CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20913/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 1 1 2000

NDA 20-912/S-004
NDA 20-913/S-004

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

Dear Dr. Elia:

Please refer to your supplemental new drug applications dated October 18, 1999, received October 20, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrastat (tirofiban hydrochloride) Injection, and Aggrastat (tirofiban hydrochloride) Premixed Injection.

We note that these supplements were submitted as 'Special Supplements - Changes Being Effected' under 21 CFR 314.70(c).

These supplemental new drug applications provide for the following labeling changes:

1. Throughout the **DESCRIPTION, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, OVERDOSAGE, DOSAGE AND ADMINISTRATION,** and **HOW SUPPLIED** sections. has been replaced with "mc."

2. The heading for the **PRECAUTIONS/** subsection has been changed to *Geriatric Use* to comply with 21 CFR 201.57 (f)(10)(ii).

3. Information on bleeding has been added to the **ADVERSE REACTIONS/***Post-marketing Experience* subsection. The sentence in this subsection has been changed from the following:

to 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.

4. In the **DOSAGE AND ADMINISTRATION** section the describing the IntraVia container has been changed to "®", and the corresponding footnote revised accordingly.

5. The following statement has been added to the **DOSAGE AND ADMINISTRATION**/*Directions for Use* subsection as the last sentence of the last paragraph:

   AGGRASTAT should not be administered in the same intravenous line as diazepam.

Your submission stated on or before March 1, 2000 as the implementation date for the changes.

We have completed the review of these supplemental applications 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 included with your October 18, 1999 submission). Accordingly, these supplemental applications are approved effective on the date of this letter.

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 contact:

Ms. Colleen LoCicero
Regulatory Project Coordinator
(301) 594-5334.

Sincerely yours,

/S/ 1/11/00

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20913/S004

FINAL PRINTED LABELING

20-912

MERCK & CO., INC.
West Point, PA 19486, USA

9123304
07-19-04-909

APPROVED
JAN 11 2000

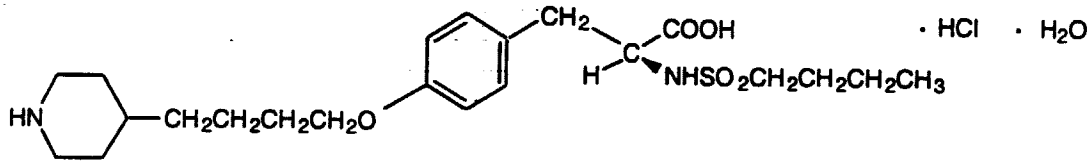
AGGRASTAT®
(TIROFIBAN HYDROCHLORIDE INJECTION PREMIXED)
AGGRASTAT®
(TIROFIBAN HYDROCHLORIDE INJECTION)

DESCRIPTION

AGGRASTAT® (tirofiban hydrochloride), a non-peptide antagonist of the platelet glycoprotein (GP) IIb/IIIa receptor, inhibits platelet aggregation.

Tirofiban hydrochloride monohydrate, a non-peptide molecule, is chemically described as *N*-(butylsulfonyl)-*O*-[4-(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate.

Its molecular formula is $C_{22}H_{36}N_2O_5S \cdot HCl \cdot H_2O$ and its structural formula is:



Tirofiban hydrochloride monohydrate is a white to off-white, non-hygroscopic, free-flowing powder, with a molecular weight of 495.08. It is very slightly soluble in water.

AGGRASTAT Injection Premixed is supplied as a sterile solution in water for injection, for intravenous use only, in plastic containers. Each 500 mL of the premixed, iso-osmotic intravenous injection contains 28.09 mg tirofiban hydrochloride monohydrate equivalent to 25 mg tirofiban (50 mcg/mL) and the following inactive ingredients: 4.5 g sodium chloride, 270 mg sodium citrate dihydrate, and 16 mg citric acid anhydrous. The pH ranges from 5.5 to 6.5 and may have been adjusted with hydrochloric acid and/or sodium hydroxide.

The flexible container is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

AGGRASTAT Injection is a sterile concentrated solution for intravenous infusion after dilution and is supplied in a 50 mL vial. Each mL of the solution contains 0.281 mg of tirofiban hydrochloride monohydrate equivalent to 0.25 mg of tirofiban and the following inactive ingredients: 0.16 mg citric acid anhydrous, 2.7 mg sodium citrate dihydrate, 8 mg sodium chloride, and water for injection. The pH ranges from 5.5 to 6.5 and may have been adjusted with hydrochloric acid and/or sodium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

AGGRASTAT is a reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. When administered intravenously, AGGRASTAT inhibits *ex vivo* platelet aggregation in a dose- and concentration-dependent manner. When given according to the recommended regimen, >90% inhibition is attained by the end of the 30-minute infusion. Platelet aggregation inhibition is reversible following cessation of the infusion of AGGRASTAT.

