



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 10, 2008

To: M. Dianne Murphy, MD
Director, Office of Pediatric Therapeutics (OPT), OIASI
Office of the Commissioner

CDR Lisa L. Mathis, USPHS, MD
Pediatric and Maternal Health Team
Office of New Drugs

Felicia Collins, MD
Medical Officer
Pediatric and Maternal Health Team
Office of New Drugs

Thru: Laura Governale, Pharm.D., MBA, Drug Use Data Analyst
Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Vicky Borders-Hemphill, Pharm.D./ Drug Use Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Levaquin[®] (levofloxacin) oral solution, 250 mg/10 ml BPCA
Drug Use Review

Drug Name(s): Levaquin[®] (levofloxacin)

Application Type/Number: NDA 21-721

Applicant/sponsor: Ortho McNeil Pharmaceutical, Inc./Johnson and Johnson
PRD

OSE RCM #: 2008-330

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EXECUTIVE SUMMARY

This review examines drug utilization patterns for Levaquin[®] (levofloxacin), a quinolone antibacterial, in the pediatric population, patients aged 0-5, 6-11, 12-18 and 19+ years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on March 14, 2007. Since around 75% of Levaquin[®] bottles and packets of pills were sold to U.S. retail settings and approximately 25% were sold to non-retail [mainly non-federal hospitals (~54% of non-retail)] settings during the pre- and post-exclusivity periods, this review focused on the outpatient setting. Outpatient proprietary drug use databases licensed by FDA were used to examine the patterns of use for oral Levaquin[®] during the three 12-month periods from April 1, 2005 through March 31, 2008.

For each of the three 12-month periods from April 1, 2005 through March 31, 2008:

- Oral Levaquin[®] represented approximately 39% of the total projected number of select oral quinolone antibacterial dispensed prescriptions.
- Oral Levaquin[®] prescriptions in the pediatric population (ages 0-18 years) accounted for approximately 1% of total dispensed oral Levaquin[®] prescriptions.
- Around 1.2% of total projected patients who filled a prescription for oral Levaquin[®], were aged 0 through 18 years
- General Practice/Family Medicine/Doctors of Osteopathy was the top prescribing specialty for Levaquin[®] oral dosage forms.
- The top diagnosis code associated with the use of oral Levaquin[®] for patients aged 0 to 5 years was “Urinary Tract Infection NOS” (ICD-9 599.0), “Cellulitis NOS” (ICD-9 682.9) was the top diagnosis code associated with the use for patients aged 6 to 11 years, and “Chronic Sinusitis NOS” (ICD-9 743.9) was the top diagnosis code associated with the use for patients aged 12 to 18 years.

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for oral Levaquin[®] in the pediatric population as well as in the adult population and includes data for three 12-month periods starting two years before and one year following the granting of pediatric exclusivity on March 14, 2007.

2 METHODS AND MATERIALS

IMS Health, IMS National Sales PerspectivesTM data (*see Appendix 2*) were used to determine the setting in which oral Levaquin[®] was sold. Sales of this product by number of bottles of oral solution and bottles and packets of tablets (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from April 1, 2005 through March 31, 2008 (*data not provided*).¹ During the three 12-month periods of this review, retail settings (chain stores, independent pharmacies, food stores, and mail service) accounted for the majority of oral Levaquin[®] sales (75%) and approximately 25% were sold to non-retail [mainly non-federal hospitals (~54%)] settings. Thus, the examination of oral Levaquin[®] utilization patterns focused on the outpatient setting.

