

One Year Post-Exclusivity Adverse Event Review: Ciprofloxacin

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Background Drug Information

- **Drug:** CIPRO[®] (ciprofloxacin)
- **Therapeutic Category:** anti-bacterial
- **Sponsor:** Bayer
- **Pediatric Indications:**
 - inhalational anthrax (post-exposure)
 - 2nd line therapy for complicated urinary tract infections and pyelonephritis (1-17 years of age)
- **Original Market Approval:** October 22, 1987
- **Pediatric Exclusivity Granted:** December 18, 2003

Drug Use Trends

- **Systemic ciprofloxacin accounted for roughly 41% of the 33.5 million prescriptions dispensed for the quinolone class in the U.S. in 2004.¹**
- **Dispensed prescriptions for systemic ciprofloxacin increased slightly from approximately 13.6 million (2003) to 13.8 million (2004).¹**
- **Pediatricians were responsible for approximately 1% of prescriptions dispensed for ciprofloxacin tablets in the US during 2004 and roughly 17% (~8,000 prescriptions) of the suspension formulation dispensed during the same time period.¹**
- **From 2002-2004, 13-26% of the total use in pediatrics was for treatment of urinary tract infections (UTIs)². Unclear what fraction of these infections were complicated UTIs.**

¹IMS Health, National Prescription Audit *Plus*TM, Moving Annual Totals, Aug 2001 – Jul 2004, Extracted Oct 2004

²IMS National Disease and Therapeutic IndexTM, Calendar Years 2002-2004. Data extracted February 2005

Pediatric Exclusivity Trials

- 1. Controlled Safety Trial (Efficacy Data Collected)**
- 2. Open Label Safety Trial**

Controlled Safety Trial

Trial 1:

- Patients with complicated urinary tract infections or pyelonephritis (n=689)
- Prospective, randomized, double-blind, active-controlled, parallel group, multicenter trial
- Age range: 1 to < 17 years
- Compared ciprofloxacin (IV/oral) to either ceftazidime (IV), cefixime (oral), or trimethoprim/sulfamethoxazole (oral)
- Subset of patients (n=207) participated in PK study which contributed to labeled pediatric dosing recommendations

Musculoskeletal Evaluation

- **An Independent Pediatric Safety Committee (IPSC) performed a blinded review of:**
 - all cases of musculoskeletal adverse events
 - patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent).
- **Cases evaluated for evidence of clinically diagnosed or possible evidence of arthropathy**
- **Arthropathy broadly defined as any condition affecting a joint or periarticular tissue that may have been temporary or permanent.**

Musculoskeletal Events Evaluated by IPSC

- **arthralgia**
- **abnormal gait**
- **abnormal joint exam**
- **joint sprains**
- **leg pain**
- **back pain**
- **arthrosis**
- **bone pain**
- **pain**
- **myalgia**
- **arm pain**
- **decreased range of motion in a joint**
 - **knee, elbow, ankle, hip, wrist, shoulder**

Results of the Controlled Safety Trial

- **Arthropathy Events:**
 - At 6 weeks of follow-up, 9.3% of the ciprofloxacin patients vs. 6% of the comparator (all events resolved by 1 year)
 - At one year cumulative follow-up, 13.7% of the ciprofloxacin patients vs. 9.5% of the comparator patients
- **Neurological adverse events (dizziness, nervousness, somnolence, insomnia):**
 - At 6 weeks of follow-up, 3% of the ciprofloxacin patients vs. 2.0% comparator patients
- **Other adverse events (at 6 weeks of follow-up):**
 - Most frequent AE were gastrointestinal (GI): 15% of ciprofloxacin patients vs. 9% of comparator patients.

Controlled Safety Trial: Efficacy Data

- **Favorable clinical response in 96% of ciprofloxacin patients vs. 93% of the comparator patients**
- **Bacterial eradication in 84% of ciprofloxacin patients vs. 78% of the comparator patients**

Open Label-Safety Trial

Trial 2:

- **Prospective, non-randomized, open label, multi-center observational study**
- **Enrollment based on physician discretion (n=487 patients treated with ciprofloxacin)**
- **Recruited patients with multiple indications for treatment (on and off-label indications)**
- **Age range: 2 months-16 years**
- **Choice of antibiotic, dosing regimen, and treatment duration determined by enrolling physician**
- **Evaluated long-term musculoskeletal and neurological system health in pediatric patients receiving ciprofloxacin versus a non-quinolone antibiotic**
- **Used the same definition of arthropathy as in Trial 1**

Results of Open-Label Safety Trial

- **Incidence rate of ciprofloxacin adverse events at 6 weeks of follow up:**
 - **Any musculoskeletal event: 9%**
 - **Arthropathy: 8%**
 - **Neurologic (e.g. insomnia, dizziness, convulsion): 7.2%**
- **Incidence rate of ciprofloxacin adverse events by the 1-year post-treatment follow-up:**
 - **Any musculoskeletal event: 13%**
 - **Arthropathy: 11%**
 - **Neurologic (e.g. insomnia, dizziness, convulsion): 11%**

Ciprofloxacin Labeling Changes Resulting from Exclusivity Studies

- **Approved as 2nd line treatment of complicated urinary tract infections (cUTIs) and pyelonephritis in pediatric patients (1-17 years of age)**
- **Not a drug of first choice due to increased incidence of adverse events compared to controls including events related to joints and/or surrounding tissues**
- **Most frequent adverse events observed within 6 weeks of treatment initiation during the cUTI clinical trial:**
 - **Gastrointestinal: ciprofloxacin 15% vs. control 9%**
 - **Arthropathy: ciprofloxacin 9.3% vs. control 6%**
- **Information on PK and dosing for IV and oral formulations**

