

PRODUCT INFORMATION

Concentrate for IV infusion

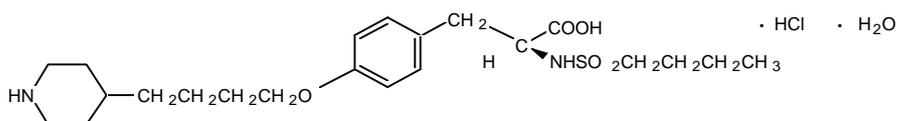
AGGRASTAT[®]
(tirofiban hydrochloride)

DESCRIPTION

AGGRASTAT[®] (tirofiban hydrochloride, MSD), a non-peptide antagonist of the platelet glycoprotein (GP) IIb/IIIa receptor, is a platelet aggregation inhibitor.

Tirofiban hydrochloride monohydrate is chemically described as *N*-(butylsulfonyl)-*O*-[4-(4-piperidiny)butyl]-*L*-tyrosine monohydrochloride monohydrate. The CAS No is 150915-40-5.

Its empirical 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 Concentrate for Infusion is a sterile concentrated solution for intravenous infusion after dilution and is supplied in a 50 mL glass 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 and 8 mg sodium chloride and water for injections. The pH ranges from 5.5 to 6.5 and may have been adjusted with hydrochloric acid and/or sodium hydroxide.

PHARMACOLOGY

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 ischaemic syndromes of unstable angina and myocardial infarction, as well as to cardiac ischaemic 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.

Pharmacokinetics

Distribution

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 litres.

Metabolism

Profiling of ¹⁴C-labelled tirofiban in urine and faeces 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.

Elimination

Following an intravenous dose of ¹⁴C-labelled tirofiban in healthy subjects, 66% of radioactivity is recovered in the urine and 23% in the faeces. 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.

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 (\leq 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 haemodialysis (see DOSAGE AND ADMINISTRATION, Patients with Severe Renal Insufficiency). Tirofiban is removed by haemodialysis.

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 μ g/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 μ g/kg/min for 30 minutes followed by 0.1 μ g/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.

Clinical Studies**Unstable Angina/Non-Q-Wave Myocardial Infarction****PRISM-PLUS (Platelet Receptor Inhibition for Ischaemic Syndrome Management - Patients Limited by Unstable Signs and Symptoms)**

In the multi-centre, randomised, parallel, double-blind PRISM-PLUS trial, 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 randomised to either AGGRASTAT (30 minute loading infusion of 0.4 μ g/kg/min followed by a maintenance infusion of 0.10 μ g/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). A third group of patients was initially randomised to AGGRASTAT (30 minute loading dose of 0.6 µg/kg/min followed by a maintenance infusion of 0.15µg/kg/min) with no heparin. This arm was discontinued when an increase in mortality was noted at seven days [16 deaths (4.6%) with tirofiban, as compared with 4 deaths (1.1%) with heparin].

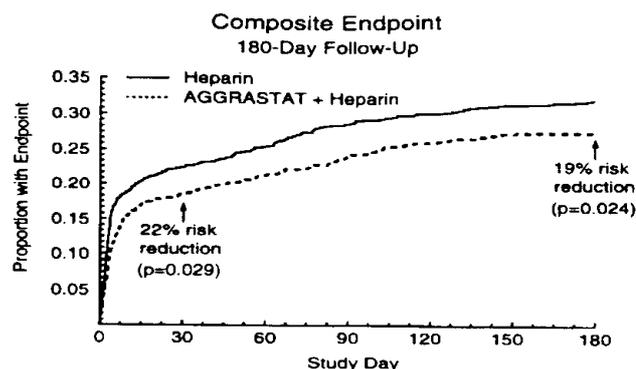
All patients received concomitant aspirin unless contraindicated. Therapy with AGGRASTAT commenced within 12 hours of the last episode of chest pain. Patients underwent 48 hours of medical stabilisation on study drug therapy, after which angiography and angioplasty/atherectomy remained options while 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.

The primary endpoint of the study was a composite of refractory ischaemia, 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 Ischaemic 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 Ischaemia	9.3%	12.7%	29.6%	0.023

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 death and myocardial infarction (p=0.027).

At 6 months, the risk of the composite endpoint was reduced by 18.9% (p=0.024); in addition, there was 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.