¹ IMS Health, IMS National Sales PerspectivesTM, Data extracted 5-12-2008, Source file: 0805lev1.DVR

Outpatient use and patient demographics (stratified by ages 0-5, 6-11, 12-18 and 19+ years for oral Levaquin[®]) were measured from Verispan, LLC: Vector One[®]: National (VONA) and Total Patient Tracker (TPT) (**Appendix 2**). Indications for use were obtained from the Verispan's Physician's Drug and Diagnosis Audit (PDDA) (**Appendix 2**). From these data sources, estimates of the number of prescriptions dispensed, the number of patients who received a prescription for oral Levaquin[®], and the number of drug mentions by office-based physicians, were obtained from April 1, 2005 through March 31, 2008, inclusive. For comparative purposes, other select systemic quinolone antibacterials currently on the market (oral, solid, liquid dosage forms only) were also examined: including ciprofloxacin, moxifloxacin, gemifloxacin, ofloxacin, norfloxacin, gatifloxacin, lomefloxacin. The following six fluoroquinolones have been taken off the U.S. market due to various safety concerns and therefore were not included in the analysis; temafloxacin, trovafloxacin, grepafloxacin, alatrofloxacin, sparfloxacin, and gatifloxacin (as Tequin[®]).

3 RESULTS

During the three 12-month periods from April 1, 2005 through March 31, 2008, dispensed prescriptions for Levaquin[®] represented approximately 39% of the projected number of select quinolone antibacterial prescriptions dispensed in the United States. The projected number of Levaquin[®] dispensed prescriptions decreased by over 2% from the pre-exclusivity period (April 1, 2006 through March 31, 2007) to the post-exclusivity period (April 1, 2007 through March 31, 2008) (**Table 1**).

During the three 12-month periods from April 1, 2005 through March 31, 2008, dispensed prescriptions for Levaquin[®] in the pediatric population (ages 0-18 years) accounted for approximately 1% of the total projected number of dispensed prescriptions for Levaquin[®]. Of the prescriptions dispensed to patients aged 0 to 18 years, around 2.8% were dispensed to patients aged 0-5 years, 4.5% dispensed to patients ages 6 to 11 years, and around 93% dispensed to patients ages 12-18 years (**Table 2**). Of the patients who filled a prescription for Levaquin[®] in the outpatient retail pharmacy setting, 1.2% of total projected patients were aged 0 to 18 years, and the proportion of projected pediatric patients aged 0 to 5 years, 6 to 11 years, and 12 to 18 years were similar to the proportion of dispensed prescriptions for the same age groups (**Table 3**).

During the three 12-month periods from April 1, 2005 through March 31, 2008, General Practice/Family Medicine/Doctors of Osteopathy group was the top prescribing specialty for levofloxacin oral dosage forms at roughly 30% of dispensed prescriptions (**Table 4**). Pediatricians accounted for approximately 1% of dispensed prescriptions during the entire study period.

According to office-based physician practices in the U.S., "Urinary Tract Infection NOS" (ICD-9 599.0) was the top diagnosis codes associated with the use of oral solid and liquid dosage forms of levofloxacin for patients aged 0 to 5 years, "Cellulitis NOS" (ICD-9 682.9) was the top diagnosis code associated with the use for patients aged 6 to 11 years, and "Chronic Sinusitis NOS" (ICD-9 743.9) was the top diagnosis code associated with the use for patients aged 12 to 18 years. Adults aged 18 years and older accounted for the majority (~96%) of office-based physician visits reportedly associated with the use of oral Levaquin[®] during the three 12-month study periods (**Table 5**).

4 LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that oral Levaquin[®] is distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives[™]. Non-federal hospitals (~14%) are the second most common distribution channel. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Verispan's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Verispan recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSIONS

Use of Levaquin[®] (levofloxacin) oral formulations in the pediatric and adult populations has been declining over the three 12-month study periods examined.

CONCURRENCE

Laura Governale, Pharm D., MBA.
Team Leader
Division of Epidemiology (DEPi)
Solomon Iyasu, M D, MPH
Director
Division of Epidemiology (DEPi)

APPENDICES

APPENDIX 1: Tables

Table 1. Projected Number of Systemic Quinolone Antibacterial Prescriptions (In Thousands) Dispensed from U.S Retail Pharmacies, MAT April1, 2005 through March 31, 2008

	MAT/MAR/2006		MAT/MAR/2007		MAT/MAR/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
15180 QUINOLONES	33,300	100.0%	35,720	100.0%	38,114	100.0%
ciprofloxacin	14,965	44.9%	17,301	48.4%	19,714	51.7%
levofloxacin	13,908	41.8%	13,935	39.0%	13,590	35.7%
moxifloxacin	3,056	9.2%	4,004	11.2%	4,510	11.8%
gemifloxacin mesylate	247	0.7%	269	0.8%	214	0.6%
ofloxacin	109	0.3%	83	0.2%	57	0.1%
norfloxacin	51	0.2%	36	0.1%	28	0.1%
gatifloxacin	964	2.9%	92	0.3%	1	0.0%

Verispan, LLC: Vector One®: National (VONA) Data extracted 6-23-2008. Source File: 2008-330 VONA 6-23-08 levaquin comparators
BPCA.qry

For Oral Solid, Liquid Dosage forms Only

Table 2. Projected Number of oral Levaquin® Prescriptions Dispensed from U.S Retail Pharmacies stratified by age, April1, 2005 through March 31, 2008

	MAT/MAR/2006		MAT/MAR/2007		MAT/MAR/2008	
	Retail TRxs	Share %	Retail TRxs	Share %	Retail TRxs	Share %
Levofloxacin[†]	13,908,323	100.0%	13,934,607	100.0%	13,590,077	100.0%
0-18	155,059	1.1%	143,296	1.0%	129,071	0.9%
0-5	5,057	3.3%	3,597	2.5%	3,243	2.5%
6-11	6,508	4.2%	6,290	4.4%	6,290	4.9%
12-18	143,494	92.5%	133,409	93.1%	119,538	92.6%
19+	13,685,786	98.4%	13,757,998	98.7%	13,430,100	98.8%
UNSPEC.	67,478	0.5%	33,313	0.2%	30,906	0.2%

Verispan, LLC: Vector One®: National (VONA) Data extracted 5-12-2008. Source File:2008-330 VONA 6-23-08 levaquin age
BPCA.qry

[†] For Oral Solid, Liquid Only

Table 3. Projected Number of Patients who filled an oral Levaquin[™] Prescription at a U.S. Retail Pharmacy, April 1, 2005 – March 31, 2008

	MAT Ending 03-06		MAT Ending 03-07		MAT Ending 03-08	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
Levaquin[†] Total	10,495,809	100.0%	10,420,296	100.0%	10,170,712	100.0%
0-18	140,490	1.3%	127,938	1.2%	111,973	1.1%
0 - 5	3,961	2.8%	2,260	1.8%	1,885	1.7%
6 - 11	5,291	3.8%	4,720	3.7%	4,188	3.7%
12 - 18	131,260	93.4%	120,993	94.6%	105,918	94.6%
19 - 85	10,240,759	97.6%	10,213,846	98.0%	9,985,111	98.2%
UNKNOWN AGE	144,943	1.4%	105,235	1.0%	99,153	1.0%

[†] For Oral Solid, Liquid Only

Verispan, Total Patient Tracker, data extracted 6-23-08. Source Files: 2008-330 TPT 6-23-08 levaquin ages BPCA.xls and 2008-330 TPT 6-23-08 levaquin ages2 BPCA.xls

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts. – means no data

Table 4. Total Number of oral Levaquin[®] Prescriptions Dispensed (In Thousands) from U.S. Retail Pharmacies by Prescriber Specialty (Top 10), April1, 2005 through March 31, 2008