Adverse Event Reports since Market Approval: Ciprofloxacin

10/22/87 – 01/31/05

- **Total number of reports, all ages^{†*}:**
 - **10,354 reports (7,902 US)**
 - **6655 serious (4,389 US)**
 - **788 deaths (282 US)**
- **Pediatric reports^{*}:**
 - **228 reports (142 US)**
 - **142 serious (68 US)**
 - **13 deaths (3 US)**

[†]Includes reports with unknown age

^{*}Counts may include duplicate reports

Adverse Event Reports during the 1-Year Post-Exclusivity Period: Ciprofloxacin 12/22/03 – 01/31/05

- **Total number of reports, all ages^{†*}:**
 - **686 reports (261 US)**
 - **660 serious (239 US)**
 - **115 deaths (29 US)**
- **Pediatric reports^{*}:**
 - **19 reports (7 US) [17 unduplicated]**
 - **19 serious (7 US)**
 - **1 death (1 US)**

[†]Includes reports with unknown age

^{*}Counts may include duplicate reports

Pediatric Adverse Events During the One-Year Post-Exclusivity Period (n=17)

- **Death (1)**
- **Musculoskeletal (4)**
- **Central Nervous System (CNS) (2)**
- **GI (1)**
- **Allergic / Hypersensitivity (3)**
- **Hematologic (5)**
- **Body (1)**

12/17 patients with reported adverse events received ciprofloxacin for an unapproved indication for pediatric use.

Post-Exclusivity Pediatric Death

(n=1)

- Adolescent female with chronic mucocutaneous candidiasis (CMC) and common variable immunodeficiency admitted with one-week history of progressive dyspnea on exertion
- Complicated hospital course
- Treated with multiple medications (anti-fungals and anti-bacterials including ciprofloxacin)
- Diagnosed with *Candida tropicalis fungemia*
- Developed mucosal and gastrointestinal (GI) bleeding, liver and renal dysfunction
- Died due to uncontrollable GI bleeding
 - Possible etiologies for bleeding include:
 - Diffuse Intravascular Coagulation (DIC) due to fungal sepsis
 - Liver or renal dysfunction
 - Hematological / coagulation dysfunction related to ciprofloxacin

Post-Exclusivity Musculoskeletal Events (n=4)

- **12 year old experienced tendonitis, back, hip, knee, and heel pain 3 weeks after taking ciprofloxacin for temporal osteomyelitis.**
 - Patient with history of Crouzon's syndrome, acanthosis, ventriculoperitoneal shunt, osteitis
 - Received total of 5 weeks of ciprofloxacin oral therapy (500-750mg BID) for outpatient treatment of osteomyelitis (other medications given during hospitalization)
 - MRI (by report): knee effusion and some thickening of cartilage
 - Diagnosis: tendonitis of tibia, patella and Achilles tendon
 - Patient could not stand or ambulate. Required a wheelchair a month after the medication was discontinued.

Post-Exclusivity Musculoskeletal Events

(n=4) (cont.)

- **10-year old treated for a postoperative abscess with persistent leg pain and inability to run (foreign report)**
 - Started ciprofloxacin therapy for postoperative abscess
 - Developed knee pain during treatment and ciprofloxacin was stopped after 4 days of therapy
 - Patient was confined to bed during entire hospitalization (3 weeks)
 - Pain was persistent and considered disabling. Patient unable to run.

Post-Exclusivity Musculoskeletal Events (n=4) cont.

- 14 year old with osteomyelitis of little finger treated for 14 days with ciprofloxacin 750 mg BID. Patient developed Achilles tendonitis after one week of therapy which increased in severity by 10-14 days. Ciprofloxacin discontinued and patient improved (foreign report)**
- 15 year old with chronic osteomyelitis of the left radius developed joint stiffness and ecchymoses in both knees while on ciprofloxacin. Symptoms resolved within two weeks of discontinuing therapy.**

Post-Exclusivity Musculoskeletal Events

- The potential for severe adverse events in joints and tendons subsequent to the use of quinolones is addressed in several sections in the ciprofloxacin label: **WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS** .
- These adverse events include:
 - rupture of the Achilles tendon
 - pain and inflammation of tendons
 - joint stiffness
 - tendonitis
 - pain in extremities
 - effects on joints

Post-Exclusivity CNS events (n=2)

- 8 year old patient had seizures before and after ciprofloxacin therapy, in the setting of numerous concomitant medications and underlying brain cancer.
- 15 year old developed status epilepticus while on ciprofloxacin and cefepime therapy for treatment of UTI. Both drugs were discontinued and the patient recovered. (foreign report)
- Convulsions are addressed in the **WARNINGS** section, and also in the **ADVERSE REACTIONS** section of the labeling where it states that during clinical trials convulsive seizures were reported in adults.

Post-Exclusivity GI events (n=1)

- 8 year old with severe pseudomembranous colitis and ascites following therapy with co-trimoxazole, cefotaxime and ciprofloxacin.
- The event resolved with “corrective treatment” and did not recur.
- In the **WARNINGS** section of the ciprofloxacin label: Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening.

Summary: Pediatric Adverse Events

- Review of the 17 unduplicated pediatric cases showed mostly labeled adverse events.
- 12 out of the 17 patients who developed adverse events were receiving ciprofloxacin for an unapproved indication for pediatric use.
- This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.
- FDA recommends routine monitoring of AEs for this drug in all populations.
- Does the Advisory Committee concur?

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