CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20912/S001

FINAL PRINTED LABELING
AGGRASTAT®
(TROFIBAN HYDROCHLORIDE INJECTION
PREMIxED)

DESCRIPTION
AGGRASTAT® (tirofiban hydrochloride), a non-peptide antagonist of the platelet glycoprotein-IIIb/IIa (GP-IIIb/IIa) receptor, inhibits platelet aggregation. Tirofiban hydrochloride monohydrate is a non-peptide molecule, chemically designated as N,N'-[9-phenanthrenylmethylenediyl]bis(L-tyrosine monohydrochloride monohydrate. Its molecular formula is C30H28N2O4.HCl.H2O and its structural formula is:

Tirofiban hydrochloride monohydrate is a white to off-white, non-hygroscopic, free-flowing powder, with a molecular weight of 493 with a total of 8.1% as a compound in water. AGGRASTAT injection Premixed is supplied as a sterile solution in water for injection, for intravenous use only, in plastic containers. Each 50 mL of the premixed, isotonic, intravenous injection contains 28.05 mg tirofiban hydrochloride monohydrate equivalent to 25 mg tirofiban (500 μg/mL) and the following inactive ingredients: 4.5 g sodium chloride, 270 mg sodium citrate dihydrate, and 16.5 mg citric acid monohydrate. The pH ranges from 5.3 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 (PL2408). 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 injection after dilution and is supplied in a 50 mL vial. Each mL of the solution contains 0.28 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, 8.9 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-IIIb/IIa 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, >50% inhibition of platelet aggregation is obtained by the end of the 30-minute infusion. All patients manifest 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 by glomerular filtration, 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 μg/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 36 to 69% of plasma clearance. The recommended regimen of a loading infusion followed by a maintenance infusion produces a peak plasma tirofiban concentration that is similar to the steady state concentration during long-term 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 diphosphate (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 μg/kg/min, ex vivo platelet aggregation returns to near baseline in approximately 50% 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 μg/kg/min for 30 minutes followed by 0.1 μg/kg/min for up to 48 hours in the presence of heparin and aspirin), produces approximately 50% inhibition of ex vivo ADP-induced platelet aggregation with a 2.5 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, usually exercise-induced stress, with at least 1.2 mm or greater change 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-Q-wave ST-segment elevation. The three studies examined AGGRASTAT alone and as an antiplatelet agent, 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 multicenter, randomized, parallel, double-blind PRISM-PLUS trial, the use of AGGRASTAT in combination with heparin (n=733) was compared to heparin alone (n=197) in patients with documented unstable angina/non-Q-wave myocardial infarction within 12 hours of entry into the study and intravenous aspirin within 48 hours. All patients manifest 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 by glomerular filtration, 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 μg/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 36 to 69% of plasma clearance. The recommended regimen of a loading infusion followed by a maintenance infusion produces a peak plasma tirofiban concentration that is similar to the steady state concentration during long-term 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.
AGGRASTAT® (Tirofiban Hydrochloride Injection Premixed)
AGGRASTAT® (Tirofiban Hydrochloride Injection)

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 loss more than the composite because a patient could have more than one, e.g., by dying after having a new infarction). There was a 41% 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)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AGGRASTAT: Hazard Rate (n=1961)</th>
<th>Heparin: Hazard Rate (n=1971)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Endpoint</td>
<td>12.9%</td>
<td>17.9%</td>
<td>.004</td>
</tr>
<tr>
<td>Myocardial infarction and Death</td>
<td>4.5%</td>
<td>5.3%</td>
<td>.006</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>3.9%</td>
<td>4.0%</td>
<td>.006</td>
</tr>
<tr>
<td>Death</td>
<td>1.5%</td>
<td>1.9%</td>
<td>.003</td>
</tr>
<tr>
<td>Refractory Ischemia</td>
<td>0.2%</td>
<td>0.3%</td>
<td>.002</td>
</tr>
</tbody>
</table>

The benefit seen at 7 days was maintained over time. At 30 days, the risk of the composite endpoint was reduced by 29% (p=.029) and there was a 30% reduction in the composite of myocardial infarction and death (p=.027). At 5 months, the risk of the composite endpoint was reduced by 19% (p=.024). The risk reduction in the composite endpoint at 30 days and 8 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, subsite 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/revascularization 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, except for angioplasty/stent placement. The effects of AGGRASTAT at Day 30 did not appear to differ among the subpopulations 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=1618) was compared to heparin (n=1618) 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; 33% 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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AGGRASTAT: Hazard Rate (n=1618)</th>
<th>Heparin: Hazard Rate (n=1618)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Days</td>
<td>3.4%</td>
<td>5.0%</td>
<td>.035</td>
</tr>
<tr>
<td>7 Days</td>
<td>12.2%</td>
<td>17.5%</td>
<td>.002</td>
</tr>
<tr>
<td>30 Days</td>
<td>18.0%</td>
<td>17.1%</td>
<td>.34</td>
</tr>
</tbody>
</table>

