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PRODUCT CIRCULAR **SG-ARS-IV/SI-102001**

Concentrate for Infusion

AGGRASTAT™
(tirofiban hydrochloride)

I. THERAPEUTIC CLASS

AGGRASTAT* (tirofiban hydrochloride), a non-peptide antagonist of the platelet GP IIb/IIIa receptor, is a platelet aggregation inhibitor.

II. INDICATIONS

AGGRASTAT, in combination with heparin, is indicated for patients with unstable angina or non-Q-wave myocardial infarction to prevent cardiac ischemic events and is also indicated for patients with coronary ischemic syndromes undergoing coronary angioplasty or atherectomy to prevent cardiac ischemic complications related to abrupt closure of the treated coronary artery. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

III. DOSAGE AND ADMINISTRATION

The vial of AGGRASTAT (concentrate) must be diluted prior to administration (see INSTRUCTIONS FOR USE).

AGGRASTAT is for intravenous use only using sterile equipment. AGGRASTAT may be co-administered with heparin through the same line.

AGGRASTAT is recommended for use with a calibrated infusion device. Care should be taken to avoid a prolonged loading infusion. Care should also be taken in calculating the bolus dose and infusion rates based on patient weight.

In clinical studies patients received aspirin, unless contraindicated.

Unstable Angina Pectoris or Non-Q-Wave Myocardial Infarction:
AGGRASTAT should be administered intravenously, in combination with heparin, at the initial infusion rate of 0.4 microgram/kg/min for 30 minutes. Upon completion of the initial infusion, AGGRASTAT should be continued at a maintenance infusion rate of 0.1 microgram/kg/min. The table below is provided as a guide to dosage adjustment by weight.

AGGRASTAT Injection must first be diluted prior to administration (see INSTRUCTIONS FOR USE).

Patient Weight (kg)	Most Patients		Severe Renal Insufficiency	
	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

In the study that demonstrated efficacy, AGGRASTAT in combination with heparin was generally continued for a minimum of 48 hours and up to 108 hours; on average patients received AGGRASTAT for 71.3 hours. This infusion can be continued through angiography and should be continued up to 12 to 24 hours post-angioplasty/atherectomy. Arterial sheaths should be removed when the patient's activated clotting time is <180 seconds or 2-6 hours following cessation of heparin. (See CLINICAL PHARMACOLOGY, *Clinical Studies.*)

Angioplasty/Atherectomy:
In patients in whom AGGRASTAT is initiated in the setting of angioplasty/atherectomy, AGGRASTAT should be administered intravenously, in combination with heparin, as an initial bolus of 10 microgram/kg administered over 3 minutes followed by a maintenance infusion rate of 0.15 microgram/kg/min (see CLINICAL PHARMACOLOGY, *Clinical Studies*). The table below is provided as a guide to dosage adjustment by weight.

AGGRASTAT Injection must first be diluted prior to administration (see INSTRUCTIONS FOR USE).

Patient Weight (kg)	Most Patients		Severe Renal Insufficiency	
	Bolus to be administered over 3 minutes (mL)	Maintenance Infusion Rate (mL/hr)	Bolus to be administered over 3 minutes (mL)	Maintenance Infusion Rate (mL/hr)
30-37	7	6	4	3
38-45	8	8	4	4
46-54	10	9	5	5
55-62	12	11	6	6
63-70	13	12	7	6
71-79	15	14	8	7
80-87	17	15	9	8
88-95	18	17	9	9
96-104	20	18	10	9
105-112	22	20	11	10
113-120	23	21	12	11
121-128	25	23	13	12
129-137	26	24	13	12
138-145	28	26	14	13
146-153	30	27	15	14

The AGGRASTAT maintenance infusion should be administered for 36 hours. Upon completion of the procedure, heparin should be discontinued and arterial sheaths should then be removed when the patient's activated clotting time is <180 seconds.

Patients With Severe Renal Insufficiency
As specified in the above dosing tables, the dosage of AGGRASTAT should be decreased by 50% in patients with severe renal insufficiency (creatinine clearance <30 mL/min). (See PRECAUTIONS, *Severe Renal Insufficiency* and CLINICAL PHARMACOLOGY, *Pharmacokinetics, Characteristics in Patients, Renal Insufficiency.*)

Other Patient Populations
No dosage adjustment is recommended for elderly patients (see USE IN THE ELDERLY) or female patients.

