M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: ODS POSTMARKETING SAFETY REVIEW
Consult: One-Year Post Pediatric Exclusivity Postmarketing Adverse Events Review
Drug: Ciprofloxacin
NDA: 19-537, 19-847, 19-857, 20-780, 21-473, 21-554
Pediatric Exclusivity Approval Date: December 22, 2003

1. Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of Cipro (ciprofloxacin hydrochloride) in pediatric patients. Up to the "data lock" date of January 31, 2005, AERS contained 10,354 cases for ciprofloxacin (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent 2.2% of the total (n=228).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, December 22, 2003, to December 22, 2004. We used an AERS data lock date of January 31, 2005, to allow time for reports received up to December 22, 2004, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 686 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent 2.8% of the total number of cases (n=19).

We reviewed 17 unique pediatric cases reported to the FDA during the 13 month period after pediatric exclusivity was granted. Note that raw counts indicate 19 cases; however, one is a duplicate and the other report was excluded because it indicated adverse effects in an infant following maternal exposure (congenital hypothyroidism). The 17 cases described hematological events (5), joint/tendon events (4), allergic hypersensitivity reactions (3), CNS/convulsions (2), and one each of pseudomembranous colitis, ear pain and worsening of underlying disease.

During the first 13 months of pediatric exclusivity there was one death, two reports of disability and four of hospitalization. The fatality was associated with a worsening disease progression in a patient diagnosed with chronic mucocutaneous candidiasis (CMC) despite therapy with several antibiotics and antifungal drugs. This patient appears to have a family predisposition for fungal infections[1]. The disabilities involved inability to walk in a 12-year old girl treated for osteomyelitis and inability to run in a 12-year old boy treated for a postoperative abscess. The hospital admissions were for pseudomembranous colitis, pancytopenia, tendonitis and Stevens Johnson Syndrome (one adverse event per patient). The remaining 10 cases indicated that the outcome was medically significant, and were captured in the MedWatch form outcome section as "other".

Of the 20 most frequently reported adverse events reported during the pediatric exclusivity period in the pediatric population, an individual review of the 17 unique reports showed that there were only two events mentioned more than once. These were arthralgia (n=3), which is a labeled event, and eyelid edema (n=2) which is unlabeled. Eyelid edema was reported as manifestations of Stevens Johnson's Syndrome (SJS) in one patient, and as part of an allergic reaction in another. Note that even though eyelid edema is not specifically mentioned in the oral formulations labeling, hypersensitivity and allergic reactions including facial edema and SJS are labeled. Eyelid edema is mentioned in the **ADVERSE REACTIONS** section of the ophthalmic solution labeling. Also, note that an additional 41 unlabeled events were mentioned only once and thus are included in the list of top 20 events. In this latter group of unlabeled events, some events are associated with a pre-existing illness or disease of the patient, and others may be adequately covered by similar terms listed in the labeling. Since these events were mentioned only once in the current labeling it is premature to recommend any labeling changes at this time.

Despite labeling coverage of adverse events in tendons and joints, it was concerning to see a case of severe tendonitis with contractures of knees and ankles in a 12-year patient with a history of bowed legs (case # 3804136). She received 5 weeks of ciprofloxacin oral therapy at recommended doses. Even though ciprofloxacin was stopped, she could not stand or ambulate and required a wheelchair a month later.

In summary, in the 13-month period of review the 17 unique pediatric cases showed mostly labeled hematological, musculoskeletal, allergic/hypersensitivity, and CNS

[1] Dixon, T.C., Steinbach, W.J., Benjamin Jr., D.K. et al. Disseminated Candida Tropicalis in a patient with chronic mucocutaneous candidiasis. Southern Medical Jouranl Aug 2004: Vol 97, number 8: 788-790

events. At this time we have not identified new safety concerns in the pediatric population that are not adequately addressed in the labeling. However, because one report was concerning due to the patient requiring a wheelchair after developing drug associated symptoms we will assiduously monitor the pediatric cases to determine if permanent disability is reported in this age group, and if the label should be amended to reflect this finding. We will continue to monitor adverse events in pediatric patients and communicate any emerging safety signals to the review division.

2. Products, indications, pediatric filing history, and pediatric labeling

2.1 Products; indications and dosing in pediatric population

To date there are ten approved NDAs with ciprofloxacin as the active ingredient. Table 1 shows relevant information regarding pediatric use.

Table 1. Ciprofloxacin approved NDAs up to January 31, 2005

NDA #	Trade name	Dosage form	Approval date	Pediatric indication Pediatric population	Pediatric dose
19-537	Cipro® (ciprofloxacin hydrochloride) Tablets	Tablet	10-22-87	Complicated urinary tract infections and pyelonephritis due to E. coli, post exposure inhalation anthrax, 1 to 17 years	10-20 mg/kg to a maximum of 750 mg per dose x 12 hours x 10-21 days
19-847	Cipro® IV (ciprofloxacin) 1% Solution Vials, 200 mg, 400 mg and 1200 mg	Injection	12-26-90	Complicated urinary tract infections and pyelonephritis due to E. coli, post exposure anthrax inhalation; 1to 17 years	6-10 mg/kg, maximum 400 mg per dose, every 8 hrs fro 10-21 days; for anthrax, 10 mg/kg, maximum 400 mg per dose, for 60 days
19-857	Cipro® IV (ciprofloxacin) 0.2% Solution in 5% Dextrose, 200 mg and 400 mg	Injection	12-26-90	Complicated urinary tract infections and pyelonephritis due to E. coli, post exposure anthrax inhalation; 1 to 17 years	6-10 mg/kg, maximum 400 mg per dose, every 8 hrs fro 10-21 days; for anthrax, 10 mg/kg, maximum 400 mg per dose, for 60 days
20-780	Cipro® Oral Suspension, 5% and 10%	Oral suspension	9-26-97	Complicated urinary tract infections and pyelonephritis due to E. coli, post exposure inhalation anthrax; 1 to 17 years	10-20 mg/kg to a maximum of 750 mg per dose x 12 hours x 10-21 days
21-473	Cipro® XR (ciprofloxacin) Extended-Release Tablets, 500 mg	Extended release tablets	12-13-02	Not approved for use in pediatric population	Not applicable
21-554	Cipro® XR (ciprofloxacin) Extended-Release Tablets, 1000 mg	Extended release tablets	8-23-03	Not approved for use in pediatric population	Not applicable
19-992	Ciloxan® (ciprofloxacin HCl ophthalmic solution) 0.3% as	Ophthalmic solution	12-31-90	Corneal ulcer infections Conjunctivitis; 1 year and older	1-2 drops at short intervals, for up to 14 days depending on the illness

Table 1. Ciprofloxacin approved NDAs up to January 31, 2005					
NDA #	**Trade name**	**Dosage form**	**Approval date**	**Pediatric indication Pediatric population**	**Pediatric dose**
	base Sterile				
20-369	Ciloxan® (ciprofloxacin hydrochloride ophthalmic ointment) 0.3% as Base Sterile Ophthalmic Ointment	Ophthalmic ointment	3-30-98	Bacterial conjunctivitis; 2 years and older	½ inch ribbon tid x 2 days, then bid x 5 days
21-537	Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension	Otic suspension with dexamethasone	7-18-03	Acute otitis externa, acute otitis media in patients with tympanostomy tubes; 6 months and older	4 drops bid x 7 days; same dose for all age groups
20-805	Cipro® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension)	Otic suspension with hydrocortisone	2-10-98	Acute otitis externa; 1 year and older	3 drops bid x 7 days; same dose for all age groups

2.2. Pediatric filing history

Oral and IV formulations of ciprofloxacin were approved between 1987 and 2000 to treat the following infections in adults: acute sinusitis, bone and joint infections, chronic bacterial prostatitis, complicated intra-abdominal infections, infectious diarrhea, lower respiratory tract infections, skin and skin structure infections, typhoid fever, uncomplicated cervical and urethral gonorrhea and urinary tract infections. In August 2000, ciprofloxacin was approved for post-exposure of inhalation anthrax in adults and children.

