

20-912 / S-008

20-913 / S-007



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

SEP 25 2001

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

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:

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

AGGRASTAT should be used with caution in patients with platelet count $<150,000/\text{mm}^3$, 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:

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:

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:

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

RHPM Review of Final Printed Labeling
NDA 20-912/S-008
NDA 20-913/S-007

Product: Aggrastat Injection, 0.25 mg/mL
(NDA 20-912)
Aggrastat Premixed Injection, 0.05 mg/mL
(NDA 20-913)

Sponsor: Merck & Co., Inc.

Date of labeling submission: January 12, 2001

Date of labeling amendment: March 23, 2001

Date labeling review completed: September 6, 2001

Background

These “Changes Being Effective” supplemental applications were submitted in response to the Agency’s September 20, 2000 correspondence to the original new drug application (NDA) requesting that the sponsor revise the **ADVERSE REACTIONS** section of the package insert to include information on severe allergic reactions, based on post-marketing adverse drug reaction reports. In addition to the revisions to the **ADVERSE REACTIONS** section, the sponsor revised several other sections of the package insert.

During my initial review of the final printed labeling included in the January 12, 2001 electronic submissions, I noted that the labeling changes approved in NDA 20-912/S-005, a chemistry supplement that provided for a 25 mL vial and approved on draft labeling on December 15, 2000, were not included. I contacted Dr. Michael Elia of Merck to verify that this was an oversight. He confirmed that it was and offered to submit revised final printed labeling that would include the changes approved in S-005. On March 23, 2001, revised labeling was submitted to both supplemental applications. The March 23, 2001 submitted labeling, however, is not in the final printed package insert format specified in the Guidance for Industry, *Providing Regulatory Submissions in Electronic Format-New Drug Applications*, issued in January 1999. Additionally, the labeling submitted to NDA 20-913 does not include the changes approved in NDA 20-912/S-005, although NDA 20-912 and NDA 20-913 share a single common package insert.

So as not to prolong the review of these supplemental applications by requesting and reviewing additional labeling, I based my review on the January 12, 2001 submitted final printed labeling. The omission of the language approved in S-005 can be addressed in the action letter by specifying that the sponsor include the missing text in the labeling at the time of next printing.

Evaluation

I reviewed the January 12, 2001 submitted final printed labeling for both supplemental applications in their entirety and noted the following changes from the last approved package insert (package insert approved on draft on December 15, 2000 for NDA 20-912/S-005):

1. The first sentence of the last paragraph of the **DESCRIPTION** section does not include the text that was added and approved in S-005 to reflect the addition of the 25 mL vial.
2. 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**).

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

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.

4. 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.

5. 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 time (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.

The underlined text was proposed in NDA 20-913/S-006 and NDA 20-912/S-007, submitted September 14, 2000 and approved on March 23, 2001.

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

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.

7. 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.

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

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).

The language describing bleeding and "body as a whole" events was proposed in NDA 20-913/S-006 and NDA 20-912/S-007. These supplements were approved on draft labeling on March 23, 2001, provided the statement on fatal bleeding events was revised to the following:

Fatal bleeding events have been reported.

The sponsor submitted final printed labeling for these supplements, with the statement on bleeding events revised as specified in the March 23, 2001 approval letter, on June 20, 2001.

The language on hypersensitivity reactions was added in response to the Agency's September 20, 2000 correspondence to the original NDA requesting that the Aggrastat label be revised to include information on severe allergic reactions. In this correspondence, the Agency provided specific language for the hypersensitivity information to be included in labeling. The language proposed in this supplemental application is identical to the language specified in the Agency's September 20, 2000 correspondence, with the exception of the last sentence that was changed from the following:

to the following:

Some cases have been associated with severe thrombocytopenia (platelet counts <10,000/mm³).

9. The text approved in S-005 as the first paragraph under the **DOSAGE AND ADMINISTRATION/Directions for Use** subsection was not included in this labeling.
10. The following sentence has been added, in bold, to immediately precede 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*.
11. The **HOW SUPPLIED** section does not contain the language approved in S-005 that reflects the addition of the 25 mL vial.

Medical Review

Dr. Throckmorton found the change from ' ' to "some" in the language on hypersensitivity reactions added to the **ADVERSE REACTIONS/Post-Marketing Experience** subsection to be acceptable. He noted that the language on fatal bleeding events added to the **WARNINGS** section (see item 2 under Evaluation) should be revised to be consistent with the language on fatal bleeding events added to the **ADVERSE REACTIONS/Post-Marketing Experience** subsection, approved March 23, 2001 in NDA 20-913/S-006 and NDA 20-912/S-007.

Conclusion

I will draft an approval letter for Dr. Lipicky's signature for these supplemental applications. The letter will 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 approved on March 23, 2001 for NDA 20-913/S-006 and NDA 20-912/S-007.

Accordingly, the letter will specify that the language on fatal bleeding events added to the **WARNINGS** section be revised to be consistent with the language on fatal bleeding events added to the **ADVERSE REACTIONS/Post-Marketing Experience** subsection, approved March 23, 2001 for NDA 20-913/S-006 and NDA 20-912/S-007.

Furthermore, the letter will note that the final printed package insert submitted electronically on January 12, 2001 does not include the language approved December 15, 2000 for NDA 20-912/S005 that reflects the addition of the 25 mL vial. The letter will specify that, if the sponsor has not already done so, they include this language in the final printed labeling at the time of its next printing.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Colleen LoCicero
9/25/01 01:01:03 PM
CSO