PRODUCT MONOGRAPH

Pr AGGRASTAT®

tirofiban hydrochloride injection

12.5 mg / 250 mL tirofiban

(5 mg / 100 mL in bags of 250 mL)

Sterile Solution for Intravenous Infusion only

Platelet aggregation inhibitor

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AGGRASTAT®
Solution for Infusion

Tirofiban hydrochloride injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	5 mg/100 mL in 250 mL bags	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

AGGRASTAT® (tirofiban hydrochloride) is indicated for the:
management of adult patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) including patients who may subsequently undergo percutaneous coronary intervention (PCI) to decrease the rate of refractory ischemic conditions, new myocardial infarction and death.

AGGRASTAT® is intended for use in combination with anticoagulants (e.g. heparin) and other antiplatelet therapies, including acetylsalicylic acid (ASA).

Pediatrics (<18 years of age):
Safety and effectiveness in children have not been established.

CONTRAINDICATIONS

AGGRASTAT® is contraindicated in:
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with active or recent (within the previous 30 days) internal bleeding or a history of bleeding diathesis
- Patients with a history of intracranial hemorrhage or neoplasm, arteriovenous malformation, or aneurysm
- Patients who developed thrombocytopenia following prior exposure to AGGRASTAT® or any

other GPIIb/IIIa inhibitor
- Patients with a history, symptom or findings suggestive of aortic dissection
- Patients with known coagulopathy, platelet disorder or history of thrombocytopenia
- Patients who had a stroke within 30 days prior to hospitalization or any history of hemorrhagic stroke
- Patients who had a major surgical procedure or relevant trauma within the previous 6 weeks
- Patients with malignant or severe uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure of >110 mmHg)
- Patients currently taking another GP IIb/IIIa inhibitor
- Patients with acute pericarditis
- Patients with cirrhosis or clinically significant liver disease
- Patients with angina precipitated by obvious provoking factors (e.g., arrhythmia, severe anemia, hyperthyroidism or hypotension)
- Patients who had a recent epidural procedure

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **AGGRASTAT® is intended for use in combination with anticoagulants (e.g. heparin) and other antiplatelet therapies, including ASA. Caution should be employed when used with other drugs affecting hemostasis (see Laboratory Monitoring, Adverse Reactions and Post Marketing Experience).**

General

AGGRASTAT® is not recommended in the following patients with:
• major surgical procedure or severe physical trauma >6 weeks but <3 months previously
• organ biopsy or lithotripsy within the past two weeks
• active or known history of vasculitis
• hemorrhagic retinopathy
• intraaortic balloon pump
• clotting disturbances (e.g. prothrombin time >1.3 time normal or INR >1.5)
• concomitant use of drugs that increase the risk of bleeding to a relevant degree, including thrombolytics (see DRUG INTERACTIONS).

AGGRASTAT® should be used with caution in patients with:
• recent clinically relevant bleeding (<1 year), including a history of gastrointestinal bleeding, or genitourinary bleeding of clinical significance
• platelet count <150,000 cells/mm^3
• history of cerebrovascular disease within 1 year
• cardiopulmonary resuscitation

• chronic hemodialysis
• puncture of a non-compressible vessel with 24 hours
• severe acute or chronic heart failure
• cardiogenic shock
• mild to moderate liver insufficiency
• haemoglobin concentration less than 11 g/dl or haematocrit <34%
• concurrent administration of non-thienopyridines P2Y12 inhibitors, adenosine, dipyridamole, sulfinpyrazone, and prostacyclin.

Bleeding Precautions
AGGRASTAT® (tirofiban hydrochloride) inhibits platelet aggregation and therefore caution should be employed when it is used with other drugs that affect hemostasis (e.g. warfarin) or in patients requiring cardiopulmonary resuscitation. The efficacy and safety of AGGRASTAT® when used in combination with thrombolytic agents has not been established. Consequently, the use of AGGRASTAT® is not recommended in combination with thrombolytic therapy. AGGRASTAT® should be discontinued immediately if circumstances arise that require emergency coronary artery bypass graft (CABG) operation.

During therapy with AGGRASTAT®, patients should be monitored for potential bleeding. When bleeding cannot be controlled with pressure, infusion of AGGRASTAT® and heparin should be discontinued. Transfusions may be given if required.

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 [a Seldinger (through and through) technique for obtaining sheath access should be avoided]. Arterial sheaths should be removed when the patient's activated clotting time is < 180 sec or 2 - 6 hours following cessation of heparin. Care should be taken to obtain proper hemostasis after removal of the sheaths followed by close observation.

Cardiovascular
AGGRASTAT® should be used with caution in patients with a history of cerebrovascular disease within 1 year. AGGRASTAT® is not recommended in patients with active or known history of vasculitis, intra-aortic balloon pump.

Hematologic
AGGRASTAT® should be used with caution in patients with a platelet count <150,000 cells/mm^3.

Ophthalmologic
AGGRASTAT® is not recommended in patients with hemorrhagic retinopathy.

Renal

AGGRASTAT® should be used with caution in the patients with chronic hemodialysis (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

There is evidence from clinical studies that the risk of bleeding increases with decreasing creatinine clearance and hence also reduced plasma clearance of AGGRASTAT®. Patients with decreased renal function (creatinine clearance < 60 ml/min) should be carefully monitored for bleeding during treatment with AGGRASTAT® and the heparin effect should be carefully monitored.

In severe kidney failure (creatinine clearance < 30 ml/min), the AGGRASTAT®dosage should be reduced by 50% (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women: There are no or limited amount of data from the use of tirofiban hydrochloride in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. AGGRASTAT® is not recommended during pregnancy unless clearly necessary.