A Pediatric Exclusivity Written Request (WR) was originally issued May 12, 1999, amended October 1, 2001, and a final amendment was issued on September 23, 2003. The sponsor's response to the WR contained the results of two clinical trials in pediatric patients, a population pharmacokinetic analysis, and an animal toxicology study. In the response the sponsor requested that the **PRECAUTIONS**, **Pediatric Use** and **ANIMAL PHARMACOLOGY** sections of the labeling be updated.

Pediatric Exclusivity was granted in December 2003.

Data submitted in September 2003 supported updating the Cipro® labeling to include recommendations for pediatric patients between the ages of 1 and 17 with complicated urinary tract infections or pyelonephritis. Approval for this indication was granted on March 25, 2004. As part of the post marketing commitments, the sponsor agreed to provide biannual updates on Cipro usage patterns in the pediatric population, and to

provide expedited reporting to the Agency of all spontaneous adverse events in patients 17 years of age or younger until April 30, 2007.

2.3 Pediatric Labeling

Various sections in the labeling address use and adverse events in the pediatric population. These are **INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS.**

2.3.1 INDICATIONS AND USAGE:

CIPRO is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations

Pediatric patients (1 to 17 years of age):

Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli* .

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS , Pediatric Use , ADVERSE REACTIONS** and **CLINICAL STUDIES** .) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY** .)

Adult and Pediatric Patients:

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis* .

2.3.2 WARNINGS

Pediatrics: Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in the **INDICATIONS AND USAGE** section. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS** .)

In pre-clinical studies, oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY** .)

2.3.3 PRECAUTIONS

Pediatric Use: Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness. (See **ANIMAL PHARMACOLOGY** .)

Inhalational Anthrax (Post-Exposure)

Ciprofloxacin is indicated in pediatric patients for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate. For information regarding pediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION.**

Complicated Urinary Tract Infection and Pyelonephritis

Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli.* Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including events related to joints and/or surrounding tissues. The rates of these events in pediatric patients with complicated urinary tract infection and pyelonephritis within six weeks of follow-up were 9.3% (31/335) versus 6.0% (21/349) for control agents. The rates of these events occurring at any time up to the one year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate of all adverse events regardless of drug relationship at six weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES** .)

Cystic Fibrosis

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and tobramycin I.V. 3 mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

Musculoskeletal adverse events in patients with cystic fibrosis were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. Other adverse events were similar in nature and frequency between treatment arms. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

2.3.4 ADVERSE REACTIONS

Adverse Reactions in Pediatric Patients: Ciprofloxacin, administered I.V. and/or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety within 6 weeks of therapy and through one year of follow-up in the 335 ciprofloxacin- and 349 comparator-treated patients enrolled.

An Independent Pediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent). These events were evaluated in a comprehensive fashion and included such conditions as arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0 % (21/349) in comparator-treated patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless of whether they received I.V. or oral therapy. Ciprofloxacin-treated patients were more likely to report more than one event and on more than one occasion compared to control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the control group. At the end of 1 year, the rate of these events reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-treated patients.

An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

Findings Involving Joint or Peri-articular Tissues as Assessed by the IPSC		
	Ciprofloxacin	Comparator
All Patients (within 6 weeks)	31/335 (9.3%)	21/349 (6.0%)
95% Confidence Interval *	(-0.8%, +7.2%)	
Age Group		
>/=12 months < 24 months	1/36 (2.8%)	0/41
>/= 2 years < 6 years	5/124 (4.0%)	3/118 (2.5%)
>/= 6 years < 12 years	18/143 (12.6%)	12/153 (7.8%)

>/= 12 years to 17 years	7/32 (21.9%)	6/37 (16.2%)
All Patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval *	(-0.6%, +9.1%)	
*The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than + 6%. At both the 6 week and 1 year evaluations, the 95% confidence interval indicated that it could not be concluded that ciprofloxacin group had findings comparable to the control group.		

The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.

In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse event was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.

In addition to the events reported in pediatric patients in clinical trials, it should be expected that events reported in adults during clinical trials or post-marketing experience may also occur in pediatric patients.

3. AERS Search Results

AERS was searched on February 14, 2005, to retrieve reports listing ciprofloxacin as a suspect drug, in adult and pediatric populations. The search included all sources, foreign and domestic. In the tables below, the US counts are in parenthesis.

3.1 Adverse events in AERS through January 31, 2005:

3.1.1 Counts of reports:

Table 2: Raw counts[1] of total ciprofloxacin reports in AERS through cut-off date of January 31, 2005 (US counts in parentheses)

	All reports (US)	Serious[2] (US)	Death (US)
All ages[3]	10354 (7902)	6655(4389)	788 (282)
Adults (≥ 17 yrs.)	8664 (6502)	5833 (3814)	737 (260)
Pediatrics (0-16 yrs.)	228 (142)	142 (68)	13 (3)

[1] May include duplicates
[2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.
[3] Includes reports where age was not provided

3.1.2. Reporting trend for pediatric reports through January 31, 2005:

Table 3: Reporting trend in AERS reports through January 31, 2005[1]		
Number of cases, all ages [2]	**Year**	**Number of pediatric cases (0-16 years)[3]**
2	1983	-
2	1987	-
375	1988	13
564	1989	8
506	1990	9
284	1991	5
643	1992	13
1113	1993	16
527	1994	9
403	1995	5
764	1996	9
377	1997	10
630	1998	10
940	1999	24
615	2000	19
542	2001	23
658	2002	16
756	2003	20
599	2004	16
55	2005	3

[1] Raw counts, may include duplicates
[2] May include reports where age was not specified
[3] Only includes reports where age was listed in the pediatric age grouping of 0-16 years

