

Adverse Event Review: Levaquin® (levofloxacin)

**Pediatric Advisory Committee Meeting
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Outline

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Background Drug Information

- **Drug:** Levaquin® (levofloxacin)
- **Therapeutic Category:** antibacterial (fluoroquinolone)
- **Sponsor:** Ortho McNeil Janssen
- **Original Market Approval:**
 - December 20, 1996 (oral tablet and injectable)
 - October 21, 2004 (oral solution)
- **Pediatric Exclusivity Granted:** March 14, 2007
- **Pediatric Labeling Changes:** September 11, 2007
- **Indication:**
 - Adult: Multiple bacterial infections
 - No pediatric indication related to exclusivity studies
 - Inhalational anthrax (post-exposure) in pediatric patients \geq 6 months (May 5, 2008)

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Drug Use Trends

April 1, 2005 – March 31, 2008

Levaquin® (levofloxacin)

Outpatient/Oral

- Overall pediatric use of levofloxacin is decreasing (-17%)¹
- Patients 0-18 represented ~ 1.2% of total projected patients who filled a prescription² (~112,000) and ~ 1% of total dispensed prescriptions (~130,000, 93% age 12-18yr)³
- General Practice/Family Medicine/Doctors of Osteopathy was the top prescribing specialty¹
- Top diagnosis codes⁴:
 - 0-5 years : Urinary Tract Infection NOS
 - 6-11 years: Cellulitis NOS
 - 12-18 years: Chronic Sinusitis NOS

¹SDI LLC: Vector One®, National (VONA), Data extracted June 23, 2008

²SDI LLC: Vector One®, Total Patient Tracker, Data extracted June 23, 2008

³SDI LLC: Vector One®, National (VONA), Data extracted May 12, 2008

⁴SDI Physician Drug and Diagnosis Audit, Data extracted May 13, 2008

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Pediatric Exclusivity Studies:

Levaquin® (levofloxacin)

- Pharmacokinetic Studies :
 - Systemic exposure at 10 mg/kg bid patients < 5 years and 10 mg/kg qd in patients ≥ 5 years, po and IV, not equal to adult exposure.
- Phase III studies in patients 6 months to 17 years
 - Active controlled
 - Community Acquired Pneumonia (CAP)* (6 mo-16 yrs)
 - Acute Otitis Media (AOM)** (6 mo-5 yrs, clinical outcome)
 - Uncontrolled study acute otitis media (bacteriologic outcome)
 - Long-term (1 year), prospective, surveillance study of musculoskeletal disorders in patients 6 mo-16 yrs (tendinopathy, arthritis, arthralgia, gait abnormality)

Efficacy was comparable and not inferior to comparator

No indication for CAP/AOM secondary to musculoskeletal events

** Comparator: Augmentin or IV ceftriaxone (pts < 5 yrs) OR IV ceftriaxone + IV erythromycin or clarithromycin (pts ≥ 5 yrs)*

***Comparator: Augmentin*

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Pediatric Exclusivity Studies

Safety

Levaquin® (levofloxacin)

CAP Study (n =712 subjects)

- Deaths: n= 2 (levofloxacin group, neither thought to be related to treatment)
 - 13 ½ y/o with multiple foci pneumonia with pneumatocele, fever and respiratory distress. Cardio-respiratory arrest on day 3 of study, 5 minutes after bronchoscopy. Rx 250 mg bid x 3 days
 - 2.2 y/o died after presentation to ED with febrile illness with purulent pharyngitis, leukocytosis, airway trapping and respiratory distress. Patient completed 10 day course for pneumonia; considered to be clinically cured.
- SAEs: 33 (6%) of levofloxacin-treated vs. 8 (4%) comparator-treated subjects. Most considered doubtfully related or not related to study drug
- Musculoskeletal disorders: 2% in levofloxacin-treated vs. 1% in comparator-treated subjects.

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Pediatric Exclusivity Studies

Safety

Levaquin® (levofloxacin)

AOM Study (controlled, n=1607 subjects)

Not requested in WR, provided for safety data

- Deaths: None
- Serious Adverse Events:
 - 10 (1%) levofloxacin-treated vs. 13 (2%) in comparator
 - Most were considered doubtfully related or not related to study drug
- Musculoskeletal AEs: levofloxacin-treated (2%) vs. comparator (<1%) (p value = 0.02)

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Pediatric Exclusivity Studies

Safety

Levaquin® (levofloxacin)

AOM Study (uncontrolled, n=204 subjects)

Not requested in WR, provided for safety data

- Deaths: None
- Serious Adverse Events:
 - N=8 (3%, 7 subjects)
 - Maculopapular rash, dehydration n=2 (relationship “possible”)
 - Bloody diarrhea n=1 (relationship “very likely”)
- Musculoskeletal AEs: n=6 (1.47%)

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Pediatric Exclusivity Studies Safety

Levaquin® (levofloxacin)

Long-Term Surveillance Study (n=2003 subjects)

- Musculoskeletal disorders reported more frequently in levofloxacin treated subjects over the 1 year period
- Incidence of Musculoskeletal disorders: levofloxacin vs. comparator

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

- Most frequently occurring MS disorder: arthralgia

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Pediatric Exclusivity Studies Labeling Changes

Levaquin® (levofloxacin)

Labeling changes (September 2007):

- To reflect that levofloxacin is not indicated for pediatric patients
- To describe musculoskeletal adverse events
- To provide information on clinical studies and AE profile

Highlights (Changes):

- Use In Specific Populations

Pediatrics: Musculoskeletal disorders (arthralgia, arthritis, tendonopathy, and gait abnormality) seen in more LEVAQUIN®-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.3, 8.4, 13.2).