INSTRUCTIONS FOR USE
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit.

The vial of AGGRASTAT (concentrate) must be diluted prior to administration (see *Directions for Preparation of AGGRASTAT Solution for Infusion from Concentrate*).

Directions for Preparation of AGGRASTAT Solution for Infusion from Concentrate
1. Withdraw 50 mL from a 250 mL bag of sterile 0.9% saline or 5% dextrose in water and replace it with 50 mL of AGGRASTAT (from one 50 mL vial) to achieve a concentration of 50 microgram/mL. Mix well before administration.
2. Administer according to the appropriate dosage adjustments by weight above.
3. Any unused intravenous solution should be discarded.

AGGRASTAT may be administered in the same intravenous line as atropine sulfate, dobutamine, dopamine, epinephrine HCl, furosemide, lidocaine, midazolam HCl, morphine sulfate, nitroglycerin, potassium chloride, propranolol HCl, and PEPCID* (famotidine) Injection. AGGRASTAT should not be administered in the same intravenous line as diazepam.

IV. CONTRAINDICATIONS

AGGRASTAT is contraindicated in patients who are hypersensitive to any component of the product.

Since inhibition of platelet aggregation increases the risk of bleeding, AGGRASTAT is contraindicated in patients with active internal bleeding; a history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm; and in patients who developed thrombocytopenia following prior exposure to AGGRASTAT.

V. PRECAUTIONS

AGGRASTAT should be used with caution in the following patients:
- recent (<1 year) bleeding, including a history of gastrointestinal bleeding, or genitourinary bleeding of clinical significance
- known coagulopathy, platelet disorder, or history of thrombocytopenia
- platelet count <150,000 cells/mm^3
- history of cerebrovascular disease within 1 year
- major surgical procedure or severe physical trauma within 1 month
- recent epidural procedure
- history, symptoms, or findings suggestive of aortic dissection
- severe uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
- acute pericarditis
- hemorrhagic retinopathy
- chronic hemodialysis

Bleeding Precautions
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 treatment of bleeding is required, discontinuation of the drug should be considered. Consideration may also be given to transfusions.

Fatal bleedings have been reported (see SIDE EFFECTS).

Femoral artery access site: AGGRASTAT is associated with minor 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, avoiding a Seldinger (through and through) technique for obtaining sheath access. Care should be taken to obtain proper hemostasis after removal of the sheaths followed by close observation.

Laboratory Monitoring: Platelet counts, and hemoglobin and hematocrit should be monitored prior to treatment, within 6 hours following the bolus or loading infusion, and at least daily thereafter during therapy with AGGRASTAT (or more frequently if there is evidence of significant decline). In patients who have previously received GP IIb/IIIa receptor antagonists, consideration should be given to earlier monitoring of platelet count. If the patient experiences a platelet count decrease to <90,000 cells/mm^3, additional platelet counts should be performed to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, AGGRASTAT and heparin should be discontinued and the condition appropriately monitored and treated.

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.

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

VI. PREGNANCY

There are no adequate and well-controlled studies in pregnant women. AGGRASTAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

VII. NURSING MOTHERS

It is not known whether AGGRASTAT is excreted in human 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.

VIII. PEDIATRIC USE

Safety and effectiveness in children have not been established.

IX. USE IN THE ELDERLY

In clinical studies the efficacy of AGGRASTAT in the elderly (≥65 years) was comparable 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. 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. The overall incidence of non-bleeding adverse events was higher in older patients (compared to younger patients); however, the incidence of non-bleeding adverse events in these patients was comparable between the AGGRASTAT with heparin and the heparin alone groups. No dose adjustment is recommended (see DOSAGE AND ADMINISTRATION, *Other Patient Populations*).

X. 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 SIDE EFFECTS). Caution should be employed when AGGRASTAT is used with other drugs that affect hemostasis (e.g., warfarin) (see PRECAUTIONS, *Bleeding Precautions*).

AGGRASTAT has been used concomitantly in clinical studies with beta-blockers, calcium channel blockers, non-steroidal anti-inflammatory agents (NSAIDS) and nitrate preparations without evidence of clinically significant adverse interactions.