	MAT/MAR/2006		MAT/MAR/2007		MAT/MAR/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
levofloxacin[†]	13,908	100.0%	13,935	100.0%	13,590	100.0%
GP/FM/DO*	3,816	27.4%	3,980	28.6%	3,969	29.2%
IM	3,370	24.2%	3,468	24.9%	3,363	24.7%
UROL	1,057	7.6%	1,012	7.3%	910	6.7%
UNSPEC	1,067	7.7%	709	5.1%	651	4.8%
EM	663	4.8%	668	4.8%	647	4.8%
NP	315	2.3%	376	2.7%	426	3.1%
PA	289	2.1%	347	2.5%	395	2.9%
ENT	373	2.7%	382	2.7%	378	2.8%
PUD	329	2.4%	345	2.5%	343	2.5%
GEN SURG	293	2.1%	281	2.0%	254	1.9%

* GP/FM/DO = General Practice, Family Medicine, Doctors of Osteopathy

[†] For Oral Solid, Liquid Only

Source: Verispan, LLC: Vector One[®]: National (VONA) Data extracted 6-23-2008. File: 2008-330 VONA 6-23-08 levaquin specialty BPCA.qry

Table 5. Physician Reports of the Top Diagnosis Associated with the Use of oral Levaquin[®], MAT April1, 2005 through March 31, 2008

	MAT/MAR/2006		MAT/MAR/2007		MAT/MAR/2008	
	Uses (000)	Share %	Uses (000)	Share %	Uses (000)	Share %
levofloxacin[†]	12,955	100.0%	11,447	100.0%	12,150	100.0%
0-5	--	--	10	0.1%	--	--
5990 URIN TRACT INFECTION NOS	--	--	10	100.0%	--	--
6-11	--	--	3	0.0%	7	0.1%
6829 CELLULITIS NOS	--	--	--	--	7	100.0%
1369 INFECT/PARASITE DIS NOS	--	--	3	100.0%	--	--
12-18	149	1.2%	146	1.3%	156	1.3%
4739 CHRONIC SINUSITIS NOS	17	11.3%	18	12.4%	24	15.6%
4900 BRONCHITIS NOS	13	8.8%	8	5.4%	22	13.9%
7881 DYSURIA	--	--	--	--	16	10.5%
4660 ACUTE BRONCHITIS	--	--	7	4.9%	16	10.0%
6829 CELLULITIS NOS	--	--	3	2.2%	9	5.9%
Others (32)	120	80.0%	111	75.0%	70	44.2%
19+	12,383	95.6%	10,981	95.9%	11,689	96.2%
5990 URIN TRACT INFECTION NOS	2,025	16.4%	1,907	17.4%	2,011	17.2%
4900 BRONCHITIS NOS	1,284	10.4%	1,346	12.3%	1,402	12.0%
4860 PNEUMONIA, ORGANISM NOS	1,316	10.6%	1,215	11.1%	1,382	11.8%
4739 CHRONIC SINUSITIS NOS	1,232	9.9%	1,126	10.3%	1,043	8.9%
4660 ACUTE BRONCHITIS	455	3.7%	264	2.4%	432	3.7%
Others (365)	6,917	49.0%	5,121	47.4%	5,417	46.8%
UNSPEC.	423	3.3%	307	2.7%	297	2.4%
5990 URIN TRACT INFECTION NOS	24	5.6%	37	12.2%	67	22.4%
5959 CYSTITIS NOS	13	3.0%	21	6.9%	19	6.5%
6829 CELLULITIS NOS	22	5.2%	7	2.3%	18	6.0%
5621 DIVERTICULA OF COLON	19	4.5%	23	7.3%	16	5.4%
7071 CHRONIC ULCER LOWER LIMB	--	--	--	--	15	5.1%
Others (63)	344	81.8%	219	71.2%	163	54.5%

Verispan, LLC. Physician Drug and Diagnosis Audit, Extracted 5-13-08; File: 2007-1386 PDDA 5-13-08 olanzapine diagnosis BPCA.xls

[†] For Oral Solid, Liquid Only

-- means no data

APPENDIX 2: Database Descriptions

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

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Vicky Borders-Hemphill
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Laura Governale
7/14/2008 11:55:26 AM
DRUG SAFETY OFFICE REVIEWER