Pharmacokinetics

Tirofiban has a half-life of approximately 2 hours. It is cleared from the plasma largely by renal excretion, with about 65% of an administered dose appearing in urine and about 25% in feces, both largely as unchanged tirofiban. Metabolism appears to be limited.

Tirofiban is not highly bound to plasma proteins and protein binding is concentration independent over the range of 0.01 to 25 mcg/mL. Unbound fraction in human plasma is 35%. The steady state volume of distribution of tirofiban ranges from 22 to 42 liters.

In healthy subjects, the plasma clearance of tirofiban ranges from 213 to 314 mL/min. Renal clearance accounts for 39 to 69% of plasma clearance. The recommended regimen of a loading infusion followed by a maintenance infusion produces a peak tirofiban plasma concentration that is similar to the steady state concentration during the infusion. In patients with coronary artery disease, the plasma clearance of tirofiban ranges from 152 to 267 mL/min; renal clearance accounts for 39% of plasma clearance.

Special Populations

Gender

Plasma clearance of tirofiban in patients with coronary artery disease is similar in males and females.

Elderly

Plasma clearance of tirofiban is about 19 to 26% lower in elderly (>65 years) patients with coronary artery disease than in younger (≤65 years) patients.

Race

No difference in plasma clearance was detected in patients of different races.

Hepatic Insufficiency

In patients with mild to moderate hepatic insufficiency, plasma clearance of tirofiban is not significantly different from clearance in healthy subjects.

Renal Insufficiency

Plasma clearance of tirofiban is significantly decreased (>50%) in patients with creatinine clearance <30 mL/min, including patients requiring hemodialysis (see DOSAGE AND ADMINISTRATION, *Recommended Dosage*). Tirofiban is removed by hemodialysis.

Pharmacodynamics

AGGRASTAT inhibits platelet function, as demonstrated by its ability to inhibit *ex vivo* adenosine phosphate (ADP)-induced platelet aggregation and prolong bleeding time in healthy subjects and patients with coronary artery disease. The time course of inhibition parallels the plasma concentration profile of the drug. Following discontinuation of an infusion of AGGRASTAT, 0.10 mcg/kg/min, *ex vivo* platelet aggregation returns to near baseline in approximately 90% of patients with coronary artery disease in 4 to 8 hours. The addition of heparin to this regimen does not significantly alter the percentage of subjects with >70% inhibition of platelet aggregation (IPA), but does increase the average bleeding time, as well as the number of patients with bleeding times prolonged to >30 minutes.

In patients with unstable angina, a two-staged intravenous infusion regimen of AGGRASTAT (loading infusion of 0.4 mcg/kg/min for 30 minutes followed by 0.1 mcg/kg/min for up to 48 hours in the presence of heparin and aspirin), produces approximately 90% inhibition of *ex vivo* ADP-induced platelet aggregation with a 2.9-fold prolongation of bleeding time during the loading infusion. Inhibition persists over the duration of the maintenance infusion.

Clinical Trials

Three large-scale clinical studies were conducted to study the efficacy and safety of AGGRASTAT in the management of patients with Acute Coronary Syndrome (unstable angina/non-Q-wave myocardial infarction). Acute Coronary Syndrome is characterized by prolonged (≥10 minutes) or repetitive symptoms of cardiac ischemia occurring at rest or with minimal exertion, associated with either ischemic ST-T wave changes on electrocardiogram (ECG) or elevated cardiac enzymes. The definition includes "unstable angina" and "non-Q-wave myocardial infarction" but excludes myocardial infarction that is associated with Q-waves or non-transient ST-segment elevation. The three studies examined AGGRASTAT alone and as an addition to heparin, prior to and after angioplasty (if indicated) (PRISM-PLUS), in comparison to heparin in a similar population (PRISM), and in addition to heparin in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) or atherectomy (RESTORE). These trials are discussed in detail below.

PRISM-PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management – Patients Limited by Unstable Signs and Symptoms)

