

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: March 15, 2005

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SUBJECT: One Year Post-Pediatric Exclusivity Post-Marketing Adverse Event Review:
Drug Use Data: **Systemic Ciprofloxacin**
Cipro[®] oral tablet (NDA 19-537SE5-49),
Cipro[®] oral suspension (NDA 20-780)
Cipro[®] XR oral tablets (NDA 21-473)
Cipro[®] injectable (NDA's 19-847, 19-857)
Pediatric Exclusivity Grant Date: December 18, 2003

EXECUTIVE SUMMARY

This consult examines the systemic (oral and intravenous) drug utilization of ciprofloxacin in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on December 18, 2003.

An estimated 33.5 million prescriptions were dispensed in the U.S. for the fluoroquinolones class during calendar year 2004. Ciprofloxacin was the second most commonly dispensed fluoroquinolone in the U.S. accounting for roughly 41% of fluoroquinolone prescriptions in 2004. The total prescription volume for systemic ciprofloxacin increased slightly from 2003 to 2004 (13.6 million and 13.8 million prescriptions, respectively). In 2004, oral tablets accounted for the

vast majority (~99.5%) of dispensed ciprofloxacin prescriptions in the U.S., followed by suspension and intravenous dosage forms (~0.4% and 0.1% of dispensed prescriptions, respectively). Generic ciprofloxacin tablet and suspension formulations entered the market in June, 2003, resulting in a large decline in brand name Cipro® dispensed prescriptions from 2003 to 2004. The generic versions accounted for nearly 69% of the tablet market and 43% of the suspension market in year 2004.

Children aged 0-16 years accounted for roughly 1% (n=93,000) of the estimated 9.6 million drug mentions for systemic ciprofloxacin during office-based physician-patient encounters during calendar year 2004. The most common diagnosis associated with the mention of systemic ciprofloxacin for pediatric patients was urinary tract infection, site unspecified (ICD-9 =599.0), which accounted for 28% of mentions in children during the pre-exclusivity (2003) period and 13% of mentions in children during the post-exclusivity (2004) period. Due to the small numbers, we were unable to analyze the diagnoses associated with ciprofloxacin use in sub-groups (e.g., infants) of the pediatric population.

Pediatricians were responsible for approximately 1% of prescriptions dispensed for ciprofloxacin tablets in the U.S. during 2004 and roughly 17% of the suspension formulation dispensed.

Among an insured population in Caremark, a large pharmacy benefits manager, the pediatric age group (1-16 years) accounted for slightly over 1% of oral ciprofloxacin claims in 2004. Applying these percentages from Caremark to the number of prescriptions dispensed from NPA Plus™, an estimated 174,000 prescriptions of the oral dosage forms of ciprofloxacin were dispensed to the pediatric population in year 2004.

Children aged 0-16 years accounted for 515 (0.6%) of the 87,050 actual discharges associated with systemic ciprofloxacin in 2004 in a sample of Premier's 450 acute short stay hospitals.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of the drug in children during the one-year period following the date when the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs. Since anti-infectives, including ciprofloxacin are used for treating both outpatients and inpatients, we focused on use in both of these settings.

Cipro® is currently available as an oral 100mg, 250mg, 500mg or 750mg tablet (NDA 19-537), as a 500mg or 1000mg extended release tablet (NDA 21-473), and as a 5% and 10% oral

suspension (NDA 20-780). Cipro[®] is also available as a premixed intravenous solution containing either 200mg or 400mg of ciprofloxacin in flexible PVC bags containing 100ml or 200 ml of 5% dextrose respectively (NDA 19-857) or as bulk vials containing 200mg/20mls or 400mg/40mls (NDA 19-847). Cipro[®] oral tablets and Cipro[®] oral suspensions are now off patent and are available generically.

INDICATIONS AND USAGE

The indication section of the label reads as follows:¹

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.

Adult Patients:

- Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.
- Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus*.
- Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis*.
- Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

- Acute Sinusitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*.
- Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.
- Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*.

¹ Physicians Desk Reference-Online™, accessed January 2005

- Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused by Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, or Bacteroides fragilis.
- Infectious Diarrhea caused by Escherichia coli (enterotoxigenic strains), Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri or Shigella sonnei when antibacterial therapy is indicated.
- Typhoid Fever (Enteric Fever) caused by Salmonella typhi .