PRISM-PLUS was not designed to provide definitive results in subsets of the overall population. Nonetheless, demographic results were examined for age, gender and race. No difference in benefit was noticed for age and gender but too few non-Caucasians were enrolled to make a definite statement about racial differences in treatment effect.

PRISM (Platelet Receptor Inhibition for Ischaemic Syndrome Management).

In the PRISM study, a randomised, 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.

Patients were randomised to either AGGRASTAT alone (30 minute loading dose of 0.6 µg/kg/min, followed by a maintenance infusion of 0.15 µg/kg/min) or heparin alone (bolus of 5,000 U followed by an infusion of 1000U/hr titrated to maintain an APTT of approximately 2 times control). 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 ischaemia. Exclusion criteria were similar to PRISM-PLUS. The primary, prospectively identified endpoint was the composite endpoint of refractory ischaemia, myocardial infarction or death after a 48-hour drug infusion with AGGRASTAT. The results are shown in Table 2.

Table 2
Cardiac Ischaemic 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.

INDICATIONS

AGGRASTAT, in combination with heparin, is indicated for patients with unstable angina or non-Q-wave myocardial infarction to prevent cardiac ischaemic events. (See PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

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 haemorrhage, 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 haemorrhagic stroke
- major surgical procedure (including epidural or spinal anaesthesia) or severe physical trauma within 1 month
- history, symptoms, or findings suggestive of aortic dissection
- severe uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
- concomitant use of another parenteral GP IIb/IIIa inhibitor
- acute pericarditis

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/mm³
- history of cerebrovascular disease within 1 year
- recent epidural procedure
- haemorrhagic retinopathy
- chronic haemodialysis

Bleeding Precautions

Because AGGRASTAT inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect haemostasis. 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 ADVERSE REACTIONS).

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 haemostasis after removal of the sheaths followed by close observation.

Laboratory Monitoring

Platelet counts, and haemoglobin and haematocrit 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/mm³, 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 adjusted accordingly (see also DOSAGE and ADMINISTRATION). Potentially life-threatening bleeding may occur especially when heparin is administered with other products affecting haemostasis, 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 PHARMACOLOGY-Clinical Studies).

CARCINOGENICITY/MUTAGENICITY AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of tirofiban hydrochloride has not been evaluated.

Tirofiban was not genotoxic in a series of assays for gene mutations (*Salmonella typhimurium*, *Escherichia coli* and Chinese hamster lung cells), chromosomal

aberrations (Chinese hamster ovary cell *in vitro* and mouse bone marrow *in vivo*) or DNA damage (alkaline elution assay).

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.

USE IN PREGNANCY (Category B1)

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 foetus.

Studies of developmental toxicity in rats and rabbits showed no evidence of maternal or foetal toxicity. In addition, a study of the potential developmental toxicity through sexual maturity of rats exposed *in utero* and during lactation showed no drug-related effects on mortality, growth, development, and sexual maturation of the F₁ generation. In the developmental toxicity studies, dams were given tirofiban hydrochloride intravenously at doses up to 5 mg/kg/day.

USE IN LACTATION

It is not known whether AGGRASTAT is excreted in human milk, but it is excreted 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. Tirofiban hydrochloride crosses the placenta in rats and rabbits.

USE IN CHILDREN

Safety and effectiveness in children have not been established.

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).

This drug is known to be excreted by the kidney. A 50% reduction in dose is recommended for patients with severe renal insufficiency (creatinine clearance < 30 mL/min) (see DOSAGE AND ADMINISTRATION, and PRECAUTIONS). Plasma clearance of AGGRASTAT is about 19 to 26% lower in elderly (> 65 years) patients with coronary artery disease compared to younger (≤ 65 years) patients.

INTERACTIONS WITH OTHER DRUGS

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 haemostasis (e.g., warfarin) (see PRECAUTIONS-Bleeding Precautions). The safety of AGGRASTAT when used in combination with thrombolytic agents has not been established.

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

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 interactions of these drugs on the plasma clearance of tirofiban: acebutolol, alprazolam, amlodipine, aspirin preparations, atenolol, bromazepam, captopril, diazepam, digoxin, diltiazem, docusate sodium, enalapril, frusemide, glibenclamide, heparin, insulin, isosorbide, thyroxine sodium, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, omeprazole, oxazepam, paracetamol, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam.

EFFECTS ON LABORATORY TESTS

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

ADVERSE REACTIONS

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. (See also PRECAUTIONS-Effects on Laboratory Tests.)

