CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634/S-008, S-009
20-635/S-007, S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 2 2000

NDA 20-634/S-008, S-009
NDA 20-635/S-007, S-008

The R. W. Johnson Pharmaceutical Research Institute
Attention: Mary Ellen Zamstein
Principal Regulatory Scientist, Regulatory Affairs
Route 202
P. O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Zamstein:

Please refer to your supplemental new drug applications 20-634/S-008 and 20-635/S-007 dated March 31, 1999, received April 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVAQUIN® (levofloxacin) Tablets, 250 mg, 500 mg, and LEVAQUIN® Injection, 25 mg/mL, 5 mg/mL. These supplements provide for the use of LEVAQUIN® for the treatment of levofloxacin-susceptible strains of penicillin-resistant *Streptococcus pneumoniae* in patients with community-acquired pneumonia.

Please refer to your supplemental new drug applications 20-634/S-009 and 20-635/S-008 dated April 1, 1999, received April 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVAQUIN® (levofloxacin) Tablets and LEVAQUIN® Injection which provide for a combined package insert for LEVAQUIN® Tablets and LEVAQUIN® Injection.

We acknowledge receipt of your amendments to all of the above supplements dated December 13, 1999 and January 28, 2000. The amendments included revisions to the **PRECAUTIONS** section of the labeling under **Information for Patients** and **Drug Interactions** and to the **ADVERSE REACTIONS** section of the labeling (see summary below).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter. The FPL must be identical to the submitted final draft labeling (package insert submitted January 28, 2000). Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded or unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-634/S-008, S-009, 20-635/S-007, S-008." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 for the treatment of penicillin-resistant *Streptococcus pneumoniae* in patients with community-acquired pneumonia. We are deferring submission of your pediatric studies for this indication until February 2, 2003. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement *for this indication*, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products for the revised indication. The Agency wishes to emphasize the importance of responsible promotion and prudent use of LEVAQUIN® in order to prevent the premature development of levofloxacin resistance. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you of your Phase 4 commitments along with the timeframe for their completion as described below.

1. You have agreed to prepare and submit on an annual basis data from an active surveillance study of antimicrobial resistance among *S. pneumoniae* isolates. This report should be similar in content and nature to the report entitled "Tracking Resistance in the United States Today (Trust III Report)" that was submitted to these supplements September 30, 1999. This report will include data on rates of penicillin resistance, levofloxacin resistance, and combined penicillin and levofloxacin resistance among *S. pneumoniae* isolates. This report will be prepared for the first five years following approval of the supplements, at which time the usefulness of continuing this reporting mechanism will be discussed.

2. Since the original approval of levofloxacin, it has become clear that prolongation of the QT interval on the electrocardiogram may occur to various degrees with selected antimicrobials and other drug products. From a public health perspective, it is important to investigate this effect for these agents. For the quinolone class of antimicrobials, it is important to compare the relative effect on QT prolongation among agents in this class. In addition, new techniques that have been developed for evaluating drug toxicities are employed in the evaluation of new products, and our understanding of these techniques is strengthened by information from products that have already had substantial market exposure. While no new cardiac safety concerns have been raised since levofloxacin was first marketed or during the review of supplemental new drug applications

20-634/S-008 and 20-635/S-007, you have agreed to perform the following phase 4 commitments in your submission dated January 28, 2000:

- Studies to investigate *in vitro* the effect of levofloxacin and similar agents on the IKr channel
- Dose-response studies to measure the QTc and absolute QT intervals in male and female normal volunteers over a broad age range, including subjects >65 years of age. Levofloxacin should be administered at increasing dosages and should bracket the recommended doses. These studies should also include placebo and active control arms employing other antimicrobials.

These commitments should be completed by two years from the date of this letter.

Highlights of the revisions to the labeling for LEVAQUIN® Tablets and Injection approved under these supplemental new drug applications are provided below:

1. **MICROBIOLOGY**

   a. Because of the approval of penicillin-resistant *Streptococcus pneumoniae* in patients with community-aquired pneumonia, the phrase, "including penicillin-resistant strains*" was added to *Streptococcus pneumoniae* in the first list of **Aerobic gram-positive microorganisms** and removed from the second list of **Aerobic gram-positive microorganisms**, and the information, "*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value ≥ 2 µg/mL", was added.

   b. *Enterobacter agglomerans* was revised to read *Pantoea (Enterobacter) agglomerans* based on NCCLS revised nomenclature.

   c. In the Dilution techniques and Diffusion techniques subsections. "spp. including *S.*" was added whenever *Streptococcus pneumoniae* was mentioned so that it now reads "*Streptococcus* spp. including *S. pneumoniae*."

2. **INDICATIONS AND USAGE**

   a. The parenthetical phrase "(including penicillin-resistant strains, MIC value for penicillin ≥ 2 µg/mL)" has been added to *Streptococcus pneumoniae* in the subsection for **Community-acquired pneumonia** to read:

   "**Community-acquired pneumonia** due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥ 2 µg/mL), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES**.)"

3. **PRECAUTIONS**

a. In the **General** subsection, a statement has been added concerning prolongation of the QT interval to read as follows:

"Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, extremely rare cases of torsades de pointes, have been reported in patients taking levofloxacin. These reports generally involve patients who had concurrent medical conditions and the relationship to levofloxacin has not been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents."

b. In the **Information for Patients** subsection, a statement has been added concerning warfarin and is now the next-to-the-last statement as follows:

"that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin."

c. In the **Drug Interactions** subsection the statements concerning warfarin have been strengthened and revised to read:

"Warfarin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding."

4. **ADVERSE REACTIONS**

a. In the Post-Marketing Adverse Reactions subsection, "increased International Normalized Ratio (INR)/prothrombin time" and "torsades de pointes" have been added to the list of adverse events.

5. CLINICAL STUDIES

The following information on patients with community-acquired due to *Streptococcus pneumoniae*, including patients with penicillin-resistant strains, has been added.

"Additional studies were initiated to evaluate the utility of LEVAQUIN in community-acquired pneumonia due to *S. pneumoniae*, with particular interest in penicillin-resistant strains (MIC value for penicillin ≥ 2 µg/mL). In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; one double-blind study, two open label randomized studies, and three open label non-comparative studies. The total number of clinically evaluable patients with *S. pneumoniae* across all 8 studies was 250 for levofloxacin and 41 for comparators. The clinical success rate (cured or improved) among the 250 levofloxacin-treated patients with *S. pneumoniae* was 245/250 (98%). The clinical success rate among the 41 comparator-treated patients with *S. pneumoniae* was 39/41 (95%)."

"Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* (MIC value for penicillin ≥ 2 µg/mL) were identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following the completion of therapy. Fifteen out of the 15 evaluable levofloxacin-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* achieved clinical success (cure or improvement). Of these 15 patients, 6 were bacteremic and 5 were classified as having severe disease. Of the 4 comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae*, 3 were evaluable for clinical efficacy. Three out of the 3 evaluable comparator-treated patients achieved clinical success. All three of the comparator-treated patients were bacteremic and had disease classified as severe."

6. PATIENT INFORMATION ABOUT LEVAQUIN®

New information entitled "Patient Information About LEVAQUIN®" has been added to the end of the package insert (see pages 32 through 35 of the attached approved draft labeling).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jeffrey Fritsch, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**