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

- Uncomplicated cervical and urethral gonorrhea due to Neisseria gonorrhoeae .

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.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for the oral and intravenous forms of ciprofloxacin HCl (NDAs 19-537SE5-049, 19-847, 19-857 and 20-780) on December 18, 2003. Other currently marketed fluoroquinolones include gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin.

This review describes outpatient and inpatient usage of oral and intravenous forms of ciprofloxacin in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

IMS Health, National Sales Perspectives™ data were used to determine the setting in which the product was sold. National ciprofloxacin sales were examined for calendar year 2004 in terms of both units and individual tablets and milliliters sold (Table 1). The injectable form of

ciprofloxacin was predominately sold to the non-retail channels (~99.8%). The retail channel was the main purchasers of oral tablets (~84.5%) and suspension forms (65.4%) of ciprofloxacin.

Table 1: Sales of Bottles and Tablets or Milliliters Sold Through Retail and Non-Retail Channels of Distribution During Calendar Year 2004 in IMS Health, National Sales Perspectives™

CIPROFLOXACIN		Bottles or IV bag/bottles (000's)	Calendar Year 2004		
			%	Tablets or milliliters (000's)	%
All Ciprofloxacin	TOTAL	7845	(100%)	853,418	(100%)
Injectables	Total	4,935.4	(62.9%)	851,160 (mls)	(76.5%)
	*Retail	14.1	(0.3%)	851,660	(0.2%)
	**Non-Retail	4,921.3	(99.7%)	1,758	(99.8%)
Oral Tablets	Total	2810.1	(35.8%)	252,763 (tabs)	(22.6%)
	*Retail	2,394.3	(85.2%)	213,630	(84.5%)
	**Non-Retail	415.9	(14.8%)	39,135	(15.5%)
Oral Suspension	Total	99.6	(1.3%)	9,961 (mls)	(0.9%)
	*Retail	65.1	(65.4%)	6,514	(65.4%)
	**Non-Retail	34.4	34.5%)	3,447	(34.6%)

*Retail channels include chain, independent, food stores and mail service
 **Non-retail channels include non-federal hospitals, federal facilities, long term care, home health care, clinics, HMO's, and miscellaneous-prison, universities, and other
 National Sales Perspectives™ Retail and Non-Retail Combined: Calendar Years 2002-2004, Data Extracted January 2005
 Original File: 0501cip3.dvr

Since the use of this product occurs in both outpatient and inpatient settings, we further examined the utilization patterns for ciprofloxacin in these settings based on the dosage forms used. Outpatient use for the tablet and suspension dosage forms were measured by two IMS Health audits, the National Prescription Audit *Plus*™ (NPA *Plus*™) and the National Disease and Therapeutic Index™ (NDTI™), along with prescription claims for a 36-month period of time from Caremark (Dimension Rx™). Inpatient ciprofloxacin use was assessed from hospital billing data provided by Premier™.

Ciprofloxacin is available in oral, intravenous, otic, and ophthalmic dosage forms. Only oral and intravenous products are examined in this consult to represent “systemic ciprofloxacin” use.

In this review, we use the term “fluoroquinolone” to refer to the following products: ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin. We note the term “quinolone” may refer to entities such as nalidixic acid and enoxacin.

I. OUTPATIENT DRUG USE

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis included all prescriptions dispensed calendar years 2002-2004, inclusive. USC5 15180 was used to define the fluoroquinolone class.

CAREMARK™

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 70 million lives, and processing over 545 million prescription claims annually. FDA has access to Caremark's Dimension Rx™ database consisting of a subset of total Caremark paid claims representing 350 million claims per year for prescriptions filled in 57,000 pharmacies across the country. Participants whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark's Dimension Rx™ system includes participants from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in Caremark's Dimension Rx™ system to all persons receiving dispensed prescriptions in the U.S., however, is not known.

For this analysis, prescription claims in the Caremark system were examined for calendar years 2002 through 2004, inclusive.

II. INPATIENT DRUG USE

PREMIER™

Premier maintains a large hospital drug utilization and financial database. The database contains information from over 450 acute care facilities and includes approximately 14 million inpatient records. Roughly one out of every seven inpatient discharges in the United States is represented in Premier's database. Data are available from January 2000 through the present, but have a lag time of approximately six months. Premier's primary mission is to assist health care institutions improve clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end,

Premier developed this database in part to analyze utilization of resources to improve clinical efficiency.

The hospitals that contribute information to the database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, number of beds, population served, payors, and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. Based upon these analyses, we believe that most estimates of national inpatient drug use based on Premier data appear to be reasonable, but strongly recommend making this determination on a drug-specific basis. For ciprofloxacin, we did not use projected estimates, given the very competitive marketplace for these products getting on a hospital formulary. Therefore, we cannot be sure that Premier purchasing agreements are truly representative of hospitals nationwide. Rather the Premier data provides a glimpse of practice in approximately 450 acute, short-stay hospitals.

For this analysis, the total number of distinct discharges within Premier hospitals which included claims for ciprofloxacin was examined for the time period from July 1, 2003 to June 30, 2004, inclusive.

PREMIER PEDIATRIC™

Premier's pediatric database represents a subset of information from 37 pediatric hospitals. In addition, Premier maintains data on all pediatric discharges from the larger sample of approximately 450 acute care facilities. Overall, the pediatric population in Premier's pediatric database includes greater than 3 million inpatient records. Data are available from January 2000 through the present, but have a lag time of approximately six months.

For this analysis, the total number of distinct discharges associated with ciprofloxacin use within these 37 tertiary care pediatric hospitals are examined from July 1, 2003 to June 30, 2004, inclusive.

RESULTS

I. Dispensed Prescriptions

According to data from the National Prescription Audit, systemic ciprofloxacin was the second most frequently dispensed fluoroquinolone, accounting for roughly 41% of the estimated 33.5 million prescriptions dispensed for the fluoroquinolone class in the U.S. for calendar year 2004

(Table 2). Dispensed prescriptions for systemic ciprofloxacin appear to have increased slightly over time with 13.6 million dispensed prescriptions in 2003 to 13.8 million prescriptions dispensed in 2004.

Table 2: Total Projected Number of Prescriptions Dispensed in Retail Pharmacies Nationwide for Systemic Fluoroquinolone Products (USC5? 15180)						
	Total Number of Dispensed Prescriptions (000's)					
	2002		2003		2004	
	N	(%)	N	(%)	N	(%)
Systemic Fluoroquinolones	32,744,000	100.0%	33,894,000	100.0%	33,498,000	100.0%
Levofloxacin	13,063,000	(39.9%)	14,376,000	(42.4%)	14,449,000	(43.1%)
Ciprofloxacin	13,535,000	(41.3%)	13,606,000	(40.1%)	13,814,000	(41.2%)
Moxifloxacin	2,644,000	(8.1%)	3,187,000	(9.4%)	3,128,000	(9.3%)
Gatifloxacin	3,011,000	(9.2%)	2,376,000	(7%)	1,817,000	(5.4%)
Ofloxacin	338,000	(1%)	238,000	(0.7%)	181,000	(0.5%)
Norfloxacin	151,000	(0.5%)	109,000	(0.3%)	84,000	(0.5%)
Gemifloxacin					24,000	(0.1%)
Lomefloxacin	2,000	(<0.1%)	1,000	(<0.1%)	1,000	<0.10%)

IMS Health, National Prescription Audit Plus™, Calendar Years 2002-2004, Data Extracted January 2005.
Original file: 0501cip1.dvr

During 2004, ciprofloxacin oral tablets accounted for nearly all of systemic ciprofloxacin dispensed prescriptions in the retail setting in the U.S. (99.5%), followed by the oral suspension (~0.4%) and the injectable products (~0.1%), respectively (Table 3). Generic ciprofloxacin accounted for over two-thirds (68.6%) of all oral ciprofloxacin tablets, followed by Cipro® tablets (~16.9), Cipro® XR (~14.4%) and Cipro® Cystitis Pac (~0.1%) (Table 3)