Figure 1 - Ciprofloxacin AERS reports in pediatric population up to 01-31-2005

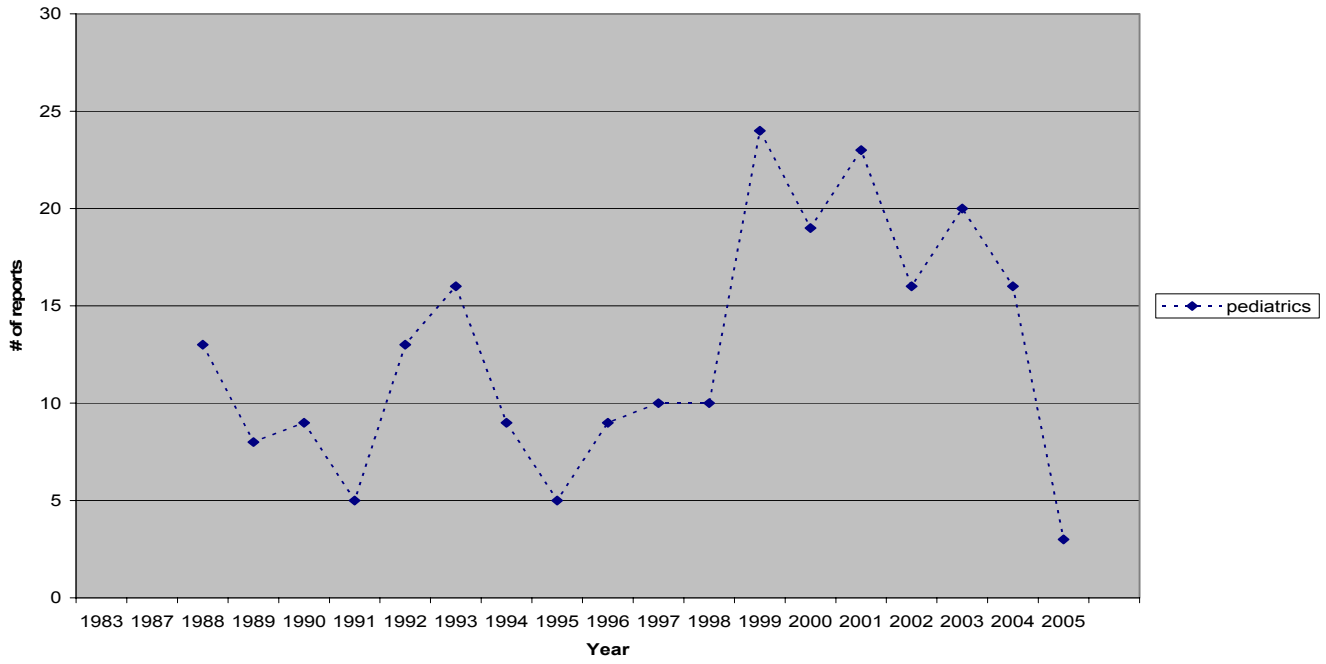
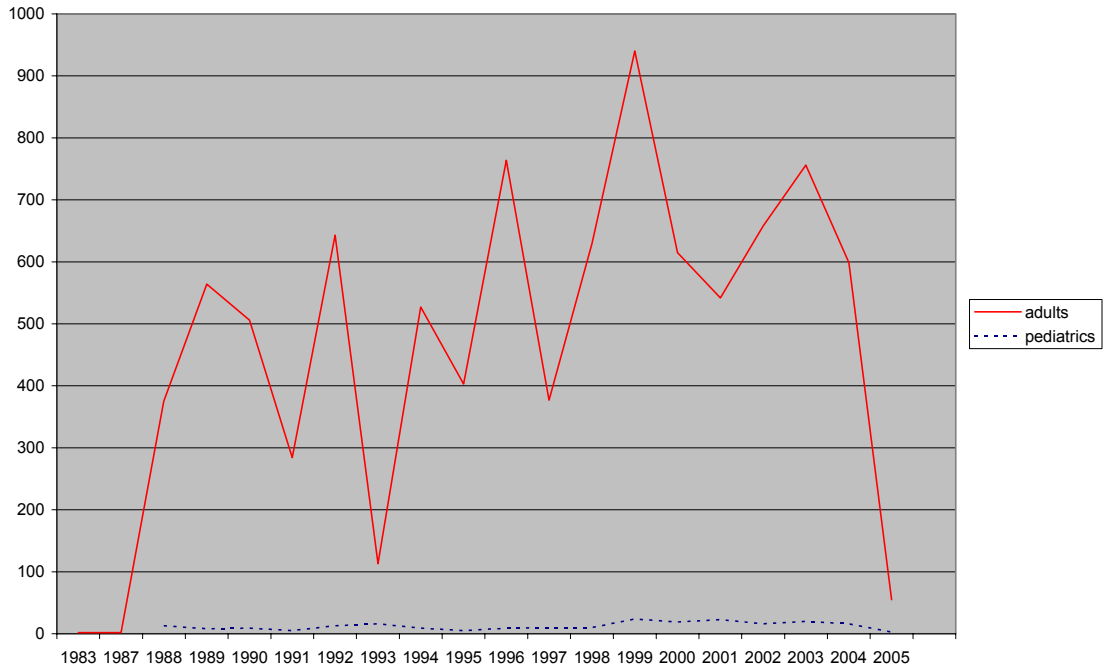


Figure 2 - AERS reports for adults and pediatric populations up to January 31, 2005



3.1.3. Top 20 reported event PTs and labeling status of these events (underlined denotes unlabeled events):

Table 4: Counts of top 20 reported events (preferred terms) through 1/31/2005[1]		
	Top 20 preferred terms	**Counts**
All ages (including reports where no age was provided)	Dermatitis	1004
	Pruritus	665
	Pyrexia	548
	Urticaria	452
	Arthralgia	425
	Drug interaction	421
	Dyspnea	407
	Blood Creatinine Increased	400
	Diarrhea	392
	Renal Failure Acute	383
	Vomiting	370
	Convulsion	364
	Dizziness	339
	Nausea	330
	Confusional state	324
	Pain	287
	Headache	258
	Face Oedema	257
	Asthenia	255
	Renal Failure	246
Adults (17+ years)	Dermatitis	840
	Pruritus	587
	Pyrexia	508
	Urticaria	393
	Arthralgia	370

Table 4: Counts of top 20 reported events (preferred terms) through 1/31/2005[1]		
	Top 20 preferred terms	**Counts**
	Blood Creatinine Increased	365
	Dyspnoea	363
	Diarrhea	354
	Drug Interaction	352
	Renal Failure Acute	352
	Vomiting	318
	Convulsion	304
	Confusional State	295
	Nausea	284
	Dizziness	277
	Pain	254
	Asthenia	237
	Headache	221
	Condition Aggravated	213
	Renal Failure	210
Pediatrics (0-16 years)	Dermatitis	20
	Pruritus	15
	Pyrexia	13
	Urticaria	11
	Arthralgia	10
	Renal Failure	10
	Convulsion	9
	Drug Interaction	9
	Face Oedema	9
	Condition Aggravated	8
	Vomiting	8
	Encephalopathy	7
	Pain in Extremity	7
	Renal Failure Acute	7
	Skin Disorder	7
	Tremor	7
	Abdominal Pain	6
	Alanine Aminotransferase Increased	6
	Dizziness	6
	Drug Level Above Therapeutic	6
[1] Raw counts include terms from duplicate reports		

3.2 Adverse event from pediatric exclusivity approval date, December 22, 2003 through January 31, 2005:

3.2.1 Counts of reports:

Table 5: Raw counts[1] of total ciprofloxacin reports from pediatric exclusivity approval date through cut-off date of January 31, 2005 (US counts in parenthesis)			
	All reports (US)	Serious [2] (US)	Death (US)
All ages [3]	686 (261)	660 (239)	115 (29)
Adults (≥17 yrs.)	609 (224)	588 (207)	113 (28)
Pediatrics (0-16 yrs.)	19 (7)	19 (7)	1 (1)
May include duplicates [2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other. [3] Includes reports where age was not specified			