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=365) was dropped at an interim analysis by the Data Safety Monitoring Commi-
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W  
SE MODEL  
75%  
AGGRASTAT® (Trofiban Hydrochloride Injection Premixed)  
AGGRASTAT® (Trofiban Hydrochloride Injection)

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. An acute bleeding experience developed by the Thrombolysis in Myocardial Infarction Study Group (TIMI) 
agreement to use AGGRASTAT at the arterial access site for cardiac catheterization.  
AGGRASTAT should be used with caution in patients with platelet count <150,000/mm³ and in patients with hemor-

References

Precautions
Bleeding Precautions
Pericoronary 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 the only 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) >150 seconds or APTT 45 seconds should be documented. Care should be taken to obtain proper hemostasis after removal of the sheath using standard compression 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 hospit-

Cardiac Event

Cardiac Event

INDICATIONS AND USAGE
AGGRASTAT, in combination with heparin, is indicated for the treatment of acute coronary syndromes, including patients who are to be managed medically and those undergoing percutaneous transluminal coronary angioplasty (PTCA) or atherectomy. This setting, AGGRASTAT has been shown in controlled trials to increase the rate of complete or successful angiography compared to heparin alone (see ADVERSE REACTIONS). AGGRASTAT has been used with other drugs that affect hemostasis (e.g., warfarin). No information is available about the concomitant use of AGGRASTAT with thrombopeptide agents (see PRECAUTIONS, Bleeding Precautions).

In a sub-set of patients (n=762) in the PRISM study, the plasma clearance of trofiban in patients receiving one of the following drugs was compared to that in patients not receiv-

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 evaluated in other studies, compared to heparin and aspirin alone (see ADVERSE REACTIONS). CAUTION: AGGRASTAT is associated with other drugs that affect hemostasis (e.g., warfarin). No information is available about the concomitant use of AGGRASTAT with thrombopeptide agents (see PRECAUTIONS, Bleeding Precautions).

In a sub-set of patients (n=762) in the PRISM study, the plasma clearance of trofiban in patients receiving one of the following drugs was compared to that in patients not receiv-

The concomitant potential of AGGRASTAT has not been evaluated.

23 Bouvill E.G. et al. Hemorragic Events During Therapy with Haphe-

The concomitant potential of AGGRASTAT has not been evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of AGGRASTAT has not been evaluated.

23 Bouvill E.G. et al. Hemorragic Events During Therapy with Haphe-

Carcinogenesis, Mutagenesis, Impairment of Fertility
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Carcinogenesis, Mutagenesis, Impairment of Fertility
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Tirofiban HCL was negative in the in vitro microbial mutagenesis and in vitro mammalian cell mutation 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 alterations in bone marrow cells of male mice after the administration of intravenous doses up to 15 mg tirofiban/kg (about 5 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 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 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.

Use in the Elderly

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. However, 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 age adjustment is recommended for the elderly population (see DOSAGE AND ADMINISTRATION, Recommended Dosage).

ADVERSE REACTIONS

In clinical trials, 1984 patients received AGGRASTAT in combination with heparin and 2022 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 was minor bleeding. The incidence of minor and major bleeding using the TIMI criteria in the PRISM-PLUS and RESTORE studies is shown below.

<table>
<thead>
<tr>
<th>Bleeding</th>
<th>AGGRASTAT® + Heparin</th>
<th>AGGRASTAT® + Heparin</th>
<th>AGGRASTAT® + Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding (TIMI Criteria)</td>
<td>1.4 (1.1)</td>
<td>3.6 (1.4)</td>
<td>2.5 (0.9)</td>
</tr>
<tr>
<td>Minor Bleeding (TIMI Criteria)</td>
<td>10.5 (8.1)</td>
<td>20.4 (14.4)</td>
<td>12.0 (7.2)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>4.8 (3.1)</td>
<td>8.2 (2.2)</td>
<td>4.3 (2.8)</td>
</tr>
</tbody>
</table>

*Patients receiving glycoprotein IIb/IIIa inhibitors had intervention rates ranging from 0.3% to 15.9% in all three groups. The intervention rates were not statistically different between groups.

