DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-616/S-004, S-005, S-006

Aventis Pharmaceuticals
ATTN: J. Michael Nicholas
Somerset Corporate Center
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807-2854

Dear Dr. Nicholas:

Please refer to your supplemental new drug applications dated August 17, 1998, received August 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Penetrex™ (enoxacin) Tablets, 200 mg and 400 mg.

These supplemental new drug applications provide for the following changes to the label. The deleted text is noted by ~~strikethrough~~ and the added text is noted by double underline as follows:

1. **WARNINGS**

The first sentence was revised to read:

THE SAFETY AND EFFECTIVENESS OF ENOXACIN IN ~~CHILDREN~~ PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANY WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS**: **Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.)

2. **PRECAUTIONS**

The first bullet of the **Information for Patients** subsection was revised to read:

- not to take magnesium-, aluminum-, or calcium-containing antacids, bismuth subsalicylate, products containing iron, multivitamins containing zinc, or Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution, for 8 hours prior to enoxacin or for 2 hours after enoxacin administration. (See **PRECAUTIONS**: **Drug Interactions**);"

In the **Drug Interactions** subsection, the sixth paragraph was revised to read:

Sucralfate and antacids: Quinolones form chelates with metal cations. Therefore, administration of quinolones with antacids containing calcium, magnesium, or aluminum; with sucralfate; with divalent or trivalent cations such as iron; with multivitamins containing zinc; or Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with drug absorption and result in insufficient plasma and tissue quinolone concentrations. Antacids containing aluminum hydroxide and magnesium hydroxide reduce the oral

absorption of enoxacin by 75%. The oral bioavailability of enoxacin is reduced by 60% with coadministration of ranitidine. These agents should not be taken for 8 hours before or for 2 hours after enoxacin administration."

The subsection concerning **Geriatric Use** was revised to read:

Geriatric Use—In multiple-dose clinical trials of enoxacin, elderly patients (≥65 years of age) experienced significantly more overall adverse events than patients under 65 years of age. However, the incidence of drug-related adverse reactions was comparable between age groups.
In elderly patients, the mean peak enoxacin plasma concentration was 50% higher than that in young adult volunteers receiving comparable single doses of enoxacin. (See **CLINCAL PHARMACOLOGY**.) Enoxacin is known to be excreted by the kidney and the risk of adverse reactions may be greater in patients with impaired renal function. The dosage should be reduced in patients with renal impairment. (See **DOSAGE AND ADMINISTRATION**.)

3. DOSAGE AND ADMINISTRATION

The first paragraph was revised to read:

Penetrex™ (enoxacin) should be taken at least one hour before or at least two hours after a meal.
Magnesium-, aluminum-, or calcium-containing antacids, bismuth subsalicylate, products containing iron, or multivitamins containing zinc, or Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 8 hours before or 2 hours after enoxacin administration.

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 product is 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 final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 17, 1998).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-616/S-004, S-005, S-006." 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, HF-2
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 Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting 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/

Marc Cavaille Coll
8/21/02 02:48:39 PM
For Renata Albrecht