3.2.2. Top 20 reported event PTs and labeling status of these events (underlined indicates unlabeled):

Table 6: Counts of top 20 reported events (preferred terms) from pediatric exclusivity through AERS cut off date of January 31,2 005[1]		
	Top 20 preferred terms	**Counts**
All ages (including reports where age is not specified) (total number of adverse events =1119)	Pyrexia Renal Failure Acute Arthralgia Drug Interaction Condition Aggravated Asthenia Toxic Epidermal Necrolysis Multi-Organ Failure Pain Aspartate Aminotrasferase Increased Pain In Extremity Blood Creatinine Increased Respiratory Failure Alanine Aminotransferase Increased Rash Renal Failure Tremor Thrombocytopenia Confusional State Dizziness	45 41 38 38 37 34 33 28 28 27 27 26 26 25 25 25 25 24 23 23
Adults (17+ years) (total number of adverse events = 1065)	Pyrexia Renal Failure Acute Condition Aggravated Toxic Epidermal Necrolysis Asthenia Drug Interaction Arthralgia Multi-Organ Failure Aspartate Aminotransferase Increased Pain In Extremity Respiratory Failure Blood Creatinine Increased Alanine Aminotransferase Increased Renal Failure Tremor Rash Confusional State Headache Pain Thrombocytopenia	42 40 34 33 32 32 30 28 26 26 26 25 24 24 24 23 22 22 22 22
Pediatrics (0-16 years)* (total number of adverse events = 73)	Arthralgia Eyelid Oedema Anemia Dermatitis Bullous Face Oedema Localized Oedema Mucosal Inflammation Pyrexia	3 3 2 2 2 2 2 2

Table 6: Counts of top 20 reported events (preferred terms) from pediatric exclusivity through AERS cut off date of January 31,2 005[1]		
	Top 20 preferred terms	**Counts**
	Rash Vesicular	2
	Stevens-Johnson Syndrome	2
	Tendonitis	2
	Thrombocytopenia	2
	Anorexia	1
	Antinuclear Antibody Positive	1
	Back Pain	1
	Blood Albumin Decreased	1
	Blood Fibrinogen Decreased	1
	Blood Sodium Decreased	1
	Candidiasis	1
	Clostridium colitis	1
	Coagulation Time Prolonged	1
	Coagulopathy	1
	Condition Aggravated	1
	Congenital Hypothyroidism	1
	Conjunctivitis	1
	Contusion	1
	Convulsion	1
	Coombs Test Positive	1
	DNA Antibody Positive	1
	Drooling	1
	Drug Exposure During Pregnancy	1
	Dystonia	1
	Ecchymosis	1
	Eosinophilia	1
	Eyelids Pruritus	1
	Fatigue	1
	Fungaemia	1
	Gastrointestinal Haemorrhage	1
	Grand Mal Convulsion	1
	Haematemesis	1
	Haematochezia	1
	Haematuria	1
	Haemolytic Aneia	1
	Hyperbilirubinaemia	1
	Hypereosinophilic Syndrome	1
	Hypersensitivity	1
	Joint Contracture	1
	Joint Stiffness	1
	Masked Facies	1
	Mucosal Haemorrhage	1
	Muscle Cramp	1
	Neutropenia	1
	Pain In Extremeity	1
	Pancytopenia	1
	Periorbital Disorder	1
	Periorbital Oedema	1
	Pneumonia Fugal	1
	Portal Hypertension	1
	Post Procedural Complication	1
	Pruritus	1
	Pulmonary Mass	1

Table 6: Counts of top 20 reported events (preferred terms) from pediatric exclusivity through AERS cut off date of January 31,2 005[1]		
	Top 20 preferred terms	**Counts**
	Renal Impairment	1
	Respiratory Distress	1
	Skin Depigmentation	1
	Skin Disorder	1
	Skin Hyperpigmentation	1
	Skin Lesion	1
	Status E[pilepticus	1
	Tendon Disorder	1
	Tic	1
	Tracheal Ulcer	1
	Varices Esophageal	1
[1] Raw counts include terms from duplicate reports		

4. Postmarketing Hands-on Review of All Pediatric Adverse Event Reports From All Sources Received During the Pediatric Exclusivity Period (December 22, 2003, to January 31, 2005)

4.1 Demographic characteristics

Our search of the AERS database yielded 19 pediatric cases. One of the cases was a duplicate and another was not considered for review because it indicated adverse effects in an infant following maternal exposure (congenital hypothyroidism). Thus, we reviewed 17 unique cases. The demographic characteristics for these 17 cases are listed in Table 7 below.

Table 7: Characteristics of pediatric cases reported during the 1-year period after receiving pediatric exclusivity (12-22-2003 through 1-31-2005)		
Gender [n=17]	Male:	9
	Female:	8
Age [n=17]	0-<1 month:	0
	>1-<2 years:	1
	2-5 years:	3
	6-11 years:	4
	12-16 years:	9
	(mean 10.5 years, median 12 years)	
Daily dose [n=12]	Mean:	688 mg
	Median:	500 mg
	Range:	50-1000 mg
	Drops:	6 drops x 1, 12 drops x 1
Duration of therapy [n=14]	Mean:	19 days
	Median:	10 days
	Range:	1-120 days
	# >10 days:	7
Indications [n=17]	Urinary tract infection:	4
	Osteomyelitis:	4
	Respiratory infection:	2
	Prophylaxis:	2
	Fungal infection:	1

Table 7: Characteristics of pediatric cases reported during the 1-year period after receiving pediatric exclusivity (12-22-2003 through 1-31-2005)		
	Swimmer's ear:	1
	Otis media:	1
	Acute sphenoidal sinusitis and ethmoiditis:	1
	Febrile episode:	1
Outcomes [n=17]	Death:	1
	Hospitalization:	4
	Congenital anomaly:	1
	Disability:	1
	Assessed as medically important:	10

4.2 Labeling status of the top 20 reported adverse events and comparison to adult adverse event profile during the pediatric exclusivity period

Of the 20 most frequently reported adverse events reported during the pediatric exclusivity period in the pediatric population individual review of the 17 unique reports showed that there were two events mentioned more than once. These were arthralgia (n=3), which is a labeled event, and eyelid edema (n=2) which is unlabeled. Eyelid edema was reported as manifestations of Stevens Johnson's Syndrome (SJS) in one patient, and as part of an allergic reaction in another. Note that even though eyelid edema is not specifically mentioned in the oral formulations labeling, hypersensitivity and allergic reactions including facial edema and SJS are labeled. Eyelid edema is mentioned in the **ADVERSE REACTIONS** section of the ophthalmic solution labeling. Also, note than an additional 41 unlabeled events were mentioned only once and thus are included in the list of top 20 events. In this latter group of unlabeled events, some events are associated with a pre-existing illness or disease of the patient, and others may be adequately covered by similar terms listed in the labeling. Since these events were mentioned only once it is premature to recommend any labeling changes at this time.

Despite labeling coverage of adverse events in tendons and joints, it was concerning to see a case of severe tendonitis with contractures of knees and ankles in a 12-year patient with a history of bowed legs (case # 3804136). She received 5 weeks of ciprofloxacin oral therapy at recommended doses. Even though the ciprofloxacin dose was decreased after one month, and stopped one week later, she could not stand or ambulate. During therapy she complained of pain in her back, hips, thigh, knees and ankles. Her diagnosis was of tendinitis of Achilles and patella tendons. She required a wheelchair a month after the medication was stopped.

Very few of the top pediatric adverse events were also on the lists for the 20 most frequently reported adverse events in adults, either during the pediatric exclusivity period or during the marketing lifetime of ciprofloxacin.

4.3 Fatalities in the pediatric population during the exclusivity period (n=1)

There was one pediatric fatality reported during the pediatric exclusivity period. A 16-year old female patient from the US diagnosed with CMC and common variable immunodeficiency presented with a one-week history of progressive dyspnea on exertion.

