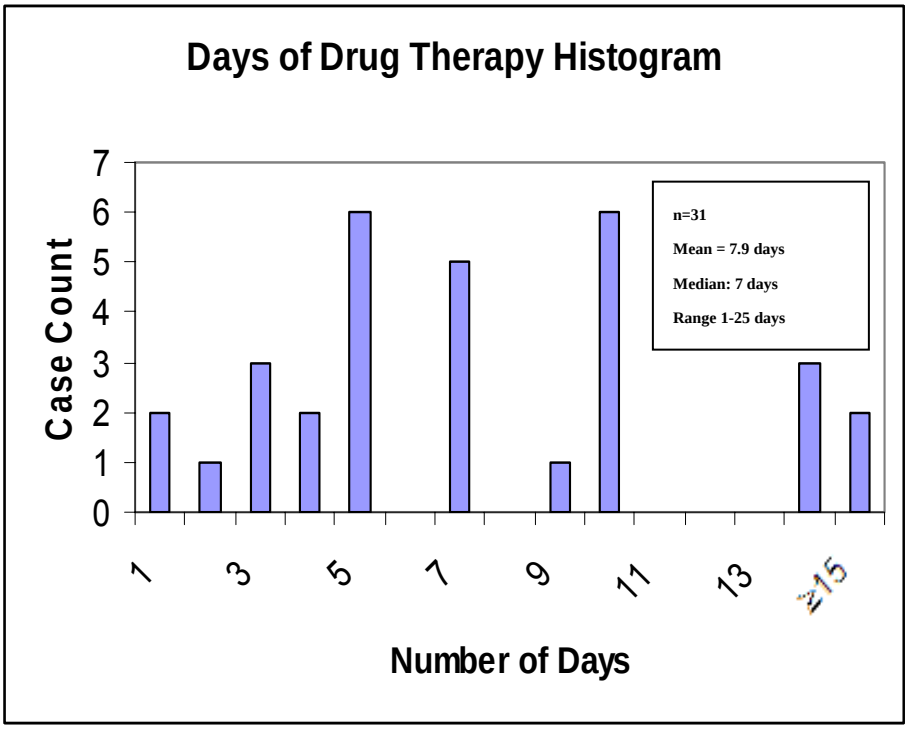


Figure 4 Days of Levofloxacin Therapy Prior to Central Nervous System Event

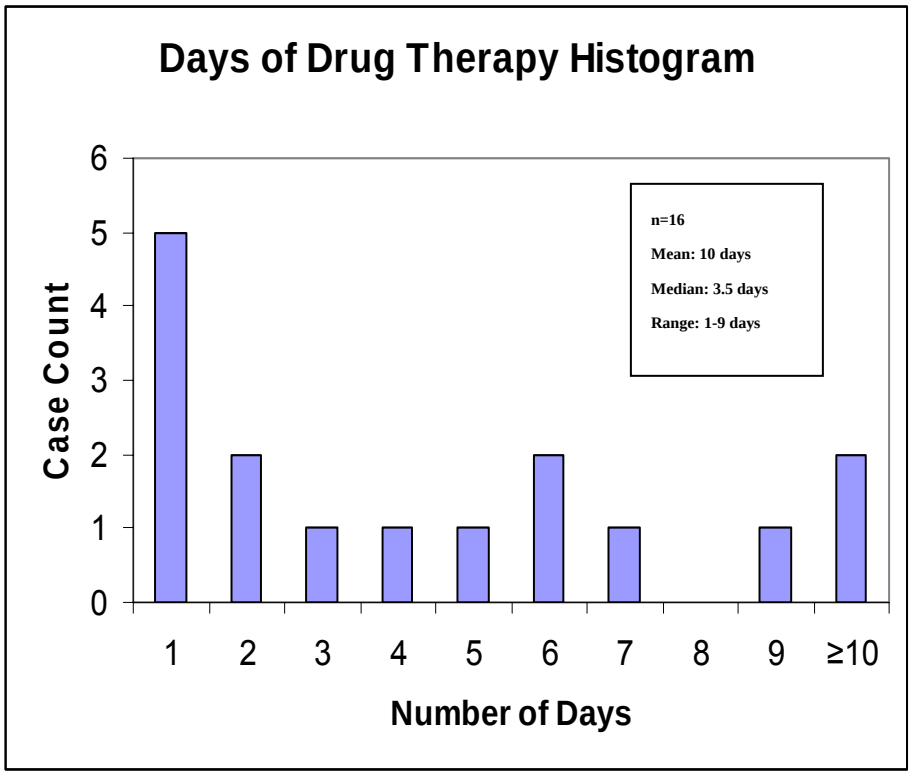


Figure 5 Levofloxacin Label Section 8.4-Pediatric Use Excerpt

8.4 Pediatric Use

Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. *[see Warnings and Precautions (5.9) and Animal Toxicology and/or Pharmacology (13.2)]*.

Inhalational Anthrax (Post-Exposure)

Levofloxacin is indicated in pediatric patients for inhalational anthrax (post-exposure). 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. The pharmacokinetics of levofloxacin following a single intravenous dose were investigated in pediatric patients ranging in age from six months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients resulting in lower plasma exposures than adults for a given mg/kg dose *[see Indications and Usage (1.13), Dosage and Administration (2.2), Clinical Pharmacology (12.3) and Clinical Studies (14.9)]*.

Adverse Events

In clinical trials, 1534 children (6 months to 16 years of age) were treated with oral and intravenous LEVAQUIN®. Children 6 months to 5 years of age received LEVAQUIN® 10 mg/kg twice a day and children greater than 5 years of age received 10 mg/kg once a day (maximum 500 mg per day) for approximately 10 days.

A subset of children in the clinical trials (1340 LEVAQUIN®-treated and 893 non-fluoroquinolone-treated) enrolled in a prospective, long-term surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendonopathy, gait abnormality) during 60 days and 1 year following the first dose of study drug. Children treated with LEVAQUIN® had a significantly higher incidence of musculoskeletal disorders when compared to the non-fluoroquinolone-treated children as illustrated in Table 9.

