



NDA 20-634/S-036

NDA 20-635/S-037

Ortho McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Manisha Padhye, Ph.D.
Associate Director, Regulatory Affairs
U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Padhye:

Please refer to your supplemental new drug applications dated October 27, 2004, received October 28, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVAQUIN[®] (levofloxacin) Tablets, LEVAQUIN[®] (levofloxacin) Injection, and LEVAQUIN[®] (levofloxacin in 5% dextrose) Injection.

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underline and deletions are ~~strike through~~):

1. LEVAQUIN[®] (LEVOFLOXACIN) ORAL SOLUTION was added.

2. DESCRIPTION

- The following paragraphs were added:

LEVAQUIN Oral Solution, 25 mg/mL is a multi-use self-preserving aqueous solution of levofloxacin with pH ranging from 5.0 –6.0. The appearance of LEVAQUIN Oral Solution may range from clear yellow to clear greenish-yellow. This does not adversely affect product potency.

LEVAQUIN Oral Solution contains the following inactive ingredients: sucrose, glycerin, sucralose, hydrochloric acid, purified water, propylene glycol, artificial and natural flavors, benzyl alcohol, ascorbic acid, and caramel color. It may also contain a solution of sodium hydroxide for pH adjustment.

3. CLINICAL PHARMACOLOGY

- The first sentence was revised to read:

The mean \pm SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral (p.o.) tablet, oral solution, or intravenous (i.v.) doses of levofloxacin are summarized in **Table 1**.

- The following sentence was added to the first paragraph in the **Absorption** subsection:

Levofloxacin oral solution and tablet formulations are bioequivalent.

- The next-to-the-last paragraph in the **Absorption** subsection was revised to read:

Oral administration of a 500-mg LEVAQUIN ~~tablet~~ with food ~~slightly~~ prolongs the time to peak concentration by approximately 1 hour and ~~slightly~~ decreases the peak concentration by approximately 14%~~-~~ following tablet and approximately 25% following oral solution administration. Therefore, levofloxacin tablets can be administered without regard to food. It is recommended that levofloxacin oral solution be taken 1 hour before, or 2 hours after eating.

- **Table 1** under **Drug-drug interactions** was revised so that oral solution information was added and tablet information was specified where appropriate. A reference for “healthy males and females 19-55 years of age” was also added to the table.

4. INDICATIONS AND USAGE

- The second sentence was revised to read:

LEVAQUIN Tablets/Injection and Oral Solution are indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

5. WARNINGS

- The second paragraph was revised to read:

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased the incidence and severity of osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in the weight bearing joints and other signs of arthropathy in immature animals of various species. The relevance of these findings to the clinical use of levofloxacin is unknown. (See [ANIMAL PHARMACOLOGY](#).)

6. PRECAUTIONS

- The fifth and sixth bullets under **Information for Patients**, “Patients should be advised:” were revised to read:
 - that levofloxacin oral tablets can be taken without regard to meals;
 - that levofloxacin oral solution should be taken 1 hour before or 2 hours after eating.

7. DOSAGE AND ADMINISTRATION

- The fourth paragraph was revised to read:

The usual dose of LEVAQUIN Tablets or ~~Injection~~ Oral Solution (25 mg/ml) is 250 mg or 500 mg or 750 mg administered orally ~~or by slow infusion over 60 minutes every 24~~

~~hours or 750 mg administered orally or by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing chart. The usual dose of LEVAQUIN Injection is 250 mg or 500 mg administered by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing chart. Levofloxacin tablets can be administered without regard to food. Levofloxacin oral solution should be taken 1 hour before, or 2 hours after eating. These recommendations apply to patients with normal renal function (i.e., creatinine clearance > 80 mL/min). For patients with altered renal function see the **Patients with Impaired Renal Function** subsection. Oral doses should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx[®] (didanosine), chewable/buffered tablets or the pediatric powder for oral solution.~~

8. HOW SUPPLIED

- The following sentences were added after the Levaquin Tablets information:

LEVAQUIN Oral Solution is supplied in a 16 oz. multi-use bottle (NDC 0045-1515-01). Each bottle contains 480 mL of the 25-mg/mL-levofloxacin oral solution.

LEVAQUIN Oral Solution should be stored at 25°C (77°F); excursions permitted to 15° - 30°C (59° to 86°F) [refer to USP controlled room temperature].

LEVAQUIN Oral Solution is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Ortho Pharmaceutical in Manati, Puerto Rico, 00674.

9. ANIMAL PHARMACOLOGY

- The first paragraph was revised to read:

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) In immature dogs (4-5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin for 8 or 9 consecutive days, with an 18-week recovery period, exhibited

musculoskeletal clinical signs by the final dose at dose levels ≥ 2.5 mg/kg (approximately 0.27 >0.2-fold the potential therapeutic dose (500 mg q24h) based upon plasma AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (equivalent to and 3-fold greater than the potential therapeutic dose, respectively). All musculoskeletal signs were resolved by week 5 of recovery; synovitis was resolved by the end of the 18-week recovery period; whereas, articular cartilage erosions and chondropathy persisted.

10. Patient Package Information (PPI)

- LEVAQUIN® (levofloxacin) Oral Solution, 25 mg/mL was added to the title.
- The first paragraph under “**How and when should I take LEVAQUIN®?**” was revised to read:

LEVAQUIN® should be taken once a day for 3, 5, 7, 10, 14 or 28 days depending on your prescription. ~~LEVAQUIN® tablets~~ should be swallowed and may be taken with or without food. ^{(b) (4)} _____
LEVAQUIN® o _____ after
eating. Try to take the tablet and oral solution at the same time each day and drink fluids liberally.

We completed our review of these applications and they are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for the package insert submitted October 27, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated “**FPL for approved supplements NDA 20-634/S-036, NDA 20-635/S-037, NDA 21-721/S-001.**” Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to these NDAs 1721 and a copy to the following address:

NDA 20-634/S-036

NDA 20-635/S-037

Page 5

MEDWATCH, HFD-410

FDA

5600 Fishers Lane

Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Robin Anderson, R.N., M.B.A., Labeling Reviewer at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.

Director

Division of Special Pathogen and Immunologic

Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Renata Albrecht
11/4/04 10:46:44 AM