NDA 20-740/S-006

Bayer Pharmaceutical Division
Attention: Frederich K. Sundermann
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

30 MAR 2001

Dear Mr. Sundermann:

Please refer to your supplemental new drug application dated August 3, 1999, received August 4, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baycol (cerivastatin sodium) tablets.

We acknowledge receipt of your submissions dated February 2 and 6, 2001.

This supplemental new drug application provides for revisions to the Package Insert to include information on the metabolism of cerivastatin and the formation of its metabolites under the Metabolism subsection of the **CLINICAL PHARMACOLOGY** section. In addition, the results of the drug interaction studies involving omeprazole and cyclosporine will be included in the Drug Interactions subsection of the **PRECAUTIONS** section of the Package Insert. The specific changes are as follows:

To the **CLINICAL PHARMACOLOGY, Metabolism** section, the following paragraph has been added:

> *In Vitro* studies show that the hepatic cytochrome P450 (CYP) enzyme system catalyzes the cerivastatin biotransformation reactions. Specifically, two P450 enzyme sub-classes are involved. The first is CYP 2C8, which leads predominately to the major active metabolite, M23, and to a lesser extent, the other active metabolite, M1. The second is CYP 3A4, which primarily contributes to the formation of the less abundant metabolite, M1. The CYP 3A4 enzyme sub-class is also involved in the metabolism of a significant number of common drugs. The potential importance of the dual pathway hepatic metabolism of cerivastatin as a protective mechanism is shown in clinical studies examining the effect of the known potent CYP 3A4 inhibitors, erythromycin and itraconazole. In these interaction studies, specific inhibition of the CYP 3A4 enzyme sub-class resulted in a minimal 1.4- to 1.5-fold mean increase in cerivastatin plasma levels following co-treatment with erythromycin or itraconazole, possibly because of effective metabolism via the alternate CYP 2C8 pathway.

To the **PRECAUTIONS, Drug Interactions** section, the following statements have been added:

> **OMEPRAZOLE:** There were no changes in the pharmacokinetic parameters of either cerivastatin or its major active metabolites, or in omeprazole in healthy young males given single 0.3 mg oral doses of cerivastatin alone or on the fifth day of a five-day omeprazole 20 mg daily pre-treatment.
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> **CYCLOSPORINE**: The single dose pharmacokinetics of 0.2 mg of cerivastatin in healthy subjects was compared to single and multiple doses in renal transplant patients who were at steady-state with respect to cyclosporine. Cyclosporine levels were unaffected by cerivastatin. Plasma concentration of cerivastatin and its metabolites increased 3- to 5-fold with no change in its elimination. No cerivastatin accumulation occurred with multiple dosing.

We have completed the review of this supplemental application, 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, the 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 February 6, 2001).

Please submit the copies of final printed labeling (FPL) electronically 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 20-740/S-006." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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

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 Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research