In a sub-set of patients (n=762) in the PRISM study (Platelet Receptor Inhibition for Ischemic Syndrome Management), 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 interactions 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, levothyroxine, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, omeprazole, oxazepam, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam.

XI. SIDE EFFECTS

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 (Platelet Receptor Inhibition for Ischemic Syndrome Management - Patients Limited by Unstable Signs and Symptoms) and RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) studies are shown below:

Bleeding	PRISM PLUS† (UAP/Non-Q-Wave MI Study)		RESTORE† (Angioplasty/Atherectomy Study)	
	AGGRASTAT+ Heparin (n=773) %	Heparin (n=797) %	AGGRASTAT+ Heparin (n=1071) %	Heparin (n=1070) %
Major Bleeding (TIMI Criteria)‡	1.4	0.8	2.2	1.6
Minor Bleeding (TIMI Criteria)§	10.5	8.0	12.0	6.3
Transfusions	4.0	2.8	4.3	2.5

† Patients received aspirin unless contraindicated.
‡ 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.

* Trademark
** 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.

WO#: AGSG0202-061014

correvio | SINGAPORE | Orion #: 132918-4
Aggrastat 0.25 mg/mL | Vial Insert | Dimensions: 296 x 480 mm
Black | AGSG0202-061014-00
PI-AGSG0202-061014-00.indd

There were no reports of intracranial bleeding in the PRISM PLUS study for AGGRASTAT in combination with heparin or in the control group (which received heparin). 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 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.

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, respectively. 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, *Other Patient Populations*).
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 cells/mm^3 was 1.5%. The percentage of patients with a decrease of platelets to <50,000 cells/mm^3 was 0.3%. Platelet decreases have been observed in patients with no prior history of thrombocytopenia upon readministration of GP IIb/IIIa receptor antagonists.

The most frequent drug-related non-bleeding side effects reported with AGGRASTAT, administered concomitantly with heparin, occurring at an incidence of >1% were nausea (1.7%), fever (1.5%), and headache (1.1%); nausea, fever and headache occurred at an incidence of 1.4%, 1.1% and 1.2%, respectively, in the control 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 hypercholesterolemia.

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.)

The following additional adverse reactions have been reported in post-marketing experience:

Bleeding: intracranial bleeding, retroperitoneal bleeding, hemopericardium, pulmonary (alveolar) hemorrhage and spinal-epidural hematoma. 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 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/mm^3).

XIa. Laboratory Test Findings

The most frequently observed laboratory adverse events in patients receiving AGGRASTAT concomitantly with heparin were related to bleeding. Decreases in hemoglobin and hematocrit, and platelet count were observed. Increases in the presence of urine and fecal occult blood were also observed.

XII. OVERDOSAGE

In clinical trials, inadvertent overdosage with tirofiban 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 microgram/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 tirofiban 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.

XIII. INCOMPATIBILITIES

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

XIV. CLINICAL PHARMACOLOGY

XIVa. Mechanism of Action

Platelet activation, adhesion and aggregation represent critical initiating steps in the formation of arterial thrombus overlying disrupted atherosclerotic plaque. Thrombus formation is central to the pathophysiology of the acute coronary ischemic syndromes of unstable angina and myocardial infarction, as well as to cardiac ischemic complications following coronary angioplasty.

AGGRASTAT is a non-peptide antagonist of the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. AGGRASTAT prevents binding of fibrinogen to GP IIb/IIIa, thereby blocking the cross-linking of platelets and platelet aggregation.

XIVb. Pharmacokinetics

XIVb-1. Distribution

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

XIVb-2. Metabolism

Profiling of ^{14}C-labeled tirofiban in urine and feces indicates that the radioactivity was accounted for mainly by unchanged tirofiban. Circulating plasma radioactivity is accounted for mainly by unchanged tirofiban (up to 10 hours postdose). These data suggest limited metabolism of tirofiban.

XIVb-3. Elimination

Following an intravenous dose of ^{14}C-labeled tirofiban in healthy subjects, 66% of radioactivity is recovered in the urine and 23% in the feces. Total radioactivity recovery is about 91%. Both urinary and biliary excretion contribute significantly to the elimination of tirofiban.

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. Half-life ranges from 1.4 to 1.8 hours.

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. Half-life ranges from 1.9 to 2.2 hours.

