CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020884

APPROVAL LETTER

NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

NOV 22 1999

Dear Dr. Brill:

Please refer to your new drug application (NDA) dated December 15, 1998, received December 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrenox™ (aspirin/extended-release dipyridamole) Capsules.

We acknowledge receipt of your submissions dated June 18, 21, and 30, July 12, August 2, 6, 11, 13, and 20, September 8, October 6 and 20, November 3, 4, 11, 12, and 16, 1999. In addition, we acknowledge receipt of your facsimiles dated November 17, 18, and 19, 1999. Your submission of August 20, 1999, constituted a complete response to our June 15, 1999, action letter.

This new drug application provides for the use of Aggrenox™ (aspirin/extended-release dipyridamole) Capsules to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis.

We have completed the review of this 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 enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted draft labeling (immediate container and carton labels submitted December 15, 1998, and October 20, 1999, respectively). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case 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 NDA 20-884." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated August 20, 1999. These commitments, along with any completion dates agreed upon, are listed below.

1. Conduct a food effect study to evaluate the effect of food/meals on the absorption of dipyridamole and aspirin, and to assess the potential for "dose-dumping" of the extended release dipyridamole pellets of the to-be-marketed Aggrenox™ Capsules. You agreed to submit study results and appropriate labeling revisions by February 20, 2000.

2. Conduct a study to provide information/data comparing the dipyridamole pharmacokinetics obtained in subjects receiving (a) the to-be-marketed Aggrenox™ Capsule, and (b) the FDA approved immediate release dipyridamole formulation given concurrently with the aspirin tablet that is included in the Aggrenox™ Capsule to substantiate the extended release claim for the dipyridamole pellet component. You agreed to submit study results and appropriate labeling revisions within 12 months of initiation of the study.

Please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Sufficient stability data has been submitted to support an 18-month expiry date for the 60-count polypropylene bottles.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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 are waiving the pediatric study requirement for this action on this application.

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

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, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure (Package Insert)

cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE
R/d Init: Collier 11/19/99
R/d Init: Talarico 11/22/99 /S/ 11-22-99
JD/November 18, 1999 (drafted)
JD/11/22/99/c:\mydocs\nda\20884911-AP-ltr-2.doc

APPROVAL (AP) (with Phase 4 Commitments)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER : 020884

APPROVABLE LETTER

DUBEAU

NDA 20-884

JUN 15 1999

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Brill:

Please refer to your new drug application (NDA) dated December 15, 1998, received December 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrenox™ (dipyridamole/aspirin) Capsules.

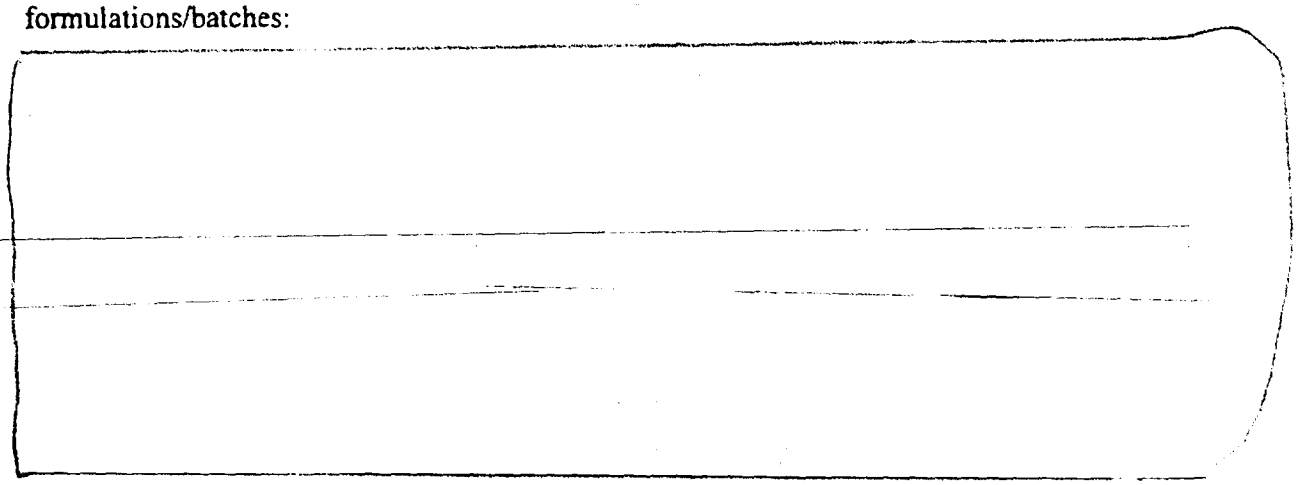
We acknowledge receipt of your submissions dated January 13, 14, 18, 20, 26, 28, 29, February 12, 24, 25, March 5, 11, 12, 18, 30. April 6, 15, 20, and May 3, 5, 19, and 27, 1999.