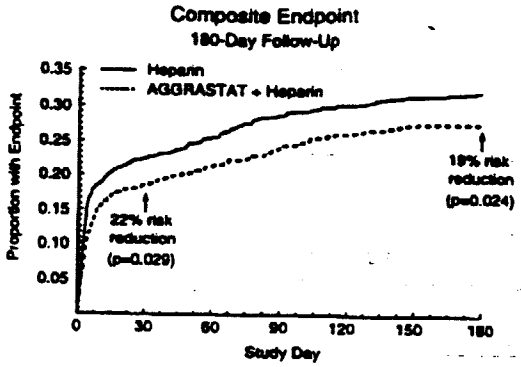
In the multi-center, randomized, parallel, double-blind PRISM-PLUS trial, the use of AGGRASTAT in combination with heparin (n=773) was compared to heparin alone (n=797) in patients with documented unstable angina/non-Q-wave myocardial infarction within 12 hours of entry into the study and initiation of treatment. All patients with unstable angina/non-Q-wave myocardial infarction had cardiac ischemia documented by ECG or had elevated cardiac enzymes. Patients who were medically managed or who subsequently underwent revascularization procedures were studied. The mean age of the population was 63 years; 32% of patients were female and approximately half of the population presented with non-Q-wave myocardial infarction. Exclusions included contraindications to anticoagulation (see CONTRAINDICATIONS), decompensated heart failure, platelet count <150,000/mm^3, and creatinine >2.5 mg/dL. In this study, patients were randomized to either AGGRASTAT (30 minute loading infusion of 0.4 mcg/kg/min followed by a maintenance infusion of 0.10 mcg/kg/min) and heparin (bolus of 5,000 units (U) followed by an infusion of 1,000 U/hr titrated to maintain an activated partial thromboplastin time (APTT) of approximately 2 times control), or heparin alone (bolus of 5,000 U followed by an infusion of 1,000 U/hr titrated to maintain an APTT of approximately 2 times control). All patients received concomitant aspirin unless contraindicated. Patients underwent 48 hours of medical stabilization on study drug therapy, and they were to undergo angiography before 96 hours (and, if indicated, angioplasty/atherectomy, while continuing on AGGRASTAT and heparin for 12-24 hours after the procedure). Some patients went on to coronary artery bypass grafting (CABG) after cessation of drug therapy. AGGRASTAT and heparin could be continued for up to 108 hours. On average, patients received AGGRASTAT for 71.3 hours. A third group of patients was initially randomized to AGGRASTAT alone (no heparin). This arm was stopped when the group was found, at an interim look, to have greater mortality than the other two groups. Note, however, that a direct comparison of heparin and tirofiban alone in the PRISM study (see below) did not show excess mortality.

The primary endpoint of the study was a composite of refractory ischemia, new myocardial infarction and death at 7 days after initiation of AGGRASTAT and heparin. At the primary endpoint, there was a 32% risk reduction in the overall composite. The components of the composite were examined separately (they total more than the composite because a patient could have more than one, e.g., by dying after having a new infarction). There was a 47% risk reduction in myocardial infarction and a 30% risk reduction in refractory ischemia. The results are shown in Table 1.

Table 1
Cardiac Ischemic Events (7 Days)

Endpoint	AGGRASTAT+ Heparin (n=773)	Heparin (n=797)	Risk Reduction	p-value
Composite Endpoint	12.9%	17.9%	32%	0.004
Components				
Myocardial Infarction and Death	4.9%	8.3%	43%	0.006
Myocardial Infarction	3.9%	7.0%	47%	0.006
Death	1.9%	1.9%	—	—
Refractory Ischemia	9.3%	12.7%	30%	0.023

The benefit seen at 7 days was maintained over time. At 30 days, the risk of the composite endpoint was reduced by 22% (p=0.029) and there was a 30% reduction in the composite of myocardial infarction and death (p=0.027). At 6 months, the risk of the composite endpoint was reduced by 19% (p=0.024). The risk reduction in the composite endpoint at 30 days and 6 months is shown in the Kaplan-Meier curve below.



PRISM-PLUS was not designed to provide definitive results in subsets of the overall population. Nonetheless, results were examined for demographic (age, gender, race) subsets and for people who did and did not receive PTCA, atherectomy, or CABG.

In PRISM-PLUS, there was a consistent treatment effect in patients either greater or less than 65 years old, and in men and women. Too few non-Caucasians were enrolled to make a definite statement about racial differences in treatment effect.

Approximately 90% of patients in the PRISM-PLUS study underwent coronary angiography and 30% underwent angioplasty/atherectomy during the first 30 days of the study. The majority of these patients continued on study drug throughout these procedures. AGGRASTAT was continued for 12-24 hours (average 15 hours) after angioplasty/atherectomy. The effects of AGGRASTAT at Day 30 did not appear to differ among the sub-populations that did or did not receive PTCA or CABG, both prior to and after the procedure.

A sub-study in PRISM-PLUS of angiograms after 48 to 96 hours found that there was a significant decrease in the extent of angiographically apparent thrombus in patients treated with AGGRASTAT in combination with heparin compared to heparin alone. In addition, flow in the affected coronary artery was significantly improved.

PRISM (Platelet Receptor Inhibition for Ischemic Syndrome Management)

In the PRISM study, a randomized, parallel, double-blind, active control study, AGGRASTAT alone (n=1616) was compared to heparin (n=1616) alone as medical management in patients with unstable angina/non-Q-wave myocardial infarction. In this study, the drug was started within 24 hours of the time the patient experienced chest pain. The mean age of the population was 62 years; 32% of the population was female and 25% had non-Q-wave myocardial infarction on presentation. Thirty percent had no ECG evidence of cardiac ischemia. Exclusion criteria were similar to PRISM-PLUS. The primary, prospectively identified endpoint was the composite endpoint of refractory ischemia, myocardial infarction or death after a 48-hour drug infusion with AGGRASTAT. The results are shown in Table 2.