Table 9: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

Follow-up Period	LEVAQUIN® N = 1340	Non-Fluoroquinolone[a] N = 893	p-value[b]
60 days	28 (2.1%)	8 (0.9%)	p = 0.038
1 year[c]	46 (3.4%)	16 (1.8%)	p = 0.025

[a] Non-Fluoroquinolone: ceftriaxone, amoxicillin/ clavulanate, clarithromycin

[b] 2-sided Fisher's Exact Test

[c] There were 1199 LEVAQUIN®-treated and 804 non-fluoroquinolone-treated children who had a one-year evaluation visit. However, the incidence of musculoskeletal disorders were calculated using all reported events during the specified period for all children enrolled regardless of whether they completed the 1-year evaluation visit.

Arthralgia was the most frequently occurring musculoskeletal disorder in both treatment groups. Most of the musculoskeletal disorders in both groups involved multiple weight-bearing joints. Disorders were moderate in 8/46 (17%) children and mild in 35/46 (76%) LEVAQUIN®-treated children and most were treated with analgesics. The median time to resolution was 7 days for LEVAQUIN®-treated children and 9 for non-fluoroquinolone-treated children (approximately 80% resolved within 2 months in both groups). No child had a severe or serious disorder and all musculoskeletal disorders resolved without sequelae.

Vomiting and diarrhea were the most frequently reported adverse events, occurring in similar frequency in the LEVAQUIN®-treated and non-fluoroquinolone-treated children.

In addition to the events reported in pediatric patients in clinical trials, events reported in adults during clinical trials or post-marketing experience *[see Adverse Reactions (6)]* may also be expected to occur in pediatric patients.