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Pediatric Exclusivity Studies Labeling Changes

Levaquin® (levofloxacin)

Full Prescribing Information:

5 Warnings And Precautions: 5.8 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

- Not indicated < 18 years due to increased musculoskeletal disorders (see 8.4) and animal studies described.

6 Serious and Otherwise Important Adverse Reactions

- Musculoskeletal Disorders in Pediatric Patients discussed in greater detail in Warnings and Precautions (5.8)

8 Use in Specific Populations: 8.4 Pediatric Use

- Not indicated and clinical trials described, including table with musculoskeletal disorder incidence

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Relevant Labeling Changes

Since Pediatric Exclusivity

Levaquin® (levofloxacin)

- Approval for inhalational anthrax, post-exposure, in pediatric patients \geq 6 months of age and dosage provided (based on a model to determine PK)
5/5/08
- Boxed Warning and Medication Guide added to provide information on risk of tendon rupture and tendinopathy *10/3/08*

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Current Labeling (10/08)

Levaquin® (levofloxacin)

Boxed Warning:

WARNING:

Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart and lung transplants [See *Warnings and Precautions (5.1)*].

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Additional Relevant Safety Labeling

Levaquin® (levofloxacin)

- Warnings & Precautions:
 - Tendinopathy and tendon rupture
 - Hypersensitivity Reactions (anaphylaxis and allergic skin reactions)
 - Other serious and sometimes fatal reactions
 - Hematologic and renal toxicities
 - Hepatotoxicity
 - Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia
 - *Clostridium difficile*-associated diarrhea/colitis
 - Peripheral neuropathy

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Additional Relevant Safety Labeling

Levaquin® (levofloxacin)

- **Warnings & Precautions (cont):**
 - Prolongation of the QT interval and isolated cases of torsade de pointes
 - Musculoskeletal disorders in pediatric patients and arthropathic effects in animals
 - Blood glucose disturbances
 - Photosensitivity/Phototoxicity
 - Development of drug resistant bacteria
- **Pregnancy: Category C**
- **Important AEs:**
 - Hypotension (after rapid or bolus IV infusion)
 - Crystalluria and cylindruria
 - Other AE's discussed in Warnings and Precautions section

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Adverse Event Reports since Market Approval (December 20, 1996)

Levaquin® (levofloxacin)

Crude counts*	All reports (US)	Serious** (US)	Death (US)
All ages	10166(8050)	8562 (6482)	924 (424)
Adults (≥ 17)	8321 (6367)	7100 (5176)	774 (317)
Pediatrics (0-16)	116 (89)	100 (77)	3 (0)
Unknown Age	1729 (1594)	1362 (1229)	147 (107)

*includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

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Adverse Event Reports of Death Since Market Approval (December 20, 1996)

Levaquin® (levofloxacin)

- 13 y/o M with cerebral palsy, mental retardation, seizures treated for bronchopneumonia and died of an unknown cause while on levofloxacin (multiple concomitant medications). (Japan)
- 12 y/o M with reactive airway disease and allergies developed dyspnea and anaphylaxis 6-10 minutes after taking levofloxacin, benzydamine HCl and cromoglicate Na for acute pharyngitis. Became comatose and died 8 days after the event. (Japan)
- 12 m/o with complex PMHx including colectomy, ileostomy, ulcerative colitis, and rheumatoid arthritis developed a “pelvic collection” and sepsis. Patient was treated with levofloxacin and metronidazole while on multiple concomitant meds. Developed metabolic acidosis, deteriorated and died of a MI. (Great Britain)

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Serious Adverse Events (n=100)

Levaquin® (levofloxacin)

Musculoskeletal Events (n=39)

- Arthralgia or arthropathy (n=21)
- Bone or Tendon symptoms (n=13)
 - Tendon rupture (n=5)
- Myalgia or myopathy (n=5)
- Top diagnosis: Sinusitis (n=14)
- Age: 12-16 years n=32 (82%)

CNS Events (n=19)

- Seizures n=5
- Abnormal behavior or confusion n=4
- Hallucinations n=3
- Panic attacks n=2
- Top diagnoses: Sinusitis (n=4) and Unknown (n=4)

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Summary:

Levaquin® (levofloxacin)

- No new safety signals were identified after completed pediatric-focused safety review on the use of levofloxacin.
- A Boxed Warning and Medication Guide were added to labeling October 3, 2008 to strengthen existing warnings about the increased risk of developing tendonitis and tendon rupture in patients of all ages.
- At this time, FDA does not recommend any additional labeling changes.
- FDA recommends to continue routine, ongoing post-marketing safety monitoring.
- Does the committee concur?

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