Table 2
Cardiac Ischemic Events

Composite Endpoint	AGGRASTAT (n=1616)	Heparin (n=1616)	Risk Reduction	p-value
2 Days	3.8%	5.6%	33%	0.015
7 Days	10.3%	11.3%	10%	0.33
30 Days	15.9%	17.1%	8%	0.34

In the PRISM study, no adverse effect of AGGRASTAT on mortality at either 7 or 30 days was detected. This result is in conflict with the PRISM-PLUS study, where the arm that included AGGRASTAT without heparin (n=345) was dropped at an interim analysis by the Data Safety Monitoring Committee due to increased mortality at 7 days. A pooled analysis of the data from these two trials (PRISM and PRISM-PLUS) demonstrated that the effect of AGGRASTAT alone on mortality (at 7 and 30 days) was comparable to that of heparin alone.

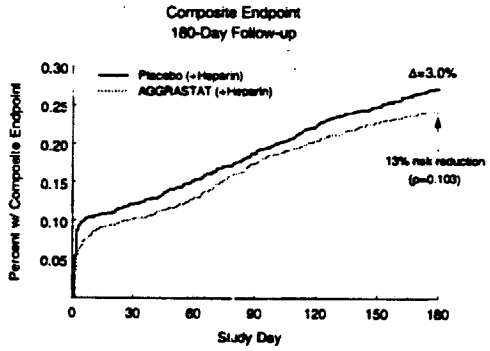
RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis)

The RESTORE study (n=2141) was a randomized, controlled comparison of AGGRASTAT and placebo, each added to heparin, in patients undergoing PTCA or atherectomy within 72 hours of presentation with unstable angina or acute myocardial infarction. The mean age of the population was 59 years; 27% were female. Two-thirds of patients underwent angioplasty for unstable angina and the remainder in association with acute myocardial infarction. Exclusions included anatomy not amenable to angioplasty, contraindications to anticoagulation (see CONTRAINDICATIONS), platelet count <150,000/mm^3, and creatinine >2.0 mg/dL. AGGRASTAT (with heparin) was initiated immediately prior to the angioplasty/atherectomy at a dose of 10 mcg/kg bolus (over 3 minutes) followed by an infusion of 0.15 mcg/kg/min along with a heparin bolus (bolus of 10,000 U, or 150 U/kg for patients <70 kg). The infusion dose of AGGRASTAT is 50% higher than the dose used in the PRISM-PLUS trial. AGGRASTAT was administered for a total of 36 hours. In general, heparin was to be discontinued at the conclusion of the angioplasty/atherectomy. Reasons for continued heparin included: imperfect outcome (e.g., large tear, intraluminal filling defect, or residual stenosis >40%), large thrombus load, continuing rest angina through the procedure, abrupt closure or very active artery during the procedure, or side branch occlusion. The primary endpoint was the composite of all deaths, non-fatal myocardial infarctions, and all repeat revascularization procedures at 30 days. For results see Table 3. A sub-study in RESTORE of angiograms after approximately 6 months found that AGGRASTAT had no significant effect on the extent of coronary artery restenosis following angioplasty.

Table 3
Cardiac Ischemic Events

Composite Endpoint	AGGRASTAT (n=1071)	Placebo (n=1070)	Risk Reduction	p-value
2 Days	5.4%	8.7%	38%	0.004
7 Days	7.6%	10.4%	28%	0.023
30 Days	10.3%	12.2%	17%	0.17

The risk reduction in the composite endpoint at 180 days is shown in the Kaplan-Meier curve below.



INDICATIONS AND USAGE

AGGRASTAT, in combination with heparin, is indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy. In this setting, AGGRASTAT has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure (for discussion of trial results and for definition of acute coronary syndrome see CLINICAL PHARMACOLOGY, *Clinical Trials*).

AGGRASTAT has been studied in a setting, as described in *Clinical Trials*, that included aspirin and heparin.

CONTRAINDICATIONS

AGGRASTAT is contraindicated in patients with:

- known hypersensitivity to any component of the product
- active internal bleeding or a history of bleeding diathesis within the previous 30 days
- a history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm
- a history of thrombocytopenia following prior exposure to AGGRASTAT
- history of stroke within 30 days or any history of hemorrhagic stroke
- major surgical procedure or severe physical trauma within the previous month
- history, symptoms, or findings suggestive of aortic dissection
- severe hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
- concomitant use of another parenteral GP IIb/IIIa inhibitor
- acute pericarditis

WARNINGS

Bleeding is the most common complication encountered during therapy with AGGRASTAT. Administration of AGGRASTAT is associated with an increase in bleeding events classified as both major and minor bleeding events by criteria developed by the Thrombolysis in Myocardial Infarction Study group (TIMI).** Most major bleeding associated with AGGRASTAT occurs at the arterial access site for cardiac catheterization.

AGGRASTAT should be used with caution in patients with platelet count <150,000/mm^3 and in patients with hemorrhagic retinopathy.