Table 3: Total Projected Number of Prescriptions Dispensed in Retail Pharmacies Nationwide for Systemic Ciprofloxacin Products						
	Total Number of Dispensed Prescriptions (000's)					
	2002		2003		2004	
	N	(%)	N	(%)	N	(%)
Ciprofloxacin (Systemic)	13,535,000	100.0%	13,606,000	100.0%	13,814,000	100.0%
Oral Tablets	13,467,000	(99.5%)	13,538,000	(99.5%)	13,746,000	(99.5%)
Ciprofloxacin*			3,739,000	(27.6%)	9,424,000	(68.6%)
Cipro	13,441,000	(99.8%)	8,624,000	(63.7%)	2,322,000	(16.9%)
Cipro XR			1,154,000	(8.5%)	1,984,000	(14.4%)
Cipro Cystitis Pac	26,000	(0.2%)	22,000	(0.2%)	16,000	(0.1%)
Oral Suspension	56,000	(0.4%)	59,000	(0.4%)	59,000	(0.4%)
Cipro	56,000	(100%)	51,000	(86.6%)	34,000	(57.3%)
Ciprofloxacin*			8,000	(13.4%)	25,000	(42.7%)
IV Injectable	13,000	(0.1%)	10,000	(0.1%)	9,000	(0.1%)
Cipro IV	13,000		10,000		9,000	
Ciprofloxacin	0		0		0	

*Generic Ciprofloxacin entered marketplace in Spring, 2003.
IMS Health, National Prescription Audit Plus™, Calendar Years 2002-2004, Extracted January 2005.
Original file: 0501cip2.dvr

Prescriber Specialty

The top two prescriber specialties for ciprofloxacin oral tablets during calendar year 2004 were internal medicine and family practice (Table 4). Pediatricians ranked 18th and accounted for nearly 1% (~121,000 prescriptions) of dispensed prescriptions. Pediatrics was the top prescriber specialty for ciprofloxacin suspension in 2004, accounting for approximately 17% (~8,000 prescriptions) of dispensed prescriptions, followed by family practice and internal medicine. The infectious disease specialty represented less than 1% of dispensed prescriptions for ciprofloxacin suspension in 2004 and was ranked 22nd in terms of dispensed prescriptions for oral ciprofloxacin tablets. There appears to have been no substantial change in prescriber specialty for ciprofloxacin during the 36-month study period from 2002 through 2004.

Table 4: Total Number of Prescriptions Dispensed by Physician Specialty Nationwide for Oral Ciprofloxacin* (excludes Long Term Care and Mail Order Channels)

		Number of Total Dispensed Prescriptions					
		2002		2003		2004	
		N (000's)	(%)	N (000's)	(%)	N (000's)	(%)
*CIPROFLOXACIN BY PHYSICIAN SPECIALTY		12,627	100.0%	12,740	100.0%	12,943	100.0%
Ciprofloxacin Oral Tablets (includes XR)		12,588	(99.7%)	12,697	(99.7%)	12,894	(99.6%)
1 st	Internal Medicine	2,663	(21.2%)	2,707	(21.3%)	2,762	(21.4%)
2 nd	Family Practice	2,519	(20%)	2,605	(20.5%)	2,667	(20.7%)
3 rd	Osteopathic Medicine	1,033	(8.2%)	1,054	(8.3%)	1,089	(8.4%)
4 th	Urology	1,084	(8.6%)	1,043	(8.2%)	1,011	(7.8%)
5 th	Unknown	806	(6.4%)	785	(6.2%)	644	(5%)
18th	Pediatrics	111	(0.9%)	118	(0.9%)	121	(0.9%)
	Total Others (70)	4,372	(34.4%)	4,385	(34.4%)	4,600	(35.4%)
Ciprofloxacin Oral Suspension		39	(0.3%)	43	(0.3%)	47	(0.4%)
1st	Pediatrics	5	(12.5%)	7	(15.1%)	8	(17%)
2 nd	Family Practice	6	(14.9%)	6	(13.8%)	6	(13.3%)
3 rd	Internal Medicine	6	(14.9%)	6	(13.8%)	6	(13.1%)
4 th	Unknown	4	(11.2%)	5	(11.5%)	5	(11.5%)
5 th	Osteopathic Medicine	3	(6.8%)	3	(6.4%)	3	(6.4%)
	Total Other (64)	15	(39.7%)	16	(39.5%)	17	(39.6%)

*Excludes any otic, ophthalmic, intravenous, or topical dosage forms

** Infectious Disease not shown in top 25 Specialties

IMS Health, National Prescription Audit Plus™, Calendar Years: 2002-2004, Data Extracted January, 2005

Original file: 0501cip5.dvr.