Tirofiban is excreted in rat milk.

XIVb-4. Characteristics in Patients

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 compared to 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 compared to healthy subjects.

Renal Insufficiency
Plasma clearance of tirofiban is lower to a clinically significant extent (>50%) in patients with creatinine clearance <30 mL/min, including patients requiring hemodialysis (see DOSAGE AND ADMINISTRATION, *Patients with Severe Renal Insufficiency*). Tirofiban is removed by hemodialysis.

XIVc. Pharmacodynamics

AGGRASTAT causes potent inhibition of platelet function as demonstrated by its ability to inhibit *ex vivo* adenosine phosphate (ADP)-induced platelet aggregation and prolong bleeding time (BT) 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, platelet function rapidly returns to baseline.

Coadministration of a 4-hour infusion of 0.15 microgram/kg/min of AGGRASTAT and aspirin results in the anticipated near maximal inhibition of platelet aggregation and a modest additive effect of BT prolongation.

In patients with unstable angina, a two-staged intravenous infusion regimen of AGGRASTAT (loading infusion of 0.4 microgram/kg/min for 30 minutes followed by 0.1 microgram/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 infusion. Inhibition was achieved rapidly with the 30-minute loading infusion and was maintained over the duration of the infusion.

In patients in whom AGGRASTAT is initiated in the setting of coronary angioplasty, a two-staged intravenous infusion regimen of AGGRASTAT (loading bolus of 10 microgram/kg over 5 minutes followed by a maintenance infusion of 0.15 microgram/kg/min for 16 to 24 hours), administered in combination with heparin and aspirin, produces approximately >90% inhibition of *ex vivo* ADP-induced platelet aggregation in nearly all patients. Near maximal inhibition is achieved rapidly with the 5-minute bolus and is maintained over the duration of the infusion. Following discontinuation of the infusion of AGGRASTAT, platelet function returns rapidly to baseline.

XIVd. Clinical Studies

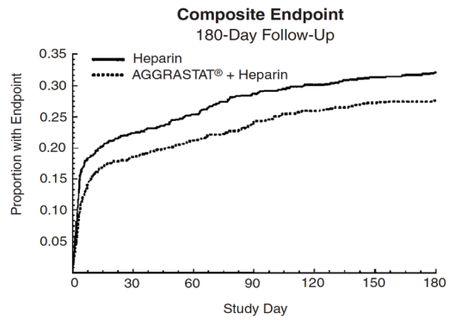
Unstable Angina/Non-Q-Wave Myocardial Infarction
In the multi-center, randomized, parallel, double-blind PRISM PLUS trial (Platelet Receptor Inhibition for Ischemic Syndrome Management - Patients Limited by Unstable Signs and Symptoms), the use of AGGRASTAT in combination with heparin versus heparin alone was evaluated in patients with documented unstable angina/non-Q-wave myocardial infarction. In this study, patients were randomized to either AGGRASTAT (30 minute loading infusion of 0.4 microgram/kg/min followed by a maintenance infusion of 0.10 microgram/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. Therapy with AGGRASTAT commenced within 12 hours of the last episode of chest pain. Patients underwent 48 hours of medical stabilization on study drug therapy, after which they could undergo angiography and angioplasty/atherectomy (if indicated), while continuing on AGGRASTAT. AGGRASTAT was generally administered for a minimum of 48 hours and was continued up to 108 hours; on average, patients received AGGRASTAT for 71.3 hours. A third group of patients received AGGRASTAT alone [see description of the PRISM (Platelet Receptor Inhibition for Ischemic Syndrome Management) study below].

The primary endpoint of the study was a composite of refractory ischemia, new myocardial infarction and death at 7 days following initiation of AGGRASTAT. At the primary endpoint, there was a 31.6% risk reduction in the overall composite, a 46.6% risk reduction in myocardial infarction, and a 42.8% risk reduction in the composite of myocardial infarction and death. 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%	31.6%	0.004
Components				
Myocardial Infarction and Death	4.9%	8.3%	42.8%	0.006
Myocardial Infarction	3.9%	7.0%	46.6%	0.006
Death	1.9%	1.9%	-	-
Refractory Ischemia	9.3%	12.7%	29.6%	0.023

The early clinical benefit was maintained at 30 days and at 6 months for most of the components. At 30 days, the risk of the composite endpoint was reduced by 21.8%; in addition, the risk of the composite of death and myocardial infarction was reduced by 29.8%. At 6 months, the risk of the composite endpoint was reduced by 18.9%; in addition, there was a 22.5% risk reduction in the composite of myocardial infarction and death. The risk reduction in the composite endpoint at 7 days, 30 days and 6 months is shown in the Kaplan-Meier curve below.