Figure 6 Reporting Trend for Pediatric Levofloxacin Reports for Musculoskeletal Events (n=27)

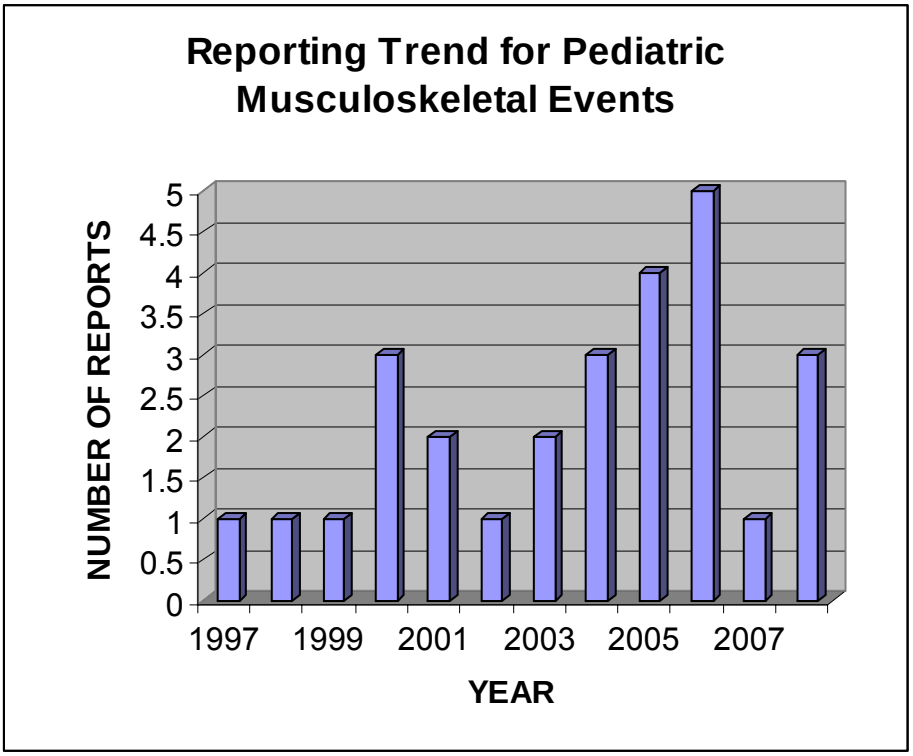
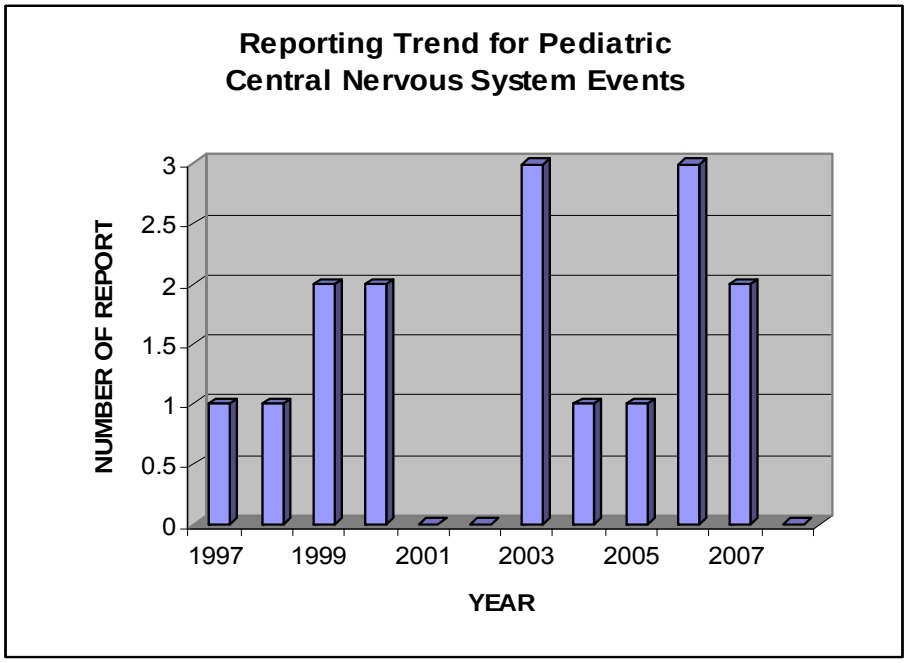


Figure 7 Reporting Trend for Pediatric Reports for Central Nervous System Events (n=17)



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