Therapy with caspofungin was continued for a possible fungal pneumonia. She also underwent a splenectomy for chronic thrombocytopenia and mucosal bleeding, sclerotherapy for management of three grade II esophageal varices and multiple transfusions for numerous episodes of hematemesis and severe anemia. Caspofungin was discontinued due to hyperbilirubinemia. She developed a fever despite therapy with trimethoprim-sulfamethoxazole, menopenem and vancomycin. Blood and catheter cultures were negative at this time. She was started on amphotericin B lipid complex and ciprofloxacin for presumptive fungal infection. She developed worsening respiratory distress. Renal function declined and she was switched to liposomal amphotericin B. Candida tropicalis was isolated from peripheral blood cultures on days consistent with a worsening clinical picture. After continued liposomal amphotericin B treatment she had several subsequent negative blood cultures. She later developed uncontrollable gastrointestinal tract bleeding, despite octreotide infusion and numerous transfusions, and died.

This case was published in August 2004 in the Southern Medical Journal[2]. The authors indicated that this patient's family there may have an uncharacterized defect predisposing them to systemic fungal infection, as the patient's father had a similar disease course. In addition, the infections experienced by the 16-year old (i.e., Epstein-Barr virus associated with chronic active hepatitis, hepatic bacillary angiomatosis due to bacteria, and granulomatous P. carinii pneumonia) suggested that she had a more profound *in vivo* T-lymphocyte defect. This deficiency may have been a consequence of therapy with immunosuppressive agents or defective T- and B-cell interactions. The authors wanted to alert clinicians of the possibility of systemic fungal infection and rare opportunistic infections, as well as the conventional mucocutaneous disease in patients with CMC.

4.4 Serious outcome reports in pediatric population during the exclusivity period (excluding fatalities) (n=16)

All of the remaining 16 reports in the pediatric population had a serious outcome by regulatory definition. Two reported disabilities described as inability to walk in a 12-year old girl treated for osteomyelitis, and as inability to run in a 12-year old boy treated for a postoperative abscess. Four reported hospitalizations due to pseudomembranous colitis, pancytopenia, tendonitis and SJS (one adverse event per patient). The remaining ten cases indicated that the outcome was medically significant, and were captured in the MedWatch form outcome section as Other.

4.5 Summary of pediatric adverse event profile during the pediatric exclusivity period (excluding fatalities) (n=16)

A hands-on review of the 17 cases in pediatric patients during the pediatric exclusivity period showed that all cases reported a serious outcome (by regulatory definition). The fatality mentioned in section 3.2 is associated with progression of worsening underlying disease, and it will not be addressed in this section. The majority of events reported in

[2] Dixon, T.C., Steinbach, W.J., Benjamin Jr., D.K. et al. Disseminated Candida Tropicalis in a patient with chronic mucocutaneous candidiasis. Southern Medical Jouranl Aug 2004: Vol 97, number 8: 788-790.

the remaining 16 cases were labeled or were related to a labeled event, and can be categorized as hematological, musculoskeletal, allergic/hypersensitivity, central nervous system (CNS), gastro intestinal (GI) and body as a whole events. Only three of the 16 cases listed Urinary Tract Infection (UTI) as the indication for use. The indications listed in the remaining 13 cases are: osteomyelitis (4), respiratory infection (2) and one each of febrile episode, meningitis prophylaxis, post-operative abscess, acute sphenoidal sinusitis and ethmoditis, UTI prophylaxis, otitis media and swimmer's ear. These last two were treated with Ciprodex® which is approved for treatment of acute otitis externa and acute otitis media.

4.5.1. Hematologic events (n=5)

Table 8: Characteristics of the hematologic events cases (n=5)	
Gender (n=5)	3M, 2F
Age (n=5)	Mean 8 years , Range 9 months to 16 years
Daily dose (n=4)	≤100 mg 2 250 mg 1 1000 mg 1
Duration of therapy (n=5)	Mean 36 days, Range 1 week to 4 months ≤14 days 3 1-4 months 2
Indication (n=5)	2 Respiratory infection 1 Prophylaxis of UTI and infectious diseases 1 Fever 1 Suspected osteomyelitis
Dechallenge (n=4)	Positive 4
Outcome (n=5)	Hospitalization 1 Other 4

The five cases in this group listed the following events: thrombocytopenia (case # 4195666), hemolytic anemia (case # 4195204), pancytopenia (case # 4146794), neutropenia (case # 4146950), and coagulopathy (case # 4115018). Abnormalities in blood platelet concentration, hemolytic anemia and pancytopenia are labeled. The label also mentions other hematologic events such as leucopenia and alterations in prothrombin time that are related to events listed in these pediatric reports. Altered hematologic parameters are listed in the **Adverse Laboratory Changes and Post-Marketing Adverse Events** subsections of the **ADVERSE REACTIONS** section.

The cases in this group are also noteworthy for the off-label use of ciprofloxacin. In all the patients, ciprofloxacin was administered for non-approved indications. In one patient, the age was below that which is recommended (patient was nine months). In another the duration of therapy (4 months) was much longer that the recommendations in the labeling.

It should be noted that some of these patients had severe underlying diseases (ex. chronic renal failure, acute myeloid leukemia and history of liver transplant) and that all were receiving two or more concomitant medications at the time of the hematologic event. Nevertheless, the temporal association to onset of events, the positive dechallenge in the

majority of the cases (4/5), and the fact that hematologic events are mentioned in the labeling suggest a role for ciprofloxacin in the development of these hematologic events.

4.5.2. Musculoskeletal events (n=4)

Table 9: Characteristics of the musculoskeletal events cases (n=4)	
Gender (n=4)	2 M, 2 F
Age (n=4)	Mean 13 years , Range 10 to 15 years
Daily dose (n=3)	500 mg 1 1000-1500 mg 2
Duration of therapy (n=4)	Mean days, Range 4 days to 5 weeks ≤14 days 2 15 to 29 days 1 1-4 months 1
Indication (n=4)	Osteomyelitis 3 Post-operative abscess 1
Dechallenge (n=3)	Positive 2 Negative 1
Outcome (n=)	Hospitalization 1 Disability 2 Other 1

There were four reports in the pediatric population during the exclusivity period describing events in joint or tendons, associated with pain in almost all (3/4), and in which ciprofloxacin was used for an unapproved indication. The most relevant events were Achilles tendinitis (cases # 3804136 and 5697583); joint stiffness and ecchymosis in both knees (case # 5657317); and knee pain (case # 5732200). The potential for severe adverse events in joints and tendons, including rupture of the Achilles tendon, pain and inflammation of tendons, joint stiffness, tendinitis, pain in extremities and effects on joints subsequent to the use of quinolones is addressed in several sections in the labeling (**WARNINGS [Pediatrics subsection], PRECAUTIONS [Information for patients, and Pediatric Use subsections] and ADVERSE REACTIONS sections).**

It should be noted that despite labeling coverage of adverse events in tendons and joints, it was concerning to see a case of severe tendonitis with contractures of knees and ankles in a 12-year patient with a history of bowed legs (case # 3804136). She received 5 weeks of ciprofloxacin oral therapy at recommended doses. Even though the ciprofloxacin dose was decreased after one month, and stopped one week later, she could not stand or ambulate. During therapy she complained of pain in her back, hips, thigh, knees and ankles. Two months after stopping ciprofloxacin an MRI of both knees suggested some thickening of the medial collateral ligaments. Her diagnosis was of tendinitis of Achilles and patella tendons. She required a wheelchair a month after the medication was stopped.