II. Patient Demographics

Among a large, insured patient population managed by Caremark, slightly over 1% of processed claims for all oral dosage forms of ciprofloxacin were for persons aged 1-16 years in 2004 (Table 5). This was similar to the results seen for 2002 and 2003. Pediatric claims for all oral ciprofloxacin dosage forms remained relatively stable over time, with 19,431 claims in 2002; 21,023 in 2003; and 20,860 in 2004.

Pediatric claims for the oral suspension form of ciprofloxacin increased from 1,349 claims (30% of all claims for the oral suspension form) in 2002 to 2,125 (39% of all claims for the oral suspension form) in 2004.

Table 5: Total Number of Paid Prescription Claims for Oral Dosage forms of Ciprofloxacin From Caremark Pharmacy Benefit Manager Database.

Dosage Form by Age Group	Number of Paid Claims by Calendar Year					
	2002		2003		2004	
	N	(%)	N	(%)	N	(%)
All Oral Ciprofloxacin	1,825,788	(100%)	1,843,086	(100%)	1,865,278	(100%)
Peds (1-16 yrs)	19,431	(1.1%)	21,023	(1.1%)	20,860	(1.1%)
Adults (17+ yrs)	1,806,313	(98.9%)	1,822,063	(98.9%)	1,844,418	(98.9%)
Ciprofloxacin Oral Tablets	1,821,129	(99.7%)	1,671,397	(90.7%)	1,567,579	(84%)
Peds (1-16 yrs)	18,018	(1 %)	17,902	(1.1%)	17,044	(1.1%)
Adults (17+ yrs)	1,803,111	(99%)	1,653,495	(98.9%)	1,550,535	(98.9%)
Ciprofloxacin Oral Suspension	4,658	(0.3%)	5,449	(0.3%)	5,733	(0.3%)
Age 1	188	(4%)	278	(5.1%)	338	(5.9%)
Age 2-11	1,048	(22.5%)	1,563	(28.7%)	1,651	(28.8%)
Age 12-16	177	(3.8%)	229	(4.2%)	233	(4.1%)
Peds (1-16 yrs)	1,349	(30.3%)	1,974	(38%)	2,125	(38.8%)
Adults (17+ yrs)	3,245	(69.7%)	3,379	(62%)	3,511	(61.2%)
Ciprofloxacin Extended Release Tablets	1	(0%)	167,240	(9.1%)	291,966	(15.7%)
Peds (1-16 yrs)	0	(0%)	1,051	(0.6%)	1,594	(0.5%)
Adults (17+ yrs)	1	(100%)	165,189	(99.4%)	290,372	(99.5%)

Caremark Dimension Rx™: Extracted January 24, 2005.

Since NPA Plus™ does not provide complete historical demographic information on patients, we applied the proportions for demographic subgroups from Caremark's Dimension Rx™ to NPA Plus™ data in an effort to approximate the number of oral ciprofloxacin prescriptions dispensed nationwide to children in the outpatient setting. Using this method, an estimated 174,000 oral ciprofloxacin prescriptions were dispensed to persons aged 1-16 years (Table 6). Within that amount, we estimate that 151,000 prescriptions for oral ciprofloxacin tablets and 23,000 oral suspension prescriptions were dispensed for children during 2004.

Table 6: Estimated Nationwide Prescriptions Dispensed for all Oral Ciprofloxacin during Calendar Year 2004 by Age Group (1-16 years)			
	January – December 2004		
Age 1-16	Total Number of Prescriptions* Dispensed for All Age Groups (From Table 3)	% Pediatric Claims** (Ages 1-16 yrs.) (from Table 5)	Estimated Number of Prescriptions Dispensed to the Pediatric Population (Ages 1-16 yrs)
Ciprofloxacin Oral Tablets (includes XR)	13,746,000	1.1%	151,206
Ciprofloxacin Oral Suspension	59,000	38.8%	22,892
Total	13,805,000	n/a	174,098
<small>*IMS Health, National Prescription Audit Plus™, Calendar Years: 2002- 2004, Data Extracted January 2005 Original file: 0501cip2.dvr (Totals exclude intravenous ciprofloxacin prescriptions) **Caremark's Dimension Rx™, Extracted January 20005</small>			