We have completed the review of this application, as amended, and it is approvable for the following indication: "To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis." This indication was based on the results of a single multinational clinical trial entitled "European Stroke Prevention Study 2 (ESPS-2)." This was a multicenter, randomized, placebo-controlled, parallel group, factorial design study, involving 7040 patients in Europe. Treatment arms were: dipyridamole 200 mg plus aspirin 25 mg, dipyridamole 200 mg alone, aspirin 25 mg alone, and placebo. Study treatment was given twice daily for two years in patients with a history of stroke (defined as completed stroke or transient ischemic attack). Endpoints assessed were all strokes, all cause deaths, and the composite endpoint of stroke or death. In that trial the combination of dipyridamole 200 mg plus aspirin 25 mg twice daily was shown to be more effective than either dipyridamole 200 mg twice daily alone or aspirin 25 mg twice daily alone in preventing subsequent stroke in patients who had suffered a completed ischemic stroke or transient ischemic attack in the three months prior to starting study treatment. Both dipyridamole 200 mg twice daily and aspirin 25 mg twice daily were also superior to placebo for preventing stroke in the study. No benefit in reducing risk of either all cause mortality or death due to stroke was demonstrated for any of the treatments. Therefore, an indication for mortality reduction is not appropriate.

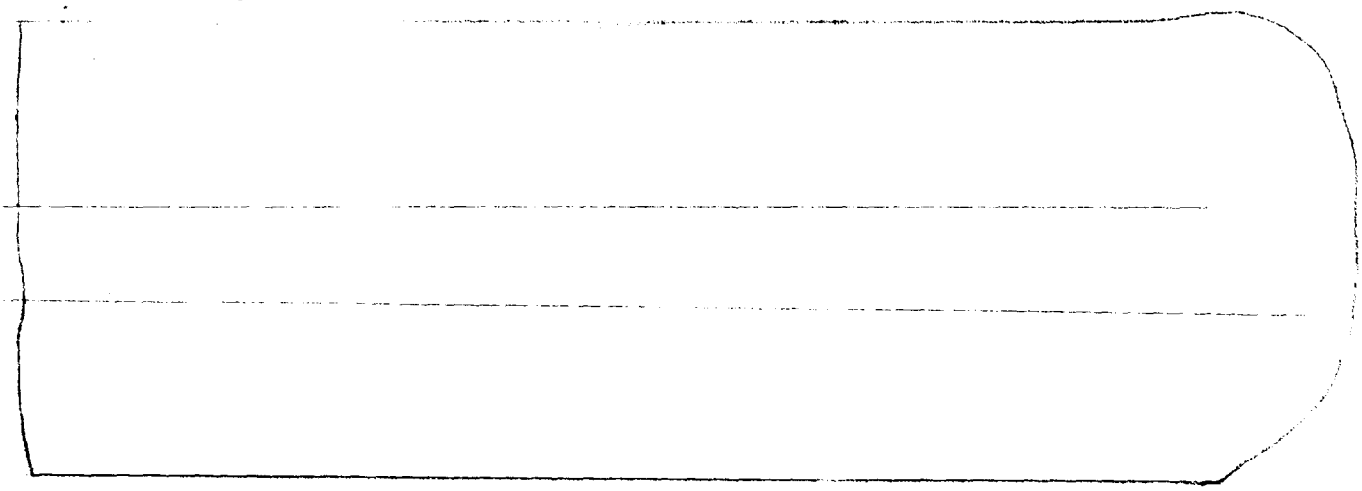
Before this application may be approved, however, it will be necessary for you to address the following:

I. Biopharmaceutics

A. Bioequivalence issue between the to-be-marketed Aggrenox™ Capsules and all clinical trial formulations/batches:



B. Dissolution analyses:



C. Food effect:

Please conduct a food effect study to evaluate the effect of food/meals on the absorption of dipyridamole and aspirin, and to assess the potential for "dose-dumping" of the extended release dipyridamole pellets of the to-be-marketed Aggrenox™ Capsules.

D. Extended release claim:

[redacted]

E. Population pharmacokinetics:

Please submit a new diskette with the population pharmacokinetic data from ESPS-2 (e.g., dosing times, drug concentrations, etc.) since the previously provided diskette is not usable.

II. Chemistry, Manufacturing, and Controls (CMC):

Please adequately address the CMC deficiencies with regard to drug product manufacture, specifications, container/closure system, stability, environmental assessment, and Drug Master Files. The specific deficiencies were described in our Information Request letter dated May 26, 1999.

III. Pharmacology:

Please adequately address the pharmacology deficiencies with regard to carcinogenicity. The specific deficiencies were described in our Information Request letter dated June 4, 1999.

In addition, it will be necessary for you to submit draft labeling incorporating the requested revisions as identified in the enclosed marked-up draft labeling (which is subject to change as new information is obtained) as well as the following revisions:

1. Summarize the results of the clinical trial (ESPS-2) supporting the indication of prevention of stroke in the Clinical Trials section of the labeling. In addition, display the results obtained in ESPS-2 for prevention of death in the Clinical Trials section of the labeling.

2. Even though the dipyridamole/aspirin combination was shown to be more effective than aspirin in ESPS-2, the aspirin dose was so low (50 mg daily) that the study did not provide substantial evidence for superiority of the combination product over the entire range of aspirin doses (50-325 mg) approved for the treatment of stroke and transient ischemic attack patients. Accordingly, express superiority of Aggrenox™ Capsules to aspirin as superior to "aspirin 50 mg daily" in the labeling and in advertising claims.

3. Revise the PRECAUTIONS section to include a statement that for stroke or transient ischemic attack patients who also have cardiovascular disease and for whom aspirin is indicated to prevent recurrent myocardial infarction or for angina pectoris, the aspirin in this product may not provide adequate treatment for the cardiac indications.

4. Revise the ADVERSE REACTIONS section to include a statement that there is no clear benefit of the dipyridamole/aspirin combination over aspirin with regard to safety.

5. Revise the WARNINGS, PRECAUTIONS, and ADVERSE EVENTS sections of the labeling to incorporate safety results from ESPS-2 and from labeling and other experience with dipyridamole alone and aspirin alone.

6. Revise the OVERDOSE section of the labeling. See enclosed marked-up draft labeling for further guidance.

7. In the HOW SUPPLIED section of the labeling, add a statement that indicates that the product should be dispensed in a tight container, with a reference to the USP.

8. In reference to your submissions dated May 5, 19, and 27, 1999, regarding your agreement with the Consumer Product Safety Commission (CPSC), please provide a copy of the proposed revised carton label which has the proposed statement concerning re-dispensing the product from a non-compliant bottle to a compliant CRC bottle.

9. After obtaining pertinent information with the intact to-be-marketed Aggrenox™ formulation, revise the labeling accordingly. Information generated from other formulations not relevant to the to-be-marketed formulation should be deleted from the labeling, if appropriate.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. 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 insert directly to:

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/

Florence Houn, M.D., M.P.H.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Marked-up Draft Labeling

APPEARS THIS WAY
ON ORIGINAL