Because AGGRASTAT inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis. The safety of AGGRASTAT when used in combination with thrombolytic agents has not been established.

During therapy with AGGRASTAT, patients should be monitored for potential bleeding. When bleeding cannot be controlled with pressure, infusion of AGGRASTAT and heparin should be discontinued.

PRECAUTIONS

Bleeding Precautions

Percutaneous Coronary Intervention – Care of the femoral artery access site: Therapy with AGGRASTAT is associated with increases in bleeding rates particularly at the site of arterial access for femoral sheath placement. Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured. Prior to pulling the sheath, heparin should be discontinued for 3-4 hours and activated clotting time (ACT) <180 seconds or APTT <45 seconds should be documented. Care should be taken to obtain proper hemostasis after removal of the sheaths using standard compressive techniques followed by close observation. While the vascular sheath is in place, patients should be maintained on complete bed rest with the head of the bed elevated 30° and the affected limb restrained in a straight position. Sheath hemostasis should be achieved at least 4 hours before hospital discharge.

Minimize Vascular and Other Trauma: Other arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation and nasogastric tubes should be minimized. When obtaining intravenous access, non-compressible sites (e.g., subclavian or jugular veins) should be avoided.

Laboratory Monitoring: Platelet counts, and hemoglobin and hematocrit should be monitored prior to treatment, within 6 hours following the loading infusion, and at least daily thereafter during therapy with AGGRASTAT (or more frequently if there is evidence of significant decline). If the patient experiences a platelet decrease to <90,000/mm^3, additional platelet counts should be performed to exclude

** Bovill, E.G.; et al.: Hemorrhagic Events during Therapy with Recombinant Tissue-Type Plasminogen Activator, Heparin, and Aspirin for Acute Myocardial Infarction, Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial, Annals of Internal Medicine, *115*(4): 256-265, 1991.

pseudothrombocytopenia. If thrombocytopenia is confirmed, AGGRASTAT and heparin should be discontinued and the condition appropriately monitored and treated.

To monitor unfractionated heparin, APTT should be monitored 6 hours after the start of the heparin infusion; heparin should be adjusted to maintain APTT at approximately 2 times control.

Severe Renal Insufficiency

In clinical studies, patients with severe renal insufficiency (creatinine clearance <30 mL/min) showed decreased plasma clearance of AGGRASTAT. The dosage of AGGRASTAT should be reduced in these patients (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, *Clinical Trials*).

Drug Interactions

AGGRASTAT has been studied on a background of aspirin and heparin.

The use of AGGRASTAT, in combination with heparin and aspirin, has been associated with an increase in bleeding compared to heparin and aspirin alone (see ADVERSE REACTIONS). Caution should be employed when AGGRASTAT is used with other drugs that affect hemostasis (e.g., warfarin). No information is available about the concomitant use of AGGRASTAT with thrombolytic agents (see PRECAUTIONS, *Bleeding Precautions*).

In a sub-set of patients (n=762) in the PRISM study, the plasma clearance of tirofiban in patients receiving one of the following drugs was compared to that in patients not receiving that drug. There were no clinically significant effects of co-administration of these drugs on the plasma clearance of tirofiban: acebutolol, acetaminophen, alprazolam, amlodipine, aspirin preparations, atenolol, bromazepam, captopril, diazepam, digoxin, diltiazem, docusate sodium, enalapril, furosemide, glyburide, heparin, insulin, isosorbide, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, oxazepam, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam. Patients who received levothyroxine or omeprazole along with AGGRASTAT had a higher rate of clearance of AGGRASTAT. The clinical significance of this is unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of AGGRASTAT has not been evaluated.

Tirofiban HCl was negative in the *in vitro* microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays. There was no induction of chromosomal aberrations in bone marrow cells of male mice after the administration of intravenous doses up to 5 mg tirofiban/kg (about 3 times the maximum recommended daily human dose when compared on a body surface area basis).

Fertility and reproductive performance were not affected in studies with male and female rats given intravenous doses of tirofiban hydrochloride up to 5 mg/kg/day (about 5 times the maximum recommended daily human dose when compared on a body surface area basis).

Pregnancy

Pregnancy Category B

Tirofiban has been shown to cross the placenta in pregnant rats and rabbits. Studies with tirofiban HCl at intravenous doses up to 5 mg/kg/day (about 5 and 13 times the maximum recommended daily human dose for rat and rabbit, respectively, when compared on a body surface area basis) have revealed no harm to the fetus. 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.

Nursing Mothers

It is not known whether tirofiban is excreted in human milk. However, significant levels of tirofiban were shown to be present in rat milk. Because many drugs are excreted in human milk, and because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of AGGRASTAT in pediatric patients (<18 years old) have not been established.