III. Indication

Children aged 0-16 years accounted for approximately 1% (~93,000) of the estimated 9.6 million drug mentions for systemic ciprofloxacin in office based physician-patient encounters in 2004 (Table 7). The most common diagnosis associated with a mention of systemic ciprofloxacin among pediatric patients in the pre- and post-exclusivity period was urinary tract infection, site unspecified (ICD-9 599.0) (28% and 13% of mentions, respectively). Post op surgical exam (ICD-9 V67.0) was the second most common indication in both time periods, accounting for 9% of mentions in the pre-exclusivity period and 10% of mentions during the post-exclusivity period (Table 7).

Table 7. Top Ten Diagnoses Associated with Mentions of Systemic Ciprofloxacin (in thousands) for the Pediatric Age Group (0-16 years) during Calendar Years 2002-2004

	2002	2003	2004
ICD-9 Code	N (%)	N (%)	N (%)
Ciprofloxacin Total Uses (Systemic)*	9,413 (100)	8,689 (100.0)	9,625 (100.0)
(0-16 Years)	97 (1)	81 (0.9)	93 (1)
599.0 Urinary Tract Infection, Site Unspecified	26 (26.6)	22 (27.7)	12 (13.1)
V67.0 Post Op Surgical Exam	8 (8)	8 (9.3)	9 (9.8)
463.0 Tonsillitis Acute	----	----	9 (9.2)
892.0 Open Wound Foot Except Toes	2 (2.2)	2 (3)	7 (7.4)
682.9 Cellulites + Abscess Unspecified Site	2 (2.2)	----	7 (7.1)
490.0 Bronchitis Not Spec. Acute or Chronic	----	----	6 (6.8)
681.9 Cellulites + Abs Unspecified Digit	----	7 (8.4)	6 (6.6)
464.1 Tracheitis Acute	----	----	6 (6.4)
462.0 Pharyngitis Acute	----	----	6 (6.2)
996.6 Infection due to Internal Device	2 (1.7)	----	6 (6.2)
Total Others (26)	58 (59.3)	42 (51.6)	19 (21)

IMS National Disease and Therapeutic Index™, Calendar Years 2002-2004. Data extracted February 2005
 File: (NDTI ciprofloxacin2002-2004.dvf)
 * Includes all systemic dosage forms (Oral tablets accounted for ~97% of uses-data not shown)

III. Inpatient Usage

There were 87,050 actual discharges associated with systemic ciprofloxacin use during a hospital visit in Premier's 450 acute short-stay hospitals for the first two quarters of 2004 (Table 8). This represents a decrease of 16% (from 104,053 actual discharges) in the last two quarters of 2003. Of the 87,050 discharges in the first half of 2004, 0.6% were for children aged 0-16 years.

Actual discharges in the pediatric population for the oral dosage form of ciprofloxacin declined by ~15.5% (297 to 251 discharges) from the last half of 2003 to the first half of 2004. Actual discharges for the intravenous dosage form in this population remained relatively stable (259 to 264 discharges).

Table 8: Total Number of Actual Discharges in which Ciprofloxacin was used (Oral and Intravenous) from Premier Inpatient Database.

Ciprofloxacin (By Route)	Number of Actual Discharges			
	July 2003 - December 2003		January 2004-June 2004	
	N	(%)	N	(%)
Total	104,053		87,050	
Oral	55,120	(53%)	44,910	(51.6%)
Peds				
(0-16 yrs)	297	(0.5%)	251	(0.6%)
Adults				
(17+ yrs)	54,823	(99.5%)	44,659	(99.4%)
Intravenous	48,933	(47%)	42,140	(48.4%)
Peds				
(0-16 yrs)	259	(0.5%)	264	(0.6%)
Adults				
(17+ yrs)	48,674	(99.5%)	41,876	(99.4%)

Premier Inc: Extracted January 3, 2005.