*All patients received heparin at a dose of 100 units/kg administered as a bolus followed by infusion of 10 units/kg/min.

*This rate is based on the rate of 10.0 units/kg to patients who were ≥65 years and 10.5 units/kg to patients who were <65 years.

*Hemoglobin ≤ 12.0 g/dL was used for the definition of anemia in this study.

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 incidence of intracranial 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 incidence of intracranial bleeding was 0.1%.

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The incidence rates of TIMI major bleeding in patients undergoing percutaneous intervention in the PRISM-PLUS study is shown below.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>AGGRASTAT® + Heparin</th>
<th>PRISM-PLUS</th>
<th>RESTORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Procedures</td>
<td>5 (2.3)</td>
<td>3 (1.3)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Percutaneous Angioplasty</td>
<td>2 (1.0)</td>
<td>2 (0.8)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Percutaneous Stent Placement</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

The incidence of TIMI major bleeding in patients undergoing CABG in the PRISM-PLUS and RESTORE studies within one day of discontinuation of AGGRASTAT is shown below.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>AGGRASTAT® + Heparin</th>
<th>PRISM-PLUS</th>
<th>RESTORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>2 (1.0)</td>
<td>2 (0.8)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

Female patients and elderly patients receiving AGGRASTAT in combination with heparin 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.

<table>
<thead>
<tr>
<th>Non-bleeding Adverse Event</th>
<th>AGGRASTAT® + Heparin</th>
<th>PRISM-PLUS</th>
<th>RESTORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>2 (1.0)</td>
<td>2 (0.8)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Gastrointestinal Infection</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Tachyarrhythmias</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

Other non-bleeding side effects (incidence at least possibly related to treatment) reported at a >1% rate with AGGRASTAT and administered concomitantly with heparin were: nausea, fever and headache; these side effects were reported at a similar incidence in the control groups. In clinical studies, the incidences of adverse events were generally similar among different race, gender, and age groups. In clinical studies, the incidence of non-bleeding adverse events in these patients were comparable between the AGGRASTAT and heparin groups and the heparin alone groups. SAEs above for bleeding adverse events were reported.

Allergic Reactions/Readministration

No patients in the clinical database developed anaphylaxis or anaphylactoid reactions in 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 effects in patients receiving AGGRASTAT concomitantly with heparin were related to bleeding. Decreases in hemoglobin (2.1%) and hematocrit (2.2%) were observed in the groups treated with 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 7.9% and 12.2%, respectively, in the heparin group. Patients treated with AGGRASTAT and heparin, were more likely to experience decreases in platelet counts than those in 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...
AGGRASTAT® (Tirofiban Hydrochloride Injection Premixed) AGGRASTAT® (Tirofiban Hydrochloride Injection)
<50,000/m³ 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: Body as a Whole—Decreased platelet counts (see Laboratory Findings above) 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 9.5 times and 21 times the recommended dose for bolus administration and loading infusion, respectively. Inadvertent overdosage occurred in doses up to 9.8 times the 0.15 µg/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).

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 µg/mL, mix well prior to administration.

AGGRASTAT® Injection Premixed is supplied as 500 mL of 0.9% sodium chloride containing 50 µg/mL tirofiban. It is supplied in Intravas™ containers (PL 240B plastic). To open the Intravas™ container, first tear off its dust cover. The plastic may be somewhat opaque because of moisture 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 vial stopper, 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 PEPID® (fentanyl) injection.

Recommended Dosage
In most patients, AGGRASTAT® should be administered intravenously, at an initial rate of 0.4 µg/kg/min for 30 minutes and then continued at 0.1 µg/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.

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Most Patients 30 Min Loading Infusion Rate (µg/hr)</th>
<th>Maintenance Infusion Rate (µg/hr)</th>
<th>Severe Renal Insufficiency 30 Min Loading Infusion Rate (µg/hr)</th>
<th>Maintenance Infusion Rate (µg/hr)</th>
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</thead>
<tbody>
<tr>
<td>50-70</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>2.5</td>
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<td>2</td>
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<tr>
<td>146-153</td>
<td>44</td>
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<td>4</td>
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</tr>
</tbody>
</table>

**Statement of Device International, Inc.**
AGGRASTAT® (Tirofiban Hydrochloride Injection Premixed)

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 µg per mL) in 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 µg 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 0008-3739-43, 500 mL single-dose Intraj/ia™ containers (Pl 2448 Plastics).

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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