Geriatric Use

Of the total number of patients in controlled clinical studies of AGGRASTAT, 42.8% were 65 years and over, while 11.7% were 75 and over. With respect to efficacy, the effect of AGGRASTAT in the elderly

(≥65 years) appeared similar to that seen in younger patients (<65 years). Elderly patients receiving AGGRASTAT with heparin or heparin alone had a higher incidence of bleeding complications than younger patients, but the incremental risk of bleeding in patients treated with AGGRASTAT in combination with heparin compared to the risk in patients treated with heparin alone was similar regardless of age. The overall incidence of non-bleeding adverse events was higher in older patients (compared to younger patients) but this was true both for AGGRASTAT with heparin and heparin alone. No dose adjustment is recommended for the elderly population (see DOSAGE AND ADMINISTRATION, *Recommended Dosage*).

ADVERSE REACTIONS

In clinical trials, 1946 patients received AGGRASTAT in combination with heparin and 2002 patients received AGGRASTAT alone. Duration of exposure was up to 116 hours. 43% of the population was >65 years of age and approximately 30% of patients were female.

BLEEDING

The most common drug-related adverse event reported during therapy with AGGRASTAT when used concomitantly with heparin and aspirin, was bleeding (usually reported by the investigators as oozing or mild). The incidences of major and minor bleeding using the TIMI criteria in the PRISM-PLUS and RESTORE studies are shown below.

	PRISM-PLUS* (UAP/Non-Q-Wave MI Study)		RESTORE* (Angioplasty/Atherectomy Study)	
Bleeding	AGGRASTAT‡‡ + Heparin‡‡‡ (n=773) % (n)	Heparin‡‡‡ (n=797) % (n)	AGGRASTAT† + Heparin†† (n=1071) % (n)	Heparin†† (n=1070) % (n)
Major Bleeding (TIMI Criteria)§	1.4 (11)	0.8 (6)	2.2 (24)	1.6 (17)
Minor Bleeding (TIMI Criteria)§	10.5 (81)	8.0 (64)	12.0 (129)	6.3 (67)
Transfusions	4.0 (31)	2.8 (22)	4.3 (46)	2.5 (27)

* Patients received aspinn unless contraindicated.
‡‡ 0.4 mcg/kg/min loading infusion; 0.10 mcg/kg/min maintenance infusion.
‡‡‡ 5,000 U bolus followed by 1,000 U/hr titrated to maintain an APTT of approximately 2 times control.
† 10 mcg/kg bolus followed by infusion of 0.15 mcg/kg/min.
†† Bolus of 10,000 U or 150 U/kg for patients <70 kg followed by administration as necessary to maintain ACT in approximate range of 300 to 400 seconds during procedure.
§ Hemoglobin drop of >50 g/L with or without an identified site, intracranial hemorrhage, or cardiac tamponade.
§ Hemoglobin drop of >30 g/L with bleeding from a known site, spontaneous gross hematuria, hematemesis or hemoptysis.

There were no reports of intracranial bleeding in the PRISM-PLUS study for AGGRASTAT in combination with heparin or in the heparin control group. The incidence of intracranial bleeding in the RESTORE study was 0.1% for AGGRASTAT in combination with heparin and 0.3% for the control group (which received heparin). In the PRISM-PLUS study, the incidences of retroperitoneal bleeding reported for AGGRASTAT in combination with heparin, and for the heparin control group were 0.0% and 0.1%, respectively. In the RESTORE study, the incidences of retroperitoneal bleeding reported for AGGRASTAT in combination with heparin, and the control group were 0.6% and 0.3%, respectively. The incidences of TIMI major gastrointestinal and genitourinary bleeding for AGGRASTAT in combination with heparin in the PRISM-PLUS study were 0.1% and 0.1%, respectively; the incidences in the RESTORE study for AGGRASTAT in combination with heparin were 0.2% and 0.0%, respectively.

The incidence rates of TIMI major bleeding in patients undergoing percutaneous procedures in PRISM-PLUS are shown below.

	AGGRASTAT + Heparin		Heparin	
	n	%	n	%
Prior to Procedures	2/773	0.3	1/797	0.1
Following Angiography	9/697	1.3	5/708	0.7
Following PTCA	6/239	2.5	5/236	2.2

The incidence rates of TIMI major bleeding (in some cases possibly reflecting hemodilution rather than actual bleeding) in patients undergoing CABG in the PRISM-PLUS and RESTORE studies within one day of discontinuation of AGGRASTAT are shown below.

	AGGRASTAT + Heparin		Heparin	
	n	%	n	%
PRISM-PLUS	5/29	17.2	11/31	35.4
RESTORE	3/12	25.0	6/16	37.5

Female patients and elderly patients receiving AGGRASTAT with heparin or heparin alone had a higher incidence of bleeding complications than male patients or younger patients. The incremental risk of bleeding in patients treated with AGGRASTAT in combination with heparin over the risk in patients treated with heparin alone was comparable regardless of age or gender. No dose adjustment is recommended for these populations (see DOSAGE AND ADMINISTRATION, *Recommended Dosage*).

NON-BLEEDING

The incidences of non-bleeding adverse events that occurred at an incidence of >1% and numerically higher than control, regardless of drug relationship, are shown below:

	AGGRASTAT + Heparin (n=1953) %	Heparin (n=1887) %
Body as a Whole		
Edema/swelling	2	1
Pain, pelvic	6	5
Reaction, vasovagal	2	1
Cardiovascular System		
Bradycardia	4	3
Dissection, coronary artery	5	4
Musculoskeletal System		
Pain, leg	3	2
Nervous System/Psychiatric		
Dizziness	3	2
Skin and Skin Appendage		
Sweating	2	1

Other non-bleeding side effects (considered at least possibly related to treatment) reported at a >1% rate with AGGRASTAT administered concomitantly with heparin were nausea, fever, and headache; these side effects were reported at a similar rate in the heparin group.

In clinical studies, the incidences of adverse events were generally similar among different races, patients with or without hypertension, patients with or without diabetes mellitus, and patients with or without hypercholesteremia.

The overall incidence of non-bleeding adverse events was higher in female patients (compared to male patients) and older patients (compared to younger patients). However, the incidences of non-bleeding adverse events in these patients were comparable between the AGGRASTAT with heparin and the heparin alone groups. (See above for bleeding adverse events.)

Allergic Reactions/Readministration

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.

Laboratory Findings

The most frequently observed laboratory adverse events in patients receiving AGGRASTAT concomitantly with heparin were related to bleeding. Decreases in hemoglobin (2.1%) and hematocrit (2.2%) were observed in the group receiving AGGRASTAT compared to 3.1% and 2.6%, respectively, in the heparin group. Increases in the presence of urine and fecal occult blood were also observed (10.7% and 18.3%, respectively) in the group receiving AGGRASTAT compared to 7.8% and 12.2%, respectively, in the heparin group.

Patients treated with AGGRASTAT, with heparin, were more likely to experience decreases in platelet counts than the control group. These decreases were reversible upon discontinuation of AGGRASTAT. The percentage of patients with a decrease of platelets to <90,000/mm^3 was 1.5%, compared with 0.6% in the patients who received heparin alone. The percentage of patients with a decrease of platelets to <50,000/mm^3 was 0.3%, compared with 0.1% of the patients who received heparin alone.

Post-Marketing Experience

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.

OVERDOSAGE

In clinical trials, inadvertent overdosage with AGGRASTAT occurred in doses up to 5 times and 2 times the recommended dose for bolus administration and loading infusion, respectively. Inadvertent overdosage occurred in doses up to 9.8 times the 0.15 mcg/kg/min maintenance infusion rate.

The most frequently reported manifestation of overdosage was bleeding, primarily minor mucocutaneous bleeding events and minor bleeding at the sites of cardiac catheterization (see PRECAUTIONS, *Bleeding Precautions*).

Overdosage of AGGRASTAT should be treated by assessment of the patient's clinical condition and cessation or adjustment of the drug infusion as appropriate.

AGGRASTAT can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

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

Use with Aspirin and Heparin

In the clinical studies, patients received aspirin, unless it was contraindicated, and heparin. AGGRASTAT and heparin can be administered through the same intravenous catheter.

Precautions

AGGRASTAT is intended for intravenous delivery using sterile equipment and technique. Do not add other drugs or remove solution directly from the bag with a syringe. Do not use plastic containers in series connections; such use can result in air embolism by drawing air from the first container if it is empty of solution. Any unused solution should be discarded.

Directions for Use

AGGRASTAT Injection is first diluted to the same strength as AGGRASTAT Injection Premixed as follows: withdraw and discard 100 mL from a 500 mL bag of sterile 0.9% sodium chloride or 5% dextrose in water and replace this volume with 100 mL of AGGRASTAT Injection (from two 50 mL vials) or withdraw and discard 50 mL from a 250 mL bag of sterile 0.9% sodium chloride or 5% dextrose in water and replace this volume with 50 mL of AGGRASTAT Injection (from one 50 mL vial), to achieve a final concentration of 50 mcg/mL. Mix well prior to administration.

AGGRASTAT Injection Premixed is supplied as 500 mL of 0.9% sodium chloride containing 50 mcg/mL tirofiban. It is supplied in IntraVia*** containers (PL 2408 plastic). To open the IntraVia® container, first tear off its dust cover. The plastic may be somewhat opaque because of moisture

*** Registered trademark of Baxter International, Inc.

absorption during sterilization; the opacity will diminish gradually. Check for leaks by squeezing the inner bag firmly; if any leaks are found, the sterility is suspect and the solution should be discarded. Do not use unless the solution is clear and the seal is intact. Suspend the container from its eyelet support, remove the plastic protector from the outlet port, and attach a conventional administration set.

AGGRASTAT may be administered in the same intravenous line as dopamine, lidocaine, potassium chloride, and PEPCID* (famotidine) Injection. AGGRASTAT should not be administered in the same intravenous line as diazepam.