4.5.3. Allergic/Hypersensitivity events (n=3)

Table 10: Characteristics of the musculoskeletal events cases (n=3)	
Gender (n=3)	2 M, 1 F
Age (n=3)	Mean 12 years , Range 9 to 15 years
Daily dose (n=3)	500 mg 2 3 drops 1
Duration of therapy (n=3)	Mean 7 days, range 1 to 20 days 1 day 2 20 days 1
Indication (n=3)	Ethmoiditis and acute sphenoiditis 1 Meningitis prophylaxis 1 Swimmer's ear infection 1
Dechallenge (n=3)	Negative 2 Positive 1
Outcome (n=3)	Hospitalization, life threatening 1 Other 2

Three cases received during the pediatric exclusivity period involved hypersensitivity reactions. These were described as Stevens Johnson Syndrome (case # 4146959); periorbital edema with eyelid edema and pruritus (case # 5704810); and facial rash, hives and swelling (case # 5680240). These three cases are similar also in that in all the adverse event occurred after short term therapy (two after one dose, and a third after 20 days of daily dosing) and in all three ciprofloxacin was used for an unapproved indication.

Hypersensitivity reactions are addressed in the **CONTRAINDICATIONS** and **WARNINGS** sections of the ciprofloxacin labeling for oral and otic preparations. Stevens Johnson Syndrome is listed under the **Post-Marketing Adverse Events** subsection of the **ADVERSE REACTIONS** section of the oral preparations. Although periorbital and eyelid edema are not specifically mentioned, the **ADVERSE REACTIONS** section under the **Adverse Reactions in Adult Patients** subsection lists edema of the face and the conjunctiva.

4.5.4. CNS events (n=2)

Table 11: Characteristics of the musculoskeletal events cases (n=2)	
Gender (n=2)	1 M, 1 F
Age (n=2)	Mean 12 years , Range 8 to 15 years
Daily dose (n=1)	500 mg
Duration of therapy (n=1)	1 day
Indication (n=2)	Urinary tract infection 2
Dechallenge (n=2)	Positive 1 Not applicable 1
Outcome (n=2)	Other 1

We retrieved two AERS reports in pediatric patients who experienced seizures following ciprofloxacin therapy. In one case, an 8-year old female patient had seizures before and after ciprofloxacin therapy, in the setting of numerous concomitant medications and underlying brain cancer. In the second case, a 15-year old male developed status

epilepticus while on ciprofloxacin and cefepime therapy. Both drugs were discontinued and the patient recovered.

In these two cases there may be other factors associated with the reported event. In the 8-year old the occurrence of the seizure prior to ciprofloxacin therapy and the underlying brain cancer are confounding factors. In the 15-year old, the concomitant use of another drug which is labeled for seizures is also a confounder.

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. Although the labeling does not indicate that this event was reported in the pediatric population clinical trials, it should be expected that events occurring in adults may also occur in pediatric patients[3].

4.5.5. GI events (=1)

One of the 17 cases, published in 2004[4], reported the occurrence of severe pseudomembranous colitis and ascites in an 8-year old male patient following therapy with co-trimoxazole, cefotaxime and ciprofloxacin (case # 5712656). Co-trimoxazole was administered for neurogenic bladder and right vesicoureteral reflux, and ciprofloxacin and cefotaxime were administered for urinary tract infection. Two weeks after the termination of therapy with ciprofloxacin the patient underwent a right ureteral implantation. The patient did not pass stools for one week after surgery, and had abdominal pain and distention as well as significant bloody mucus from the rectum on the 8th day after surgery. Enzyme immunoassay was positive for *Clostridium difficile*. CT scan demonstrated ascites and was in line with pseudomembranous colitis. The event resolved with corrective therapy and did not reoccur.

In this case, the concomitant administration of another drug (i.e., cefotaxime) also associated with pseudomembranous colitis is a confounding factor. However, the authors of this article suggested that ciprofloxacin caused the event based on temporal association.

The labeling addressed the occurrence of Pseudomembranous colitis is the **WARNINGS** section. However, the labeling does not mention the occurrence of ascites even though this is occasionally a complication of antibiotic-associated pseudomembranous colitis[5].

4.5.6. Body as a Whole events (n=1)

We retrieved one case of ear pain in a 3-year old female who was administered Ciprodex drops after surgery for bilateral myrigotomy tubes (case # 4103256). She was unable to

[3] **ADVERSE REACTIONS** section, Cipro tablets and oral suspension labeling.
[4] Angel CA, Green J, Swischuk L, Patel J Severe ciprofloxacin-associated pseudomembranous colitis in an eight-year old child. J Pediat Surg Volume:39, 2004: 1590-2.
[5] Jafri S, Marshall JB Ascites associated with antibiotic-associted pseudomembranous colitis. Southern Medical Journal 1996 Oct. 89 (10): 1014-7

tolerate the drops, despite having no problems with other ear drops. The event stopped after the drops were discontinued.

Ear pain is a labeled event under the **ADVERSE REACTIONS** section.

5. Summary

The AERS database was searched in the first two weeks of February 2005, for reports of adverse events occurring with the use of ciprofloxacin in pediatric patients. We focused on the one-year period following the approval of pediatric exclusivity (December 22, 2003), although the cut-off date for data collection was extended to January 31, 2005, to allow for all reports received up to the end of December 2004 to be entered in the database.

We found few pediatric reports (17 unique unduplicated cases) in the 13-month period of review; and in those, mostly labeled hematological, musculoskeletal, hypersensitivity, and CNS events were reported in more than one patient. Events reported in only one patient were pseudomembranous colitis and ear pain, each in a different patient. Both events are included in the labeling of ciprofloxacin products. Nevertheless, the AERS printout for adverse events in the pediatric population during the pediatric exclusivity period show a large number of unlabeled events reported only once. Many of these events are associated with a pre-existing illness or disease of the patient, or are covered by related terms listed in the labeling. Very few of the reports (3) listed use for the approved indication.

All 17 cases had a serious outcome, including one fatality associated with underlying illness and possible familial predisposition to fungal infections. Two cases indicated disabilities, which involved inability to walk in a 12-year old girl treated for osteomyelitis and inability to run in a 12-year old boy treated for a postoperative access. The four hospital admissions were for pseudomembranous colitis, pancytopenia, tendonitis and Stevens Johnson Syndrome (one adverse event per patient). The remaining 10 cases indicated that the outcome was medically significant, and were captured in the MedWatch form outcome section as “other”.

It should be noted that despite labeling coverage of adverse events in tendons and joints, it was concerning to see a case of severe tendonitis with contractures of knees and ankles in a 12-year patient with a history of bowed legs (case # 3804136). She received 5 weeks of ciprofloxacin oral therapy at recommended doses. Even though the ciprofloxacin dose was decreased after one month, and stopped one week later, she could not stand or ambulate. During therapy she complained of pain in her back, hips, thigh, knees and ankles. Two months after stopping ciprofloxacin an MRI of both knees suggested some thickening of the medial collateral ligaments. Her diagnosis was of tendinitis of Achilles and patella tendons. She required a wheelchair a month after the medication was stopped.