Nursing Women: It is not known whether AGGRASTAT® is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tirofiban hydrochloride in milk. A risk to the newborn cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue AGGRASTAT® therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Pediatrics (<18 years of age): There is no therapeutic experience with AGGRASTAT® in patients aged < 18 years. Thus, the use of AGGRASTAT® is not recommended in these patients.

Geriatrics (≥65 years of age): 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.

Gender: Female patients receiving AGGRASTAT® with heparin or heparin alone had a higher incidence of bleeding complications than male patients.

The overall incidence of non-bleeding adverse events was higher in female patients (compared to male patients) and older patients (compared to younger patients). Patients with a low body weight had a higher incidence of bleeding than patients with a higher body weight. For these reasons AGGRASTAT® should be used with caution in these patients and the heparin effect should be carefully monitored. No dose adjustment is recommended for these populations (see DOSAGE AND ADMINISTRATION, Other Patient Populations).

Monitoring and Laboratory Tests

Baseline evaluation:

Platelet count, hematocrit, hemoglobin and activated partial thromboplastin time (APTT) should be monitored prior to treatment.

Following the loading infusion:

Platelet counts, hemoglobin and hematocrit should be monitored within 6 hours following the bolus or loading infusion and at least daily thereafter (or more frequently if there is evidence of significant decline). Acute decrease in platelet count to <20,000 cells/mm^3 within one day after start of therapy with AGGRASTAT® have been reported post-marketing (see POST-MARKETING EXPERIENCE - Thrombocytopenia).

In patients previously exposed to GP IIb/IIIa receptor antagonists:

Monitor platelet count earlier and more often. Platelet decreases have been observed in patients with no prior history of thrombocytopenia upon re-administration of GP IIb/IIIa receptor antagonists (see POST-MARKETING EXPERIENCE).

If the platelet count decreases to <90,000 cells/mm^3:

Additional platelet counts should be performed to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, discontinue AGGRASTAT® and heparin and the condition should be appropriately monitored and treated.

Monitor APTT:

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common drug-related adverse event reported during therapy with AGGRASTAT® (tirofiban hydrochloride) when used concomitantly with heparin, ASA, and other oral anti-platelet agents, was bleeding which usually involved mild mucocutaneous bleeding or mild catheterization-site bleeding.

Gastro-intestinal, retro-peritoneal, intracranial, haemorrhoidal and post-operative bleeding, epidural haematoma in the spinal region, haemopericardium and pulmonary (alveolar) haemorrhage have also been reported. Rates of TIMI major and intracranial bleeding in the pivotal AGGRASTAT® studies were <2.2% and <0.1%, respectively. The most serious adverse reaction was fatal bleeding. In the pivotal studies, administration of AGGRASTAT® was associated with thrombocytopenia (platelet count <90,000/mm^3), occurring in 1.5% of patients treated with AGGRASTAT® and heparin. The incidence of severe thrombocytopenia (platelet count <50,000/mm^3) was 0.3%. The most common non-bleeding adverse drug reactions associated with

AGGRASTAT® given concurrently with heparin were nausea (1.7%), fever (1.5%) and headache (1.1%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10), common (≥1/100 to <1/10) and uncommon (≥1/1000 to <1/100).

Table 1 – Adverse reactions observed in the clinical trials

System Organ Class	Very common	Common	Uncommon
Nervous system disorders	Headache		
Vascular disorders	Haematoma		
Respiratory, thoracic and mediastinal disorders		Haemoptysis, epistaxis	
Gastrointestinal disorders	Nausea	Oral haemorrhage gingival haemorrhage	GI haemorrhage, haematemesis
Skin and subcutaneous tissue disorders	Ecchymosis		
Renal and urinary disorders		Haematuria	
General disorders and administration site conditions		Fever	
Injury, poisoning and procedural complications	Post-operative haemorrhage*	Vessel puncture site haemorrhage	

System Organ Class	Very common	Common	Uncommon
Investigations	Occult blood in stool or urine	Decreases in haematocrit and haemoglobin, platelet counts <90,000/mm^3	Platelet counts <50,000/mm^3

* Primarily related to catheterization sites.

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

PRISM-PLUS†
[Unstable Angina Pectoris (UAP)/
Non-Q-Wave Myocardial Infarction (MI) Study]

Bleeding	AGGRASTAT® + Heparin (n=773) %	Heparin (n=797) %
Major Bleeding‡	1.4	0.8
Minor Bleeding§	10.5	8.0
Transfusions	4.0	2.8

† Patients received ASA 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.

** Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, Feit F, Gore JM, Hillis LD, Lambrew CT. 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. Ann Intern Med 1991;115 (4):256-65.

There were no reports of intracranial bleeding in the PRISM-PLUS study for AGGRASTAT® in combination with heparin or in the heparin only control group. The incidences of retroperitoneal bleeding reported for AGGRASTAT® in combination with heparin, and for the heparin control group were 0.0% and 0.1%, respectively.

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 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%). The incidence of these side effects was similar in the heparin control group.

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.

In the published literature, there is no evidence of increased major bleeding with the AGGRASTAT® 25 mcg/kg dose bolus regimen. Data from the ADVANCE study suggest that the number of bleeding events is low and does not seem to be significantly increased compared to placebo. There were no TIMI major bleedings and no transfusions in either group. TIMI minor bleeding with the AGGRASTAT® 25 mcg/kg dose bolus regimen was 4% as compared with 1% in the placebo arm p=0.19).

Based upon an assessment of haemorrhagic complications performed in the context of a meta-analysis (n=4076 ACS patients), the AGGRASTAT® 25 mcg/kg dose bolus regimen does not significantly increase the rates of major bleeding, or thrombocytopenia, when compared to placebo. When considering the trials of the AGGRASTAT® 25 mcg/kg bolus regimen compared with abciximab, individual study results do not demonstrate a significant difference in major bleeding between the two treatments.

Thrombocytopenia
Patients treated with AGGRASTAT® and heparin, experienced decreases in platelet counts (<90,000 cells/mm^3) more often (1.5%) than the heparin control group (0.8%). The percentage of patients with a decrease of platelets to <50,000 cells/mm^3 was 0.3%. There were 0.1% of patients who had platelet counts < 20,000 cells/mm^3. These decreases were reversible within 4-6 days after discontinuation of AGGRASTAT®.

Analysis of the studies comparing the 25 mcg/kg dose bolus regimen against abciximab yielded a significantly lower rate of thrombocytopenia for AGGRASTAT® (0.45% vs. 1.7%; OR=0.31; p=0.004).

Abnormal Hematologic and Clinical Chemistry Findings

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.

Post-Market Adverse Drug Reactions

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

Bleeding: Intracranial hemorrhage, retroperitoneal bleeding and hemopericardium, pulmonary (alveolar) hemorrhage and spinal-epidural hematoma. Fatal bleedings have been reported.

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 cells/mm^3).

Thrombocytopenia: Acute decreases in platelet counts to less than 20,000 cells/mm^3 within one day after start of therapy with AGGRASTAT® have been reported (see PRECAUTIONS, Laboratory Monitoring and ADVERSE REACTIONS, Body as a Whole and Laboratory Test Findings).

DRUG INTERACTIONS

Serious Drug Interactions

AGGRASTAT® is intended for use in combination with anticoagulants (e.g. heparin) and other antiplatelet therapies, including acetylsalicylic acid (ASA). Caution should be employed when AGGRASTAT® is used with other drugs that affect hemostasis (e.g., warfarin, ticlopidine) (see WARNINGS and PRECAUTIONS, Bleeding Precautions).

Overview

AGGRASTAT® has been studied on a background of oral antiplatelet therapy, including but not limited to ASA and heparin.

The use of AGGRASTAT®, in combination with heparin and ASA, has been associated with an increase in bleeding compared to heparin and ASA alone (see ADVERSE REACTIONS). With the concurrent use of AGGRASTAT®, heparin, ASA and clopidogrel, there was a comparable incidence of bleeding to when heparin, ASA and clopidogrel were used alone (see ADVERSE REACTIONS).

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.

Caution should be employed when AGGRASTAT® is used with other drugs that affect hemostasis (see PRECAUTIONS, Bleeding Precautions). AGGRASTAT® is not recommended in thrombolytic therapy - concurrent or less than 48 hours before administration of AGGRASTAT® or concurrent use of drugs that increase the risk of bleeding to a relevant degree (e.g. oral anticoagulants, other parenteral GP IIb/IIIa inhibitors, dextran solutions). There is insufficient experience with the use of AGGRASTAT® in these conditions; however, an increased risk of bleeding is suspected.

Pharmacokinetics of AGGRASTAT® were not affected by a wide variety of drugs commonly administered to this patient population (e.g., antihypertensives, calcium-channel blockers, beta-blockers, diuretics, antidiabetics, lipid-lowering agents, digitalis preparations, and agents for the control of gastric acidity).

Drug-Drug Interactions
Interactions with other drugs have not been established.

In a sub-set of patients (n=762) in the PRISM study (Platelet Receptor Inhibition for Ischemic Syndrome Management), the plasma clearance of AGGRASTAT® 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 AGGRASTAT®: acebutolol, acetaminophen, alprazolam, amlodipine, ASA 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.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

In patients with NSTE-ACS who are either to be managed medically or with an early invasive strategy and not planned to undergo angiography for at least 4 hours after diagnosis, AGGRASTAT® (tirofiban hydrochloride) should be administered intravenously, in combination

with heparin, at the initial infusion rate of 0.4 mcg/kg/min for 30 minutes. Upon completion of the initial infusion, AGGRASTAT® should be continued at a maintenance infusion rate of 0.1 mcg/kg/min.

The recommended length of infusion for patients who do not exhibit any signs of refractory ischemic symptoms and do not proceed into angiography and angioplasty is at least 48 hours.

For patients proceeding into angiography and angioplasty the infusion should continue throughout both procedures and for at least 12 hours, and not more than 24 hours after angioplasty. Once a patient is clinically stable and no further coronary intervention is planned by the treating physician, the infusion should be discontinued. There are no safety data for total infusion time extended beyond 108 hours.

In high-risk NSTE-ACS patients who undergo PCI within 4 hours of diagnosis, AGGRASTAT® is administered intravenously at the start of PCI utilizing an initial bolus of 25 mcg/kg given over a 3 minute period, followed by a continuous infusion at a rate of 0.15 mcg/kg/min for 12-24 hours.

The tables below are provided as a guide to dosage adjustment by weight.

Table 2 – 0.4 mcg/kg/min Loading Dose regimen for Most Patients and those with Severe Kidney Failure

	Most Patients 0.4 mcg/kg/min Loading Dose Regimen		**Patients with Severe Kidney Failure 0.4 mcg/kg/min Loading Dose Regimen**	
Patient Weight (kg)	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

Patient Weight (kg)	**Most Patients 0.4 mcg/kg/min Loading Dose Regimen**		**Patients with Severe Kidney Failure 0.4 mcg/kg/min Loading Dose Regimen**	
	30 min Loading Infusion Rate (ml/hr)	Maintenance Infusion Rate (ml/hr)	30 min Loading Infusion Rate (ml/hr)	Maintenance Infusion Rate (ml/hr)
121-128	60	15	30	8
129-137	64	16	32	8
138-145	68	17	34	9
146-153	72	18	36	9

Table 3. 25 mcg/kg Dose Bolus dosing regimen for Most Patients and those with Severe Kidney Failure

Patient Weight (kg)	**Most Patients 25 mcg/kg Dose Bolus Regimen**		**Patients with Severe Kidney Failure 25 mcg/kg Dose Bolus Regimen**	
	Bolus (ml)	Maintenance Infusion Rate (ml/hr)	Bolus (ml)	Maintenance Infusion Rate (ml/hr)
30-37	17	6	8	3
38-45	21	7	10	4
46-54	25	9	13	5
55-62	29	11	15	5
63-70	33	12	17	6
71-79	38	14	19	7
80-87	42	15	21	8
88-95	46	16	23	8
96-104	50	18	25	9
105-112	54	20	27	10
113-120	58	21	29	10
121-128	62	22	31	11
129-137	67	24	33	12

Patient Weight (kg)	**Most Patients 25 mcg/kg Dose Bolus Regimen**		**Patients with Severe Kidney Failure 25 mcg/kg Dose Bolus Regimen**	
	Bolus (ml)	Maintenance Infusion Rate (ml/hr)	Bolus (ml)	Maintenance Infusion Rate (ml/hr)
138-145	71	25	35	13
146-153	75	27	37	13

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, Renal Insufficiency and PHARMACOLOGY, Pharmacokinetics, Special Populations, Renal Insufficiency).

Other Patient Populations
No dosage adjustment is recommended for elderly patients or female patients.

Administration
AGGRASTAT® is for hospital use only, by specialist physicians experienced in the management of acute coronary syndromes. AGGRASTAT® is for intravenous use only using sterile equipment. AGGRASTAT® should be co administered with heparin and oral antiplatelet therapy, including ASA through the same line.

AGGRASTAT® is recommended for use with a calibrated infusion device. Care should be taken to avoid a prolonged loading infusion.

Concurrent therapy (heparin, oral antiplatelet therapy, including ASA)
Treatment with unfractionated heparin is initiated with an i.v. bolus of 50-60 U/kg and then continued with a maintenance infusion of 1,000 U per hour. The heparin dosage is titrated to maintain an APTT of approximately twice the normal value.
There is limited experience with concomitant administration of AGGRASTAT® with other anticoagulants (i.e. bivalirudin). The efficacy and safety of AGGRASTAT® in combination with bivalirudin has not been established.

In clinical studies, patients received oral antiplatelet agents, including but not limited to ASA unless contraindicated. This medication should be continued at least for the duration of the infusion of AGGRASTAT®. Most studies investigating the administration of AGGRASTAT® as an adjunct to PCI have used ASA in combination with clopidogrel as oral antiplatelet therapy.

AGGRASTAT® may be administered in the same intravenous line as atropine sulfate, dobutamine, dopamine, epinephrine HCI, furosemide, lidocaine, midazolam HCI, morphine sulfate,

nitroglycerin, famotidine, potassium chloride and propranolol HCI injection.

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

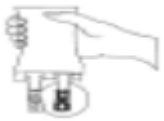
Directions for Use of AGGRASTAT® - Solution for Infusion
CAUTION:

250 ml Solution for Infusion: Instructions for use

Check the expiry date on the front of the overpouch.
Open the overpouch by tearing the foil at the notch, remove the inner container.
Check the solution; do not use unless solution is clear and seal is intact.
Check for small leaks by firmly squeezing the inner bag. If leaks are found, discard the solution as it may no longer be sterile.

CAUTION: Do not withdraw solution directly from the bag with a syringe.
CAUTION: Do not add supplementary medication to the bag.
CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

1. Preparation for administration:

	1. Identify the **blue*** infusion port.
	2. Break off the **blue*** tamper-evident cover from the Freeflex® infusion port. The membrane below the cover is sterile – disinfection of the membrane is not required!
	3. Close the roller clamp. Insert the spike into the port until the **blue*** plastic collar of the port meets the shoulder of the spike. Use a non-vented set or close the air inlet.
	4. Hang the bag on the infusion stand. Press the drip chamber to half fill the chamber with fluid. Prime the infusion set. Connect and adjust flow rate according to dosing tables.
Use according to the dosage tables. *Blue infusion port depicted as black in the diagrams above.	

OVERDOSAGE

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

The most frequently reported manifestation of overdose was bleeding; primarily minor mucocutaneous bleeding events and localized bleeding at the arterial puncture site for cardiac catheterization but also single cases of intracranial haemorrhages and retroperitoneal bleedings (see PRECAUTIONS, Bleeding Precautions).

Overdose with AGGRASTAT® should be treated in accordance with the patient's condition and the attending physician's assessment.
If treatment of haemorrhage is necessary, the AGGRASTAT® infusion should be discontinued. Transfusions of blood and/or thrombocytes should also be considered. AGGRASTAT® can be removed by haemodialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AGGRASTAT® (tirofiban hydrochloride) is a reversible non-peptide antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. When administered intravenously, tirofiban inhibits *ex vivo* platelet aggregation in a dose and concentration dependent manner.

Pharmacodynamics

Tirofiban 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 tirofiban, 0.1 mcg/kg/min, *ex vivo*-platelet aggregation returns to near baseline in approximately 90% of patients with coronary artery disease in 4 to 8 hours. Coadministration of a 4-hour infusion of 0.15 mcg/kg/min of AGGRASTAT® and ASA results in the anticipated near maximal inhibition of platelet aggregation and a modest additive effect of BT prolongation. 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 tirofiban (loading infusion of 0.4 mcg/kg/min for 30 minutes followed by 0.1 mcg/kg/min for up to 48 hours in the presence of heparin and ASA), 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 with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), an intravenous 25 mcg/kg dose bolus regimen of tirofiban (followed by a 18-24 hour maintenance infusion of 0.15 mcg /kg/min), in the presence of heparin and oral anti-platelet therapy, produced an average ADP-induced inhibition of maximal aggregation 15 to 60 minutes after onset of treatment of 92% to 95% as measured with light transmission aggregometry (LTA).

Pharmacokinetics

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

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 post-dose). The metabolism of tirofiban appears to be limited.

Excretion: In healthy subjects, tirofiban is cleared from the plasma largely by renal excretion, with about 66% of a ^{14}C labeled tirofiban dose appearing in the urine and about 23% in the feces, mainly as unchanged 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

Special Populations and Conditions

Geriatrics: 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.

Gender: Plasma clearance of tirofiban in patients with coronary artery disease is similar in males

and females.

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 AGGRASTAT® 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.

STORAGE AND STABILITY

Store between 15-30°C.
Do not freeze.
Keep container in foil overpouch to protect from light during storage.

SPECIAL HANDLING INSTRUCTIONS

No special instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each 250 mL bag of iso-osmotic solution contains: As medicinal ingredient: 12.5 mg tirofiban (as hydrochloride). As non-medicinal ingredients: 8 mg citric acid anhydrous, 135 mg sodium citrate dihydrate and 2.25 g sodium chloride. The pH ranges from 5.5 to 6.5 and may have been adjusted with hydrochloric acid and/or sodium hydroxide.

AGGRASTAT® is available in 250 mL Freeflex® non-PVC plastic bags. The Freeflex® bags are made of a colourless, multilayer polyolefine film with two ports (a white injection and blue infusion port), and wrapped in a foil pouch. AGGRASTAT® is a clear, colourless, iso-osmotic solution for infusion. It is premixed with 0.9% sodium chloride and is stable through the labeled expiration date when stored under the recommended conditions.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

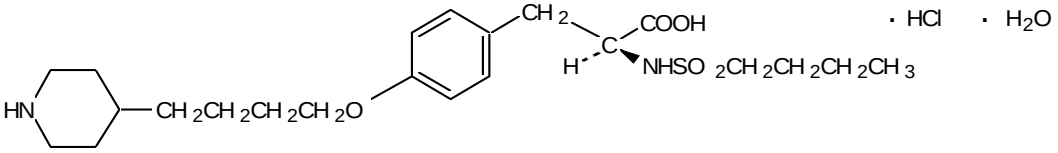
Drug Substance

Proper name: Tirofiban hydrochloride (USAN)

Chemical name: *N*-(butylsulfonyl)-*O*[4-(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate.

Molecular formula and molecular mass: $C_{22}H_{36}N_2O_5S \bullet HCl \bullet H_2O$, 495.08

Structural formula:



Physicochemical properties: Tirofiban hydrochloride is a white to off-white non-hygroscopic free-flowing powder. It is very slightly soluble in water.

The pH of a 0.2% solution of tirofiban hydrochloride is approximately 2.9.

Tirofiban hydrochloride melts with decomposition at 115°C (DSC curve).

CLINICAL TRIALS

Non-ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)

Study demographics and trial design

Table 4 - Summary of patient demographics for clinical trials in Non-ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
PRISM-PLUS	Multicenter, randomized, parallel, double-blind study designed to assess the clinical efficacy of AGGRASTAT® in the prevention of acute ischemic events in patients with unstable angina and non–Q-wave myocardial infarction	AGGRASTAT® (0.4 mcg/kg/min for 30 min followed by 0.10 mcg/kg/min) and heparin (5,000 U followed by 1,000 U/hr titrated to maintain APTT 2 times control) or heparin alone (dosage as above). Concomitant therapy: 325 mg ASA unless contraindicated.	773/797	63	68% male 32 % female

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
ADVANCE	Double-blind, single center, placebo-controlled randomised trial designed to determine the safety and efficacy of the tirofiban high bolus dose regimen as compared with placebo in patients undergoing elective or urgent PCI who exhibit high-risk characteristics	AGGRASTAT® bolus dose regimen (25 mcg/kg for 3 min, followed by 0.15 mcg/kg/min for 24-48 hours) or matched placebo. Concomitant therapy: unfractionated heparin (AGGRASTAT® arm: 50 to 70 U/kg [max 7,000 U], with additional boluses to achieve and maintain an ACT ≥200 seconds, placebo arm: 100 U/kg [max. 10,000 U], with additional boluses to achieve and maintain an ACT ≥ 300 seconds), ASA (160-325 mg orally) and a thienopyridine (either 500 mg ticlopidine or 300 mg clopidogrel followed by maintenance therapy).	101/101	69 ± 8	68% male 32 % female
EVEREST	Randomised open-label trial to compare the upstream 0.4 µg/kg/min loading dose regimen initiated in the coronary care unit with the AGGRASTAT® 25 µg/kg dose bolus regimen or abciximab 0.25 milligram/kg initiated 10 minutes prior to PCI.	AGGRASTAT® initiated upstream in the CCU (0.4 mcg/kg/min over 30 minutes followed by 1.0 mcg/kg /min) or AGGRASTAT® high dose bolus initiated in the cath lab (25 mcg/kg over 3 minutes followed by 0.15 mcg/kg /min) or Abciximab (standard dose) initiated in the cath lab. Concomitant therapy: ASA (100 to 300 mg) and a thienopyridine (ticlopidine 500 mg or clopidogrel 300 mg)	93	64.8 ± 11.2	75.3% male 24.7 % female

PRISM PLUS study:
In the multicenter, randomized, parallel, double-blind PRISM-PLUS trial (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms), the use of AGGRASTAT® (tirofiban hydrochloride) in combination with heparin (n=773) versus heparin alone (n=797) was compared in patients with documented unstable angina/non-Q-wave myocardial infarction within 12 hours of the last episode of chest pain before randomization. All patients with unstable angina/non-Q-wave myocardial infarction had cardiac ischemia documented by ECG or had elevated cardiac enzymes. The mean age of the population was 63 years; 32% of patients were female and approximately half of the population presented with non-Q-wave myocardial infarction.

Patients were randomized to either AGGRASTAT® (30 minute loading infusion of 0.4 mcg/kg/min followed by a maintenance infusion of 0.10 mcg/kg/min) and heparin (bolus of 5,000 units (U) followed by an infusion of 1,000 U/hr titrated to maintain an activated partial thromboplastin time (APTT) of approximately 2 times control), or heparin alone (bolus of 5,000 U followed by an infusion of 1,000 U/hr titrated to maintain an APTT of approximately 2 times control). All patients received concomitant acetylsalicylic acid (ASA) unless contraindicated.

ADVANCE study:
The ADVANCE (Additive Value of Tirofiban Administered With the High-Dose Bolus in the Prevention of Ischemic Complications During High-Risk Coronary Angioplasty) study determined the safety and efficacy of the AGGRASTAT® 25 mcg/kg dose bolus regimen as compared with placebo in patients undergoing elective or urgent PCI who exhibit high-risk characteristics including the presence of at least one coronary narrowing ≥70% and diabetes, need for multi-vessel intervention, or NSTE-ACS. All patients received unfractionated heparin, ASA and a thienopyridine loading dose followed by maintenance therapy. A total of 202 patients were randomised to either AGGRASTAT® (25 mcg/kg bolus IV over 3 minutes followed by a continuous IV infusion of 0.15 mcg/kg/minute for 24-48 hours) or placebo given immediately before PCI.

EVEREST study:
The randomised open-label EVEREST trial compared the upstream 0.4 mcg/kg/min loading dose regimen initiated in the coronary care unit with the AGGRASTAT® 25 mcg/kg dose bolus regimen or abciximab 0.25 milligram/kg initiated 10 minutes prior to PCI. All patients additionally received ASA and a thienopyridine. The 93 enrolled NSTE-ACS patients underwent angiography and PCI as appropriate, within 24-48 hours of admission.

Study results

Table 5 - Results of studies

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
PRISM-PLUS Composite of refractory ischemia, new myocardial infarction and death at 7 days after randomization	12.9%	17.9% (p=0.004).
ADVANCE: Composite of death, nonfatal MI, urgent target vessel revascularization (uTVR), or thrombotic bailout GP IIb/IIIa inhibitor therapy within a median follow-up of 180 days after index procedure	Cumulative: 35% Composite of death, MI, or uTVR: 31%	Cumulative: 20% (p = 0.01) Composite of death, MI, or uTVR: 20% (p = 0.048)
EVEREST: Difference in TIMI myocardial perfusion grade (TMPG) before PCI	upstream AGGRASTAT® loading dose regimen: 28.1 % AGGRASTAT® high dose bolus regimen: 66.7%	71% (p = 0.0009)

PRISM PLUS study:

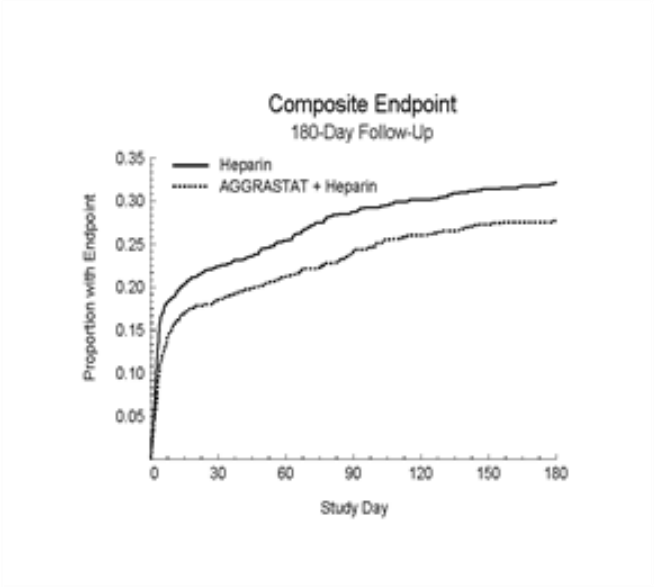
Comprehensive Management: Patients underwent 48 hours of medical stabilization on study drug therapy, after which they could undergo angiography and angioplasty (if indicated), while continuing on AGGRASTAT®. AGGRASTAT® was generally administered for a minimum of 48 hours and was continued up to 108 hours; patients received AGGRASTAT® for 71.3 hours (average for all patients).

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 5:

Table 6
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 seen at 7 days was maintained over time. At 30 days, the risk of the composite endpoint was reduced by 21.8% (p=0.029) and there was a 29.8% (p=0.027) reduction in the composite of myocardial infarction and death. At 6 months, the risk of the composite endpoint was reduced by 18.9% (p=0.024). In addition, there was a 22.5% (p=0.063) 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 PRISM-PLUS study, 90% of patients underwent coronary angiography and 30% underwent angioplasty. The majority of these patients continued on study drug throughout these procedures. AGGRASTAT® was continued for 12-24 hours (average 15 hours) after angioplasty.

Although the benefit of adding tirofiban to heparin was observed in all interventional subgroups used in the management of these patients [Percutaneous Transluminal Coronary Angioplasty (PTCA), Coronary Artery Bypass Graft (CABG) or medical management alone], a pre-specified

analysis suggested that there was some amplification of the benefit in patients undergoing PTCA.

A sub-study in PRISM-PLUS of angiograms up to 96 hours found that there was a statistically significant decrease in the extent of angiographically apparent thrombus and increase in the blood flow in patients treated with AGGRASTAT® in combination with heparin compared to heparin alone.

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

ADVANCE study:
The primary endpoint was a composite of death, nonfatal MI, urgent target vessel revascularization (uTVR), or thrombotic bailout GP IIb/IIIa inhibitor therapy within a median follow-up of 180 days after the index procedure. In the intent-to-treat (ITT) population, the cumulative incidence of the primary end point was 35% and 20% in placebo and AGGRASTAT® groups, respectively (hazard ratio [HR] 0.51 [95% confidence interval (CI), 0.29 to 0.88]; p=0.01). As compared with placebo, there was a significant reduction in the composite of death, MI, or uTVR in the AGGRASTAT® group (31% vs. 20%, HR, 0.57 95% CI, 0.99–0.33]; p=0.048.

EVEREST study:
With respect to the primary endpoints of tissue level perfusion and troponin I release, the results of EVEREST determined significantly lower rates of post-PCI TIMI Myocardial infusion grade (TMPG) 0/1 with upstream tirofiban compared with HDB tirofiban and abciximab (6.2% vs. 20% vs. 35.5%, respectively; p=0.015), and improved post-PCI Myocardial Contrast Echocardiography (MCE) score index with upstream tirofiban as compared with HDB tirofiban and abciximab (0.88 ± 0.18 vs. 0.77 ± 0.32 vs. 0.71 ± 0.30, respectively; $p<0.05$). The incidence of post-procedural cardiac Troponin I (cTnI) elevation was significantly reduced in patients treated with the upstream AGGRASTAT® regimen compared with PCI 25 mcg/kg dose bolus AGGRASTAT® or abciximab (9.4% vs. 30% vs. 38.7%, respectively; p=0.018). The cTnI levels post-PCI were also significantly decreased with the upstream regimen of AGGRASTAT® compared with PCI AGGRASTAT® (3.8 ± 4.1 vs. 7.2 ± 12; p=0.015) and abciximab (3.8 ± 4.1 vs. 9 ± 13.8; p=0.0002). The comparison between the PCI AGGRASTAT® 25 mcg/kg dose bolus and abciximab regimens indicated no significant differences in the rate of TMPG 0/1 post-PCI (20% vs. 35%; p=NS).

Meta-analysis of Randomised Trials of AGGRASTAT® 25 mcg/kg Dose Bolus Regimen in ACS

The results of a meta-analysis evaluating the efficacy of the AGGRASTAT® 25 mcg/kg dose bolus regimen versus abciximab (including 2213 ACS patients, across the ACS spectrum, with both NSTEMI and STEMI patients) did not reveal any significant difference in the OR for death or MI at 30 days between the two agents (OR, 0.87 [0.56-1.35]; p=0.54). Similarly, there were no significant differences in 30-day mortality between AGGRASTAT® and abciximab (OR, 0.73 [0.36-1.47]; p=0.38). Additionally, at the longest follow-up, death or MI was not significantly different between AGGRASTAT® and abciximab (OR, 0.84 [0.59-1.21]; p=0.35).

TOXICOLOGY

Acute Toxicity
The approximate LD_{50} of tirofiban given as a single intravenous dose to mice or rats was >5 mg/kg. The maximum dose of 5 mg/kg (21 times the maximum recommended daily human dose) was limited by compound solubility and maximum acceptable dosing volume. The approximate LD_{50} of tirofiban given as a single oral dose to mice was >500 mg/kg. No mortality, physical signs, or compound-related effects on body weight were observed in either the intravenous or oral studies.

Chronic Toxicity
The toxic potential of tirofiban hydrochloride was evaluated for up to five weeks in a series of continuous infusion intravenous toxicity studies in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level for up to 108 hours.

Carcinogenesis
The carcinogenic potential of tirofiban hydrochloride has not been evaluated.

Mutagenesis
Tirofiban hydrochloride was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays. Tirofiban was tested in these *in vitro* assays at concentrations up to 3 mM, (approximately 20,000 times greater than the mean plasma level achieved in man at the recommended therapeutic dosage level). There was no induction of chromosomal aberrations in bone marrow cells of male mice after the administration of intravenous doses up to 5 mg/kg (21 times the maximum recommended daily human dose).

Reproduction
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. These dosages are approximately 21-fold higher than the maximum recommended daily dose in humans.

Development
Studies of developmental toxicity in rats and rabbits showed no evidence of maternal or fetal 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 F_1 generation. In the developmental toxicity studies, dams were given tirofiban hydrochloride intravenously at doses up to 5 mg/kg/day.

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PART III: CONSUMER INFORMATION

AGGRASTAT®
Tirofiban hydrochloride injection
12.5 mg / 250 mL tirofiban

(5 mg/100 mL in bags of 250 mL)

This leaflet is part III of a three-part "Product Monograph" published when AGGRASTAT® Solution for Infusion was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AGGRASTAT® Solution for Infusion. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
AGGRASTAT® is used to help assist the blood flow to your heart and to help prevent chest pain and heart attacks.
This medicine may also be used in patients whose heart vessels are dilated with a balloon (percutaneous coronary intervention or PCI). This is a procedure, possibly with implantation of a small tube (stent), to improve the blood flow to the heart.

AGGRASTAT® is intended for use with aspirin and heparin.

What it does:
It works by preventing platelets, cells found in the blood, from forming blood clots.

When it should not be used:
- if you are allergic (hypersensitive) to tirofiban or any of the other ingredients of AGGRASTAT® Solution for Infusion,
- if you are bleeding internally or have a history of bleeding internally within the last 30 days,
- if you have a history of bleeding in the brain, brain tumor or abnormal blood vessels in the brain,
- if you have severe uncontrolled high blood pressure (malignant hypertension),
- if you have a low blood platelet count (thrombocytopenia) or problems with blood clotting,
- if you developed thrombocytopenia if you had received treatment with AGGRASTAT® Solution for Infusion or another medicine in the same group of drugs previously,
- if you have a history of stroke within the last 30 days or any history of stroke with bleeding,
- if you have been seriously injured or had a major operation within the previous 6 weeks,
- if you have severe liver disease (cirrhosis),
- if you have a history or symptoms of splitting of the aorta (aortic dissection),
- if you have an inflammation of the lining around your heart (pericarditis),
- if you have had a recent spinal procedure, or had a special intravenous line inserted under your collar bone within the last 24 hours,
- if you have a treatment with another GP IIb/IIIa inhibitor such as abciximab,
- if you have chest pain caused by irregular heartbeat, low levels of red blood cells (anemia), excessive sweating or low blood pressure.

What the medicinal ingredient is:
tirofiban hydrochloride

What the important nonmedicinal ingredients are:
Citric acid anhydrous,
Sodium citrate dihydrate
Sodium chloride
For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
Solution for Infusion

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

AGGRASTAT® is intended for use in combination with anticoagulants (e.g. heparin) and other antiplatelet therapies, including ASA. Caution should be employed when used with other drugs that affect bleeding.

BEFORE you use AGGRASTAT® Solution for Infusion, talk to your doctor or pharmacist if:
- You have an inflammation of the blood vessels (vasculitis),
- You have problems with the blood vessels in the back of your eye (retina),
- You have a treatment with medications that help to prevent or dissolve blood clots like warfarin,
- You have kidney problems,
- You have heart failure,
- You have very low blood pressure due to a failing heart (cardiogenic shock),
- You have a liver disorder,
- You have a low blood count or anemia,
- You have been seriously injured or had a major operation within the last 3 months,
- You have had cardiopulmonary resuscitation (CPR), a biopsy, or a procedure to break up kidney stones within the last 2 weeks,
- You have had an ulcer in the stomach or intestine (duodenum) within the last 3 months,
- You have had a recent bleeding disorder (within 1 year) such as bleeding in the stomach or intestine, or blood in your urine or stool,
- You have had a cerebrovascular disease like a stroke in the last year,
- You are being treated with non-thienopyridines P2Y12 inhibitors, adenosine, dipyridamole, sulfinpyrazone, and prostacyclin,
- You had been treated with balloon pump in your aorta, a vessel

in your heart,
- You have clotting problems,
- You have a low blood platelet count,
- You are on chronic hemodialysis,
- You have had a puncture of a blood vessel within 24 hours and the bleeding cannot be stopped.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with AGGRASTAT® Solution for Infusion include other medicines that help prevent your blood from clotting such as warfarin.

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor will decide on the appropriate dose, depending on your condition and your weight.

Overdose:
The most frequently reported symptom of overdose is bleeding.

In case of drug overdose, contact a health care practitioner or hospital emergency department immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effect of treatment with AGGRASTAT® Solution for Infusion is bleeding which could occur anywhere in the body. This can become serious and may, rarely, be fatal.

Very common side effects include bleeding after surgery, bleeding under the skin at the site of an injection, or into a muscle, causing swelling, small red bruises on the skin, invisible blood in urine or stool, feeling sick, headache.

Common side effects include nose bleeds, bleeding in the gums and mouth, bleeding from vessel puncture site, reduction in red blood cells (reduced haematocrit and haemoglobin), decrease in platelet count below 90,000/mm^3, fever.

Uncommon side effects include bleeding in the stomach or intestines, vomiting of blood, decrease in platelet count below 50,000/mm^3.

Other side effects include haematoma in the spinal region, bleeding in the abdomen of the internal organs, accumulation of blood around the heart, bleeding in the lung, acute and/or severe decreases in platelet counts below 20,000/mm^3.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	- signs of internal bleeding / coughing up blood or blood in your urine or stool			√
Not known frequency	- bleeding in the skull / pain in the head, sensory impairments (visual or hearing), difficulties in speech, numbness or problems with movement or balance			√
	- severe allergic reactions / tightness of chest, hives or nettle rash, including reactions that cause difficulty in breathing and dizziness			√

These are not all the possible side effects you may feel when taking AGGRASTAT® Solution for Infusion If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

HOW TO STORE IT

Store between 15-30°C.
Do not freeze.
Keep container in foil overpouch to protect from light during storage.

Keep out of reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.cipherpharma.com or by contacting the sponsor, Cipher Pharmaceuticals Inc. at:
1-866-992-2749

This leaflet was prepared by Cipher Pharmaceuticals Inc.

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