DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20884/S-030

SUPPLEMENT APPROVAL

Boehringer-Ingelheim
Attention: David R. Brill, Ph.D.
Director, Drug Regulatory Affairs
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Brill:

Please refer to your Supplemental New Drug Application (sNDA) dated March 9, 2012, received March 9, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aggrenox (aspirin/extended release dipyridamole) 25 mg/200 mg Capsules.

We also acknowledge receipt of your amendment dated September 6, 2012.

This Prior Approval supplemental new drug application provides for the following changes:

1. In the **HIGHLIGHTS, WARNINGS AND PRECAUTIONS**, the following bullets were removed:

    - The risk of GI bleeding is increased, especially in patients who are heavy alcohol users, have a history of peptic ulcer, or have coagulation abnormalities due to liver disease or vitamin K deficienc (b) (4) (5.1)
    - As with other antiplatelets, there is a risk of intracranial hemorrhage (5.1)

    The following bullet was added to the beginning of this section:

    - AGGENOX increases the risk of bleeding (5.1)

2. In the **HIGHLIGHTS, DRUG INTERACTION** subsection, the following bullet was removed:

    - Co-administration with anti-coagulants (b) (4) or NSAIDS can increase risk of bleeding (7.1,)

The following was added in its place:

- Co-administration with anti-coagulants, anti-platelets, or NSAIDS can increase risk of bleeding (7.1)

3. In Section 5, **WARNINGS AND PRECAUTIONS**, **5.1 Risk of Bleeding** subsection, the following paragraph was deleted:

"Coagulation Abnormalities

(b) (4)

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders [*see Drug Interactions (7.2)*]."

The following text was added to the beginning of this subsection:

"AGGRENOX increases the risk of bleeding. Risk factors for bleeding include the use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, anticoagulants heparin, fibrinolytic therapy, and chronic use of NSAIDs) *[see Drug Interactions (7.1)]*."

4. Section 7, **DRUG INTERACTIONS**, was amended to delete the following proposed language from the sponsor:

(b) (4)

5. Lastly, the following study description and results were added to Section 12, **CLINICAL PHARMACOLOGY**, subsection 12.3, **Pharmacokinetics**:

"AGGRENOX
Drug Interaction
A dedicated drug interaction study was conducted in 60 healthy volunteers to evaluate the effects of omeprazole 80 mg administered once daily on the pharmacokinetics (PK) of dipyridamole and the pharmacodynamics (PD) of acetylsalicylic acid when co-administered with AGGRENOX twice daily. Dipyridamole exposure (Cmax and AUC) at steady-state were similar with or without omeprazole co-administration. The pharmacokinetics of acetylsalicylic acid was not characterized. However, the anti-platelet activity as measured by arachidonic acid induced platelet aggregation was similar between the treatment arms at steady-state."

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety

information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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:

Alison Blaus
Regulatory Health Project Manager
301-796-1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
09/07/2012