In summary, in the 13-month period of review the 17 unique pediatric cases showed mostly labeled hematological, musculoskeletal, hypersensitivity, and CNS events. At this time we did not identify new safety concerns in the pediatric population that are not adequately addressed in the labeling. However, because one report was concerning due to the patient requiring a wheelchair we will assiduously monitor the pediatric cases to determine if permanent disability is reported in this age group, and if the label should be amended to reflect this finding. We will continue to monitor adverse events in pediatric patients and communicate any emerging safety signals to the review division.

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Attachment 1 - Pediatric cases received in the 12-months subsequent to pediatric exclusivity approval (12-22-2003 to 1-31-2005). (N=17)

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity (12-22-2003 through 1-31-2005)							
Case # Receipt date Report type	**Age Sex Out**	**Origin**	**Dose**	**Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
Fatality (n=1)							
5702476 12-17-2004 Expedited	16 yrs F D	US	NS	Fungal infection	Thrombocytopenia Respiratory distress Condition aggravated Dyspnoea Renal impairment Fungal pneumonia Mucosal hemorrhage Esophageal varices Portal hypertension Anemia Tracheal ulcer Bilirubin conjugated inc. Fever GI bleeding Fungemia Candidiasis Pulmonary mass	Amphotericin B lipid complex Immunoglobulins Caspofungin Trimethoprim/sulfahethoxazole Meropenem Vancomycin Amphotericin liposome	Patient with chronic mucocutaneous candidiasis (CMC) started therapy with amphotericin B lipid complex for presumptive fungal infection. She developed dyspnoea on exertion and was hospitalized. She was treated with Caspofungin for possible fungal pneumonia. She later underwent splenectomy for management of chronic thrombocytopenia and mucosal bleeding. She required sclerotherapy for management of grade II esophageal varices secondary to portal hypertension. She received numerous transfusions for episodes of hematemesis and severe anemia. She had ulceration in her distal trachea. She developed conjugated hyperbilirubinemia, which decreased after Caspofungin was stopped. She was treated with trimethoprim-sulfamethoxazole, menopenem and vancomycin due to fever of 40 degrees C. She was started on Amphotericin B lipid complex and Ciprofloxacin for presumptive fungal infection. She experienced worsening respiratory distress and renal function declined. Amphotericin was switched to liposomal amphotericin. Candida tropicalis was isolated from blood cultures. She developed uncontrollable GI bleed and died. The author of this literature report stated that the patient may have had a unique familial variant of CMC that predisposes to deep candidal infection.
Hematologic events cases (n=5)							
4195666 08-12-04 Expedited	5 yrs M Other	UK	50 mg qd x 4 mths	Infection disease and UTI prophylaxis	Thrombocytopenia Hematuria Contusion	Sytron Alfacalcidol Trimethoprim Co-Amoxiclav	Patient had a history of chronic renal failure, urethral valves, UTI, urinary incontinence, and vesico-ureteric reflux. The patient had been treated at different times with Sytron, Alfacalcidol, Trimethoprim and Co-amoxiclav up to 3 months prior to starting ciprofloxacillin therapy (March 2003 through December 2003). Ciprofloxacin was started in March 2004, and continued for 16 weeks at which time he developed hematuria, bruises and thrombocytopenia. Ciprofloxacin was stopped and the patient recovered in 3 days.
4195204	5 yrs	UK	125	Respiratory	Hemolytic anemia	Acyclovir	Patient with a history of acute myeloid leukemia post

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity (12-22-2003 through 1-31-2005)							
Case # Receipt date Report type	**Age Sex Out**	**Origin**	**Dose**	**Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
09-21-04 Expedited	F Other		mg bid	infection		Semptrin	bone marrow transplant received ciprofloxacin for respiratory for one week. At some unknown date, the patient developed hemolytic anemia. Ciprofloxacin was stopped and the patient developed. The patient did not have a history of renal impairment.
4146794 06-28-04 Expedited	15 yrs F H	France		Febrile episode	Pancytopenia	Solumedrol Cortancyl Cellcept Prograf Vancomycin Tazocilline Cymevan Zenapax Ursolvan Fungizone Aspegic Rovalcyte Amlor Mopral Un-alfa Ulcer Rocephine Clamosyl Loxen Lasilix albumine	The patient was treated with ciprofloxacin for 1 month for a febrile episode due to enterobacter cloacae, enterococcus fecalis and staphylococcus aureus. She had a history of atresia biliary, liver transplant and graft rejection with syndrome hepatorenal leading to second liver transplant. Approximately two months after the second transplant, while receiving ciprofloxacin and numerous concomitant medications, she developed pancytopenia. The patient recovered.
4146950 05-21-04 Expedited	16 M Other	France	500 mg bid	Suspected osteomyelitis	Neutropenia Anemia Coombs Test Positive	Unspecified antibiotics Vastarel	A 16-year old developed neutropenia, anemia and a positive Coombs test approximately 5 days after starting ciprofloxacin. The patient did not complain of fever, or had bilirubin increases. Recent medical history included meningitis, the month prior to dosing with ciprofloxacin.
4115018 03-23-04 Expedited	9 mth M Other	UK	80 mg qd	Lower respiratory tract infection	Blood fibrinogen decreased Coagulopathy Coagulation time prolonged	Domperidone Omeprazole Furosemide Methylprednisolone	Patient with a history of Down's Syndrome and respiratory disorder received 80 mg of ciprofloxacin IV daily for 8 days. The patient was also receiving other medications. Two days after starting ciprofloxacin therapy the patient developed low fibrinogen and coagulopathy with rising thrombin clotting times. He was at increased risk of hemorrhage. There was a positive dechallenge.
Musculoskeletal events (n=4)							
3804136	12 yrs	US	750	Frontal bone	Tendonitis	Cefixime	Patient with history of multiple craniofacial surgeries,

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity (12-22-2003 through 1-31-2005)							
Case # Receipt date Report type	**Age Sex Out**	**Origin**	**Dose**	**Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
4-16-04 Periodic	F DS		mg bid x 4 weeks; then 500 mg bid x 1 week	osteomyelitis	Arthralgia Tendon disorder Joint contracture Back pain Pain in extremity	Zosyn	bowed legs, Crouzon's syndrome, acanthosis, tracheostomy, ventriculoperitoneal shunt, and osteitis, was treated with ciprofloxacin and developed pain in her back, hips, knees and ankles. The patient had a recent history of osteomyelitis of the left temporal area beginning Dec. 1999. She was treated with dicloxacillin for 10 days, and with amoxicillin and cefixime the following month after surgical debridement. The patient was hospitalized for osteomylitis of the left temporal skull area in April 2000, and was treated with Zosin while inpatient followed by oral ciprofloxacin 750 mg twice a week as an outpatient. Approximately a month into therapy she complained of back, hip and knee pain, as well as tenderness of tendons in ankles bilaterally and tendons of lower spine. Ciprofloxacin was decreased to 500 mg twice a day, but the pain continued. Ciprofloxacin was stopped, and cefixime therapy started. Two months after the hospitalization the patient required a wheelchair. She had a diagnosis of tendonitis of the supraspinous ligament region, lateral hip and knee and Achilles tendon region. The pain continued even though the ciprofloxacin dose was lowered and then stopped. She was diagnosed with tendonitis of the tibia, patella and Achilles tendon. MRI was normal for the hips and lumbar region; MRI showed knee effusion and some thickening of the medial collateral ligaments. A rheumatology consult 6 months after the April hospitalization stated that the 12-year old could not stand or ambulate, and had severe contractures at knees and ankles. She had severe discomfort on palpation of Achilles tendons, quadriceps tendon, greater trochanters and lower back.
5697583 12-8-04 Expedited	14 yrs M H	Ireland	750 mg bid	Osteomyelitis little finger	Tendonitis Pain in extremity	None	A Caucasian patient was discharged from the hospital on ciprofloxacin 750 mg twice a day fro 14 days, given for osteomyelitis. He developed pain in the legs after one w3eek, becoming more severe at 10-14 days. The patient was hospitalized for Achilles tendonitis. Ciprofloxacin was stopped and the outcome improved.
5657317 10-25-04 Direct	15 yrs F OT	US	NS	Chronic osteomyelitis	Joint stiffness Ecchymosis	None	Patient with a history of fracture of L radius with subsequent chronic infection was treated with ciprofloxacin for chronic osteomyelitis. During therapy she complained of joint stiffness and ecchymosis on

