



NDA 20-634/S-033, S-034

NDA 20-635/S-033, S-034

R.W. Johnson Pharmaceutical Research Institute
Attention: Ms. Robyn S. Thomas
Regulatory Affairs
920 Route 202 South
P. O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Thomas:

Please refer to your supplemental new drug applications dated March 16, 2004, received March 17, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVAQUIN® (levofloxacin) Tablets and Injection.

We acknowledge receipt of your submissions dated April 9, 2004 to NDA 20-634/S-033 and NDA 20-635/S-033. We also acknowledge the receipt of your submissions dated August 23, 2004 to NDA 20-634/S-033, S-034 and NDA 20-635/S-033, S-034.

NDA 20-634/S-033 and NDA 20-635/S-033 were submitted as "Changes Being Effectuated" (CBE) supplemental labeling applications and provide for the addition of quinolone class labeling information to the package insert. These changes were requested in our supplement request letter dated October 27, 2003, and in our facsimiles dated March 10, and July 12, 2004.

NDA 20-634/S-034 and NDA 20-635/S-034 were submitted as prior approval supplemental applications and provide for revisions to the **PRECAUTIONS: Geriatric Use** section of the package insert regarding QTc prolongation/torsades de pointes, and the **Post-Marketing Adverse Reactions** section of the package insert providing for the addition of rhabdomyolysis.

These supplemental new drug applications provide for the following revisions to the package insert:

1. The following paragraph was added as the sixth paragraph of the **WARNINGS** section:

Peripheral Neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

2. The tenth paragraph of the **WARNINGS** section was revised as follows:

Tendon Effects: Ruptures of the shoulder, hand, ~~or~~ Achilles tendon, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially ~~in~~ the elderly. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of ~~tendinitis~~ tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

3. The last paragraph of the **PRECAUTIONS** section, **General** subsection was revised as follows:

Torsades de pointes: Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. ~~During post-marketing surveillance, rare~~ Rare cases of torsades de pointes have been ~~reported in patients taking levofloxacin. These reports generally involved patients with~~ spontaneously reported during post-marketing surveillance in patients receiving quinolones, concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including class Ia or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, and cardiomyopathy should be avoided.

including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See **WARNINGS** and **ADVERSE REACTIONS**.)

4. The following was added as the second bullet in the **PRECAUTIONS** section, **Information for Patients** subsection:

- that peripheral neuropathies have been associated with levofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians;

5. The following paragraph was added to the **PRECAUTIONS** section, **Geriatric Use** subsection:

In phase 3 clinical trials, 1,190 levofloxacin-treated patients (25%) were ≥ 65 years of age. Of these, 675 patients (14%) were between the ages of 65 and 74 and 515 patients (11%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using levofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsades de pointes (e.g. known QT prolongation, uncorrected hypokalemia). See **PRECAUTIONS: GENERAL: Torsades de Pointes.**

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

6. The following revisions were made in the **Post-Marketing Adverse Reactions** section:

Additional adverse events reported from worldwide post-marketing experience with levofloxacin include: allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, increased International Normalized Ratio (INR)/prothrombin time, peripheral neuropathy, rhabdomyolysis, Stevens-Johnson Syndrome, tendon rupture, torsades de pointes, vasodilation.

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 23, 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 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 supplement NDA 20-634/S-033, S-034 and NDA 20-635/S-033, S-034.”** Approval of this submission by FDA is not required before the labeling is used.

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

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 Christine Lincoln, R.N., MS, MBA, 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

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/s/

Renata Albrecht
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