Among patients aged 0-16 years, there were 323 actual discharges associated with systemic ciprofloxacin use during a hospital visit in a subset of 37 pediatric hospitals from Premier's entire hospital network for the first two quarters of 2004 (Table 9). This represents an increase of roughly 10.2% (from 290 actual discharges) in the last two quarters of 2003 (calculated from Table 9)

Table 9: Total Number of Actual Discharges for Patients aged 0-16 Years in which Ciprofloxacin (Oral and Intravenous) was used form Premier's Pediatric Hospital Inpatient database.

Ciprofloxacin (By Route)	Number of Actual Discharges			
	July 2003 - December 2003		January 2004-June 2004	
	N	(%)	N	(%)
Total Ciprofloxacin	290		323	
Oral	163	(56.2%)	162	(50.2%)
Intravenous	127	(43.8%)	161	(49.8%)

Premier Inc: Extracted February 1, 2005.

LIMITATIONS

NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus™ does not include complete historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels. This does not appear significant as mail order and long-term care (~5%) did not contribute substantially to total sales of systemic ciprofloxacin in the U.S. (Data not shown).

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. The small numbers associated with the diagnoses of systemic ciprofloxacin use in children aged 0-16 years in NDTI™ office-based physician encounters is reflective of the low market share (~1%) observed in the pediatric population. Furthermore, due to the sampling and data collection methodologies, the small sample size can make these data unstable and therefore the results should be interpreted with caution.

Caremark data cannot be projected to make national level estimates of use, but its large sample size can provide use estimates for less commonly used products. Although the data from Caremark may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Reliable information for patients less than the age of 1 year is not available from this data source.

The inpatient data from Premier, while providing a helpful view of the use of systemic ciprofloxacin in the hospital setting, cannot be projected to provide nationwide estimates of the use of this product in children hospitalized throughout the U.S. Although the use of ciprofloxacin within the large sample of general hospitals (~450 hospitals) and the smaller sample of children's hospitals (37 hospitals) is informative, an appropriate method for projecting these estimates is not yet available.

CONCLUSION

An estimated 33.5 million prescriptions were dispensed in the U.S. for the fluoroquinolones class during calendar year 2004 in the outpatient setting. Ciprofloxacin was the second most commonly dispensed fluoroquinolone in the U.S. accounting for roughly 41% of fluoroquinolone prescriptions in 2004. The total prescription volume for systemic ciprofloxacin increased slightly from 2003 to 2004 (13.6 million and 13.8 million prescriptions, respectively). In 2004, oral tablets accounted for the vast majority (~99.5%) of dispensed ciprofloxacin prescriptions in the U.S., followed by the suspension and intravenous dosage forms (~0.4% and 0.1% of dispensed prescriptions, respectively). Generic ciprofloxacin tablet and suspension formulations entered the market in June, 2003, resulting in a large decline in brand name Cipro® dispensed prescriptions from 2003 to 2004. The generic versions accounted for nearly 69% of the tablet market and 43% of the suspension market in year 2004.

Children aged 0-16 years accounted for roughly 1% (n=93,000) of the estimated 9.6 million drug mentions for systemic ciprofloxacin during office-based physician-patient encounters during calendar year 2004. The most common diagnosis associated with the mention of systemic ciprofloxacin for pediatric patients was urinary tract infection, site unspecified (ICD-9 =599.0), which accounted for 28% of mentions during the pre-exclusivity (2003) period and 13% of mentions during the post-exclusivity (2004) period. Due to the small numbers, we were unable to analyze the diagnosis associated with ciprofloxacin use in sub-groups (e.g., infants) of the pediatric population.

Pediatricians were responsible for approximately 1% of prescriptions dispensed for ciprofloxacin tablets in the U.S. during 2004 and roughly 17% of the suspension formulation dispensed.

Among an insured population in Caremark, a large pharmacy benefits manager, the pediatric age group (1-16 years) accounted for slightly over 1% of oral ciprofloxacin claims in 2004. An estimated 174,000 prescriptions for the oral dosage forms of ciprofloxacin were dispensed to the pediatric population in year 2004 in the outpatient setting.

Children aged 0-16 years accounted for 515 (0.6%) of the 87,050 actual discharges associated with systemic ciprofloxacin in 2004 in a sample of Premier's 450 acute short stay hospitals.

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