DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 12-836/S-054

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ms. Kelly Billingham
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Billingham:

Please refer to your supplemental new drug application dated April 27, 2001 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Persantine (dipyridamole) 25 mg, 50 mg, and 75 mg Tablets.

We acknowledge receipt of your submission dated February 4, 2004. This submission constituted a complete response to our May 31, 2002 action letter.

This "Changes Being Effected in 30 days" supplemental new drug application provides for the following changes to the package insert:

1. Under the **DESCRIPTION** section, the chemical name was revised from:

   "2,6-Bis (diethanolamino) - 4,8-dipiperidino-pyrimido (5,4-d) pyrimidine (=dipyridamole)."

   To read as follows:

   "2,2',2",2"' - [(4,8-Dipiperidinopyrimido [5,4-*d*] pyrimidine - 2,6 - diyl) dinitrilo] tetraethanol."

2. Under **DESCRIPTION,** the molecular weight was revised from 504.6 to 504.63.

3. Under **DESCRIPTION, Inactive Ingredients**, the list was revised from:

   "acacia, carnauba wax, corn starch, FD&C blue No. 1 aluminum lake, D&C yellow No. 10 aluminum lake, D&C red No. 30 aluminium lake, lactose, magnesium stearate, polyethylene glycol, povidone, shellac, sodium benzoate, sucrose, talc, titanium dioxide, white wax."

   To read as follows:

   "acacia, carnauba wax, corn starch, edible white ink, lactose monohydrate, magnesium stearate, **(b)(4)** , polyethylene glycol, povidone, sucrose, talc, titanium dioxide, and white wax."

4. Under **PRECAUTIONS**, **Carcinogenesis, Mutagenesis, Impairment of Fertility**, the text was revised from:

"In a 111 week oral study in mice and in a 128-142 week oral study in rats, dipyridamole USP produced no significant carcinogenic effects at doses up to 75 mg/kg (0.8 times and 1.5 times the maximum recommended daily human oral dose on a mg/m^2 basis in mice and rats, respectively). Mutagenicity testing with dipyridamole was negative. Reproduction studies with dipyridamole revealed no evidence of impaired fertility in rats at dosages up to 500 mg/kg, or 10 times the maximum recommended human oral dose on a mg/m^2 basis. A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was however, observed at 1250 mg/kg (25 times the maximum recommended human oral dose on a mg/m^2 basis)."

To read as follows:

"In studies in which dipyridamole was administered in the feed to mice (up to 111 weeks in males and females) and rats (up to 128 weeks in males and up to 142 weeks in females), there was no evidence of drug related carcinogenesis. The highest dose administered in these studies (75 mg/kg/day) was, on a mg/m^2 basis, about equivalent to the maximum recommended daily human oral dose (MRHD) in mice and about twice the MRHD in rats. Mutagenicity tests of dipyridamole with bacterial and mammalian cell systems were negative. There was no evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day (about 12 times the MRHD on a mg/m^2 basis). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg (more than 30 times the MRHD on a mg/m^2 basis)."

5. Under **PRECAUTIONS, Pregnancy**, *Teratogenic Effects,* the text was changed from:

"PREGNANCY CATEGORY B
Reproduction studies have been performed in mice at doses up to 125 mg/kg, rats at doses up to 1000 mg/kg and rabbits at doses up to 40 mg/kg (1.3, 20, and 1.6 times the maximum recommended daily human dose on a mg/m2 basis, respectively) and have revealed no evidence of harm to the fetus due to dipyridamole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

To read as follows:

"PREGNANCY CATEGORY B
Reproduction studies have been performed in mice, rabbits and rats at oral dipyridamole doses of up to 125 mg/kg, 40 mg/kg and 1000 mg/kg, respectively (about 1 ½, 2 and 25 times the maximum recommended daily human oral dose, respectively, on a mg/m^2 basis) and have revealed no evidence of harm to the fetus due to dipyridamole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Persantine should be used during pregnancy only if clearly needed."

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the revision listed below:

The revised list of inactive ingredients under the **DESCRIPTION** section is not acceptable, except for the addition of the name "edible white ink," and the replacement of the name "lactose" with "lactose monohydrate." As per 21 CFR 201.100(b)(5)(ii), colors, such as "FD&C blue No. 1 aluminum lake," may be designated by name without naming components; however, proprietary names, such as "**(b)(4)** **(b)(4)** ," are not acceptable without naming their specific components.

The final printed labeling (FPL) must be identical to the package insert submitted on February 4, 2004, with the exception of the revisions noted above.

These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 12-836/S-054." 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, please call Ms. Meg Pease-Fye, M.S., Regulatory Project Manager, at (301) 594-5327.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge

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