Recommended Dosage

In most patients, AGGRASTAT should be administered intravenously, at an initial rate of 0.4 mcg/kg/min for 30 minutes and then continued at 0.1 mcg/kg/min. Patients with severe renal insufficiency (creatinine clearance <30 mL/min) should receive half the usual rate of infusion (see PRECAUTIONS, *Severe Renal Insufficiency* and CLINICAL PHARMACOLOGY, *Pharmacokinetics, Special Populations, Renal Insufficiency*). The table below is provided as a guide to dosage adjustment by weight.

Patient Weight (kg)	Most Patients		Severe Renal Impairment	
	30 Min Loading Infusion Rate (mL/hr)	Maintenance Infusion Rate (mL/hr)	30 Min Loading Infusion Rate (mL/hr)	Maintenance Infusion Rate (mL/hr)
30-37	16	4	8	2
38-45	20	5	10	3
46-54	24	6	12	3
55-62	28	7	14	4
63-70	32	8	16	4
71-79	36	9	18	5
80-87	40	10	20	5
88-95	44	11	22	6
96-104	48	12	24	6
105-112	52	13	26	7
113-120	56	14	28	7
121-128	60	15	30	8
129-137	64	16	32	8
138-145	68	17	34	9
146-153	72	18	36	9

No dosage adjustment is recommended for elderly or female patients (see PRECAUTIONS, *Use in the Elderly*). In PRISM-PLUS, AGGRASTAT was administered in combination with heparin for 48 to 108 hours. The infusion should be continued through angiography and for 12 to 24 hours after angioplasty or atherectomy.

HOW SUPPLIED

FOR INTRAVENOUS USE ONLY

No. 3713 — AGGRASTAT Injection 12.5 mg per 50 mL (250 mcg per mL) is a non-preserved, clear, colorless concentrated sterile solution for intravenous infusion after dilution and is supplied as follows:

NDC 0006-3713-50, 50 mL vials.

No. 3739 — AGGRASTAT Injection Premixed 25 mg per 500 mL (50 mcg per mL) is a clear, non-preserved, sterile solution premixed in a vehicle made iso-osmotic with sodium chloride, and is supplied as follows:

NDC 0006-3739-43, 500 mL single-dose IntraVia™ containers (PL 2408 Plastic).

Storage
AGGRASTAT Injection
Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F) (see USP Controlled Room Temperature). Do not freeze. Protect from light during storage.
AGGRASTAT Injection Premixed
Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F) (see USP Controlled Room Temperature). Do not freeze. Protect from light during storage.

AGGRASTAT (Tirofiban Hydrochloride Injection Premixed) is manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA

by:
BAXTER HEALTHCARE CORPORATION
Deerfield, Illinois 60015 USA

AGGRASTAT (Tirofiban Hydrochloride Injection) is manufactured for:

MERCK & CO., INC., West Point, PA 19486, USA

by:
BEN VENUE LABORATORIES
Bedford, Ohio 44146 USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20913/S004

ADMINISTRATIVE DOCUMENTS

JAN 11 2000

RHPC Review of Final Printed Labeling
NDA 20-912 and 20-913/S-004

Date of supplements:	October 18, 1999
Date of review:	November 15, 1999
Products:	Aggrastat (tirofiban hydrochloride) Injection, 12.5 mg/50 ml Aggrastat (tirofiban hydrochloride) Premixed Injection, 25 mg/500 ml
Sponsor:	Merck Research Laboratories
Evaluation:	

This "Changes Being Effective" supplement provides for the following labeling changes:

1. Throughout the **DESCRIPTION, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, OVERDOSAGE, DOSAGE AND ADMINISTRATION,** and **HOW SUPPLIED** sections, has been replaced with "mc".

2. The heading for the **PRECAUTIONS/** subsection has been changed to *Geriatric Use* to comply with 21 CFR 201.57 (f)(10)(ii).

3. Information on bleeding has been added to the **ADVERSE REACTIONS/***Post-marketing Experience* subsection. The sentence in this subsection has been changed from the following:

to 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.

4. In the **DOSAGE AND ADMINISTRATION** section, the describing the IntraVia container has been changed to "®", and the corresponding footnote revised accordingly.

5. The following statement has been added to the **DOSAGE AND ADMINISTRATION/***Directions for Use* subsection as the last sentence in the last paragraph:

AGGRASTAT should not be administered in the same intravenous line as diazepam.

I reviewed the submitted final printed labeling in its entirety and found the changes to be as described above, with no additional changes from the last approved labeling (package insert submitted May 19, 1999, approved July 9, 1999).

Recommendation:

I recommend that the Division issue an approval letter for this supplement in accordance with 21 CFR 314.70(c)(2)(i) and (iii).

/S/

Colleen LoCicero, RHPC

cc: orig NDA 20-912
orig NDA 20-913
HFD-110/20-912 & 20-913
HFD-110/ABlount
HFD-110/LoCicero