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity (12-22-2003 through 1-31-2005)							
Case # Receipt date Report type	**Age Sex Out**	**Origin**	**Dose**	**Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
							both knees. This resolved within two weeks of stopping ciprofloxacin.
5732200 1-28-2005 Expedited	10 yrs M DS	France		Postoperative access	Arthralgia Knee pain	NS	Patient started ciprofloxacin therapy in October 2004 for postoperative abscess. He developed knee pain during the treatment (exact date not provided). Ciprofloxacin was stopped after 4 days of therapy. Because the patient was confined to bed during all hospitalization (3 weeks) the articulation had been at rest. The pain was persistent and considered disabling, since the patient can't run anymore.
Allergic reaction events (n=3)							
4146959 5-21-04 4045339 03-05-04 Expedited	9 yrs F LT, H	France	250 mg bid	Acute sphenoidal sinusitis and ethmoiditis	Stevens Johnson Syndrome	Ventoline Orelox Acetaminophen Solupred	On October 29, 2003, the patient complained of febrile syndrome, cephalea and face edema. A CT-scan showed acute sphenoidal sinusitis and ethmoiditis. Therapy with ciprofloxacine, cefposime proxetil, prednisolone and paracetamol, as well as albuterol inhaler was started on the same day and continued until November 17. The patient improved. Approximately two weeks after starting therapy with all 5 drugs, on November 14, the patient developed palpebral edema, fever, microvesicular eruption on the abdomen and thorax, face and neck edema, bullous eruption on lips, cheeks and palms of the hands. Biological tests showed hypereosinophilia (1030 per cubic mm). On November 17 therapy with salbutamol, ciprofloxacine and cefpodoxime was stopped. The next day rash worsened, reaching several mucosal membranes and bilateral conjunctivitis appeared. Cutaneous biopsy confirmed diagnosis of SJS. Two days later (November 20) the patient developed skin detachment, generalized and hemorrhagic mucitis and complete anorexia. After discharge in December 2003, the patient had depigmented arms and hyperpigmented trunk, positive antinuclear and anti-DNA antibodies, and articulation pains, cramps and fatigue.
5704810 12-20-04 Expedited	12 yrs M Other	Italy	500 mg daily	Meningitis prophylaxis	Periorbital itching Elepahral itching Periorbital edema Blepaharal edema Allergic reaction	NS	Asian patient received 500 mg ciprofloxacin owing to meningitis contact. After a single dose of ciprofloxacin the patient experienced periorbital and blepharal itching, and periorbital and blepharal edema considered serious. The patient was treated with hydrocortisone IV on the same day. The patient recovered the following day.
5680240	15 yrs	US	NS	Swimmer's ear	Face rash	NS	Patient was given Ciprodex drops topically to his right

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity (12-22-2003 through 1-31-2005)							
Case # Receipt date Report type	**Age Sex Out**	**Origin**	**Dose**	**Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
11-16-04 Direct	M OT				Hives Face swelling		ear for swimmer's ear infection. The next day he developed a rash on the right side of his face and therapy was stopped. The rash turned into hives which started to ooze a few days later. The right side of his face started to swell. The patient was treated with a steroid injection, Clarinex and oral steroids. He was also given additional antibiotics, both orally and topically (cream). It was not stated if the patient recovered.
Central nervous system events (n=2)							
4147631 05-21-04 expedited	8 yrs F Other	US	250 mg bid x 2 days	UTI	Grand mal convulsion Masked facies Dystonia Drooling TIC Convulsion	Celebrex Thalidomide FamotidineFleet Phospho-soda Robitussin Temodar Zofran Tamoxifen Megace	Patient with a history of advanced brain cancer had a seizure on the day before ciprofloxacin therapy began. On the day that ciprofloxacin therapy started the patient had a tonic-clonic seizure, with symptoms of facial grimace, uncontrolled motor activity of the hands, drooling and tics. It was determined from the symptoms that this seizure was different from the previous one the day before therapy. The patient might have had another seizure the following day when ciprofloxacin was discontinued. The reporter stated that he felt that the seizures were a symptom of the progression of the brain cancer.
5679815 11-10-04 Expedited	15 yrs M Other	Australia	NS	UTI	Status epilepticus	Cefepime	Patient received IV ciprofloxacin for UTI. On an unknown date, he developed status epilepticus. Ciprofloxacin and cefepime were withdrawn and the patient recovered. No additional information was provided.
Gatrointestinal system events (n=1)							
5712656 01-04-2005 Expedited Literature	8 yrs M H	US	250 mg bid	UTI	Clostridium colitis Ascites	Enemas Cotrimoxazole Cefixime	A patient with a history of congenital sacral agenesis and recent urethral reimplantation developed pseudomembranous colitis and ascites following therapy with ciprofloxasin, cotrimoxazole and cefotaxime. Cotrimoxazole was administered to treat neurogenic bladder and right vesicoureteral reflux and ciprofloxacin and cefotaxime were given to treat UTI. Over a period of 4 months, two UTIs occurred of which the first one was treated with ceforzxime and the second with ciprofloxacin. Two weeks after the termination of therapy with ciprofloxacin, right ureteral implantation was performed. The patient did not pass stools for one week after the surgery. Abdominal pain and distension occurred on the 8th day after surgery and significant

Table 1A – Summary of AERS pediatric cases received during the 1-year following approval of pediatric exclusivity (12-22-2003 through 1-31-2005)							
Case # Receipt date Report type	**Age Sex Out**	**Origin**	**Dose**	**Indication**	**Adverse Events**	**Concomitant drugs**	**Comments/Summary of case**
							bloody mucus passed per the rectum. He was admitted, where enzyme immunoassay showed Clostridium difficile. CT demonstrated ascites and was in line with pseudomembranous colitis. The event resolved on corrective treatments in 11 days and there was no recurrence of the eent after 16 months. Although the patient had received several antibiotics that could trigger pseudomembranous colitis, the reporters suggest that ciprofloxacin caused the event based on the temporal relationship.
Body as a Whole events							
4103256 03-03-04 Direct	3 yrs F Other	US	3 drops bid	"Otis media"	Extreme pain	NS	A father reported that his 3-year old daughter received Ciprodex otic drops after surgery for bilateral myrigotomy tubes. She was unable to tolerate them and cried once for several hours after dosing. She had never had problems with any other ear drops. The pain stopped when the drug was discontinued.

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/s/

Evelyn Farinas
4/11/05 04:32:15 PM
DRUG SAFETY OFFICE REVIEWER

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4/12/05 01:08:05 PM
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