The incidences of major and minor bleeding using the TIMI** Criteria in the PRISM PLUS (Platelet Receptor Inhibition for Ischaemic Syndrome Management - Patients Limited by Unstable Signs and Symptoms) study are shown below:

** Bovill, E.G.; et al: Haemorrhagic 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.

	PRISM PLUS[†] (UAP/Non-Q-Wave MI Study)	
Bleeding	AGGRASTAT + Heparin (n=773) %	Heparin (n=797) %
Major Bleeding (TIMI Criteria) [‡]	1.4	0.8
Minor Bleeding (TIMI Criteria) [§]	10.5	8.0
Transfusions	4.0	2.8

[†] Patients received aspirin unless contraindicated.

[‡] Haemoglobin drop of >50 g/L with or without an identified site, intracranial haemorrhage, or cardiac tamponade.

[§] Haemoglobin drop of >30 g/L with bleeding from a known site, spontaneous gross haematuria, haematemesis or haemoptysis.

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). 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.

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).

Thrombocytopenia

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/mm³ was 1.5%. The percentage of patients with a decrease of platelets to <50,000 cells/mm³ was 0.3%. Platelet decreases have been observed in patients with no prior history of thrombocytopenia upon readministration of GP IIb/IIIa receptor antagonists

Other adverse reactions

The most frequent drug-related non-bleeding adverse reactions reported with AGGRASTAT, administered concomitantly with heparin, occurring at an incidence of >1% were:

- nausea (1.7% v 1.4% control)
- fever (1.5% v 1.1% control)
- headache (1.1% v 1.2% control).

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.)

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

Bleeding: intracranial bleeding, retroperitoneal bleeding, haemopericardium, pulmonary (alveolar) haemorrhage 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: rash and urticaria. Severe allergic reactions including anaphylactic reactions. The reported cases have occurred during the first day of tirofiban infusion, during initial treatment, and during readministration of tirofiban. Some cases have been associated with severe thrombocytopenia (platelet counts < 10,000/mm³).

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

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.

AGGRASTAT should be administered intravenously at the initial infusion rate of 0.4 µg/kg/min for 30 minutes. Upon completion of the initial infusion, AGGRASTAT should be continued at a maintenance infusion rate of 0.1 µg/kg/min. AGGRASTAT should be given with heparin (usually an intravenous bolus dose of 5000 U simultaneously with the start of therapy with AGGRASTAT, then approximately 1000 U per hour titrated on the basis of APTT, which should be about twice the normal value).

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. 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 PHARMACOLOGY-Clinical Studies.)

Patients With Severe Renal Insufficiency

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 PHARMACOLOGY-Pharmacokinetics, Characteristics in Patients, Renal Insufficiency.)

The following table is provided as a guide to dosage adjustment by weight.

Patient Weight (kg)	Most Patients		Severe Kidney Failure	
	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

Other Patient Populations

No dosage adjustment is recommended for elderly patients (see Precautions-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.

Concentrate for Infusion

The vial of AGGRASTAT (concentrate) must be diluted prior to administration. It contains no antimicrobial agent. Use once only and discard any residue.

Directions for Preparation of AGGRASTAT Solution for Infusion from Concentrate

1. Withdraw and discard 50mL from a 250mL bag of sterile 0.9% saline or 5% glucose in water and replace it with 50mL of AGGRASTAT (from one 50 mL vial) to achieve a final concentration of 0.05mg/mL. Mix well before administration.

Alternatively, withdraw and discard 100 mL from a 500 mL bag of sterile 0.9% saline or 5% glucose in water and replace it with 100 mL of AGGRASTAT (from two 50 mL vials) to achieve a final concentration of 0.05mg/mL. Mix well before administration.

2. Administer according to the appropriate dosage calculations above.
3. To reduce microbiological hazard, use as soon as practicable after dilution. Discard any unused intravenous solution after 24 hours following start of infusion. If storage is necessary, hold at 2-8° C for not more than 24 hours.

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 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 catheterisation (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 haemodialysis.

PRESENTATION AND STORAGE

AGGRASTAT Concentrate for Infusion 0.25mg/mL 50 mL glass vials. **Must be diluted prior to administration (see INSTRUCTIONS FOR USE), to give a concentration of 0.05mg/mL.** Store below 30°C. Do not freeze. Protect from light during storage.

MANUFACTURER/DISTRIBUTOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED
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