DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-912/S-008
NDA 20-913/S-007

Merck & Co., Inc.
Attention: Michael C. Elia, Ph.D.
P.O. Box 4
Sumneytown Pike, BLA-20
West Point, PA 19486

25 SEP 2001

Dear Dr. Elia:

Please refer to your supplemental new drug applications dated January 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrastat Injection, 0.25 mg/mL and Aggrastat Premixed Injection, 0.05 mg/mL.

We acknowledge receipt of your submissions dated March 23, 2001.

These "Changes Being Effected" supplemental new drug applications provide for labeling revised to include information on severe allergic reactions from post-marketing adverse event reports and additional safety information.

The proposed changes are as follows:

1. The following sentence has been added as the last sentence of the first paragraph under the **WARNINGS** section:

   Fatal bleedings have been reported (see **ADVERSE REACTIONS**).

2. The second paragraph of the **WARNINGS** section has been revised from the following statement:

   AGGRASTAT should be used with caution in patients with platelet count <150,000/mm3 and in patients with hemorrhagic retinopathy.

   to the following statement that includes language on chronic hemodialysis patients:

   AGGRASTAT should be used with caution in patients with platelet count <150,000/mm3, in patients with hemorrhagic retinopathy, and in chronic hemodialysis patients.

3. The following sentence has been inserted between the first and second sentences in the first paragraph of the **PRECAUTIONS**/*Bleeding Precautions*/*Laboratory Monitoring* subsection:

   In patients who have previously received GP IIb/IIIa receptor antagonists, consideration should be given to earlier monitoring of platelet count.

4. The following text has been added at the beginning of the second paragraph of the **PRECAUTIONS**/*Bleeding Precautions*/*Laboratory Monitoring* subsection:

   In addition, the activated partial thromboplastin (APTT) should be determined before treatment and the anticoagulant effects of heparin should be carefully monitored by repeated determinations of APTT and the dose should be adjusted accordingly (see also **DOSAGE AND ADMINISTRATION**). Potentially life-threatening bleeding may occur especially when heparin is administered with other products affecting hemostasis, such as GP IIb/IIIa receptor antagonists.

5. The **ADVERSE REACTIONS**/*Allergic Reactions/Readministration* subsection has been revised from the following:

   No patients in the clinical database developed anaphylaxis and/or hives requiring discontinuation of the infusion of tirofiban (see also *Post-Marketing Experience, Hypersensitivity*). No information is available regarding the development of antibodies to tirofiban; very few patients received tirofiban twice.

to the following:

   Although no patients in the clinical trial database developed anaphylaxis and/or hives requiring discontinuation of the infusion of tirofiban, anaphylaxis has been reported in post-marketing experience (see also *Post-Marketing Experience, Hypersensitivity*). No information is available regarding the development of antibodies to tirofiban.

6. The following text was added as the last sentence of the **ADVERSE REACTIONS**/*Laboratory Findings* subsection:

   Platelet decreases have been observed in patients with no prior history of thrombocytopenia upon readministration of GP IIb/IIIa receptor antagonists.

7. The **ADVERSE REACTIONS**/*Post-Marketing Experience* subsection has been revised from the following:

   The following additional adverse reactions have been reported in post-marketing experience: *Bleeding*: Intracranial bleeding, retroperitoneal bleeding, and hemopericardium; *Body as a Whole*: Acute decreases in platelet counts (see *Laboratory Findings* above) which may be associated with chills and low-grade fever; *Hypersensitivity*: Rash and/or hives.

to the following:

   The following additional adverse reactions have been reported in post-marketing experience: *Bleeding*: Intracranial bleeding, retroperitoneal bleeding, hemopericardium and pulmonary (alveolar) hemorrhage. Fatal bleedings have been reported rarely; *Body as a Whole*: Acute and/or severe decreases in platelet counts which may be associated with chills, low-grade fever, or bleeding complications (see *Laboratory Findings* above); *Hypersensitivity*: Severe allergic reactions including anaphylactic reactions. The reported cases have occurred during the first day of tirofiban infusion, during initial treatment, and during readministration of tirofiban. Some cases have been associated with severe thrombocytopenia (platelet counts<10,000/mm3).

8. The following sentence has been added, in bold, immediately preceding the dosing chart in the **DOSING AND ADMINISTRATION** section:

   AGGRASTAT Injection must first be diluted to the same strength as
   AGGRASTAT Injection Premixed, as noted under Directions for Use.

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 products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted January 12, 2001). Accordingly, these supplemental applications are approved effective on the date of this letter.

Please note that the language on fatal bleeding events in the **ADVERSE REACTIONS**/*Post-Marketing Experience* subsection is superceded by the language on fatal bleeding events in this subsection of the labeling that was approved on March 23, 2001 for NDA 20-912/S-007 and NDA 20-913/S-006. Accordingly, at the time of your next printing, please revise the statement added as the last sentence of the first paragraph in the **WARNINGS** section from the following:

Fatal bleedings have been reported (see **ADVERSE REACTIONS**).

to the following:

Fatal bleeding events have been reported (see **ADVERSE REACTIONS**).

to be consistent with the language on fatal bleeding events that was added to the **ADVERSE REACTIONS**/*Post-Marketing Experience* subsection in NDA 20-912/S-007 and NDA 20-913/S-006 and approved on March 23, 2001.

The labeling changes approved in NDA 20-912/S-005 on December 15, 2000 that reflect the addition of the 25 mL vial were not included in the final printed package inserts submitted electronically on January 12, 2001. If you have not already done so, please include these labeling changes in your final printed package insert at the time of its next printing

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, please call:

Ms. Colleen LoCicero
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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/

Raymond Lipicky

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