In the 30% of patients who underwent angioplasty/atherectomy in the PRISM PLUS study, there was a 45.7% risk reduction in the composite endpoint following the procedure at day 30 after start of study drug, as well as a 43.2% risk reduction in the composite of death and myocardial infarction.
A sub-study in PRISM PLUS 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.

In the PRISM PLUS study, the benefit of AGGRASTAT was consistent regardless of age or gender.

AGGRASTAT alone (n=1616) has also been compared to heparin in patients with unstable angina/non-Q-wave myocardial infarction in the randomized, parallel, double-blind PRISM trial. There was a significant reduction in the primary composite endpoint (refractory ischemia, myocardial infarction or death) after a 48-hour drug infusion with AGGRASTAT. At 30 days, the composite endpoint was comparable to that seen with heparin; however, the incidence of death was significantly reduced compared to heparin. In the PRISM PLUS study, the arm that included AGGRASTAT alone (n=345) was dropped at an interim analysis by the Data Safety Monitoring Committee due to increased mortality at 7 days. However, 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.

Percutaneous Coronary Intervention (PCI)
The RESTORE trial (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) was a randomized, double-blind, placebo-controlled study of AGGRASTAT in 2,141 patients undergoing percutaneous transluminal coronary angioplasty (PTCA) or atherectomy within 72 hours of presentation with unstable angina or acute myocardial infarction. In this study, patients were randomized to either AGGRASTAT (bolus of 10 microgram/kg over 3 minutes followed by a maintenance infusion of 0.15 microgram/kg/min for 36 hours) or placebo. All patients received aspirin and heparin.

The primary endpoint of the study was a composite of all deaths, non-fatal myocardial infarctions, and all repeat revascularization procedures (coronary artery bypass grafting, repeat target vessel angioplasty or acute stent placement) due to acute closure or recurrent ischemia at 30 days following initiation of study drug. At 30 days, counting all revascularizations, the risk of the composite endpoint was reduced by 17% (p=0.169). However, at two and seven days post-angioplasty, there were significant risk reductions in the composite endpoint of 38.4% (p=0.004) and 28.2% (p=0.023), respectively. In addition, an analysis which counted only emergency revascularizations as part of the 30-day composite endpoint, showed a 24.3% (p=0.052) risk reduction.

In the RESTORE study, the benefit of AGGRASTAT was consistent regardless of age or gender.

The TARGET trial (Do Tirofiban And Reopro Give Similar Efficacy Outcomes Trial) was a randomized, double-blind, active-comparator study of 4812 patients who were scheduled to undergo PCI with planned stent placement for the treatment of stable coronary artery disease or acute coronary syndromes. At the start of the procedures, patients received either AGGRASTAT (as an initial bolus of 10 microgram/kg followed by an infusion of 0.15 microgram/kg/min for 18-24 hours) or abciximab (as an initial bolus of 0.25 mg/kg followed by an infusion of 0.125 microgram/kg/min (to a maximum of 10 microgram/min) for 12 hours). Unless contraindicated, patients also received aspirin and heparin. Most patients (>90%) also received clopidogrel.

The primary endpoint of the study was the composite of all deaths, non-fatal myocardial infarctions, and urgent target vessel revascularization procedures (coronary artery bypass grafting, repeat target vessel angioplasty or acute stent placement) at 30 days following initiation of study drug. At 30 days, the composite endpoint occurred in 7.6% of patients who had received AGGRASTAT and 6.0% of patients who had received abciximab (p=0.038).

XV. STORAGE

Concentrate for Infusion
Store between 15-30°C. Do not freeze. Protect from light during storage.

XVI. AVAILABILITY

AGGRASTAT is available in a concentrated solution for dilution (50 mL vials).

XVII. MANUFACTURER

Patheon Manufacturing Services LLC
5900 Martin Luther King Jr. Highway, Greenville, North Carolina, USA 27834.