1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AGGRASTET 0,05 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution of AGGRASTET 0,05 mg/ml contains 0,05 mg tirofiban as tirofiban hydrochloride monohydrate.

Sugar free

Contains 160,43 mmol/l of sodium.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear, colourless solution essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

AGGRASTET 0,05 mg/ml, in combination with heparin, is indicated for:

- patients with unstable angina or non-Q-wave myocardial infarction, presenting with ECG abnormalities or elevated cardiac enzymes, to prevent cardiac ischaemic events,
- patients with coronary ischaemic syndromes undergoing coronary angioplasty or atherectomy to prevent cardiac ischaemic complications related to abrupt closure of the treated coronary artery (see section 4.2).

4.2. Posology and method of administration

Posology

AGGRASTET 0,05 mg/ml is for hospital use only, under supervision of medical practitioners experienced in the management of acute coronary syndromes.

AGGRASTET 0,05 mg/ml should be administered with unfractioned heparin.

AGGRASTET 0,05 mg/ml is for intravenous use only using sterile equipment. AGGRASTET 0,05 mg/ml may be co-administered with heparin through the same line.

AGGRASTET 0,05 mg/ml is recommended for use with 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

In patients who are to be managed medically for unstable angina/non-Q-wave myocardial infarction and who may continue on to angioplasty or atherectomy, AGGRASTET 0,05 mg/ml 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, AGGRASTET 0,05 mg/ml should be continued at a maintenance infusion rate of 0,1 microgram/kg/min. Patients with severe renal insufficiency (creatinine clearance less than 30 ml/min) should receive half the usual rate of infusion.

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

	Most Patients		**Severe Renal Impairment**	
Patient weight (kg)	30 Min Loading Infusion Rate	Maintenance Infusion Rate (ml/hr)	30 Min Loading Infusion Rate (ml/hr)	Maintenance Infusion Rate (ml/hr)

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

AGGRASTET 0,05 mg/ml in combination with heparin has been administered for 48 to 108 hours, on average patients received AGGRASTET 0,05 mg/ml 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 less than 180 seconds or 2 to 6 hours following cessation of heparin.

Angioplasty/atherectomy

In patients in whom AGGRASTET 0,05 mg/ml is initiated in the setting of angioplasty/atherectomy, AGGRASTET 0,05 mg/ml 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. Patients with severe renal insufficiency (creatinine clearance less than 30 ml/min) should receive half the usual dosage.

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

	Most Patients		Severe Renal Impairment	
Patient weight (kg)	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 to 37	7	6	4	3
38 to 45	8	8	4	4
46 to 54	10	9	5	5
55 to 62	12	11	6	6
63 to 70	13	12	7	6
71 to 79	15	14	8	7
80 to 87	17	15	9	8
88 to 95	18	17	9	9
96 to 104	20	18	10	9
105 to 112	22	20	11	10
113 to 120	23	21	12	11
121 to 128	25	23	13	12
129 to 137	26	24	13	12
138 to 145	28	26	14	13
146 to 153	30	27	15	14

The AGGRASTET 0,05 mg/ml 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 less than 180 seconds.

Special populations

Elderly

No dosage adjustment is recommended for elderly patients (see section 4.4) or female

patients.

Patients with severe renal impairment

In severe renal impairment (creatinine clearance < 30 ml/min) the dosage of AGGRASTET 0,05 mg/ml should be reduced by 50 % (see sections 4.4 and 5.2).

Paediatric population

Safety and effectiveness in children aged < 18 years have not been established.

Method of administration

Directions for use

Parenteral medicine should be inspected visually for particulate matter and discolouration prior to use, whenever solution and container permit.

Check the expiry date.

See section 6.2. Incompatibilities.

To open: Tear foil over pouch (250 ml Solution for Infusion) at notch and remove inner container.

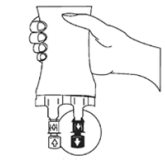
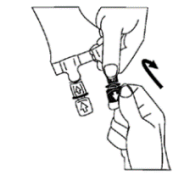
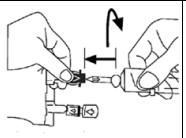
Check for minute leaks by sqeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

Do not use unless solution is clear and seal is intact.

Do not add supplementary medicine or withdraw solution directly from the bag with a syringe.

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.

Preparation for administration:

	1. Identify the **blue** infusion port.
	2. Break off the **blue** tamper-evident cover from the freeflex® infusion port. Membrane below cover is sterile - disinfection of the membrane is not necessary!
	3. Close roller clamp. Insert the spike 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 drip chamber to get fluid level. Prime infusion set. Connect and adjust flow rate.

Use according to the dosage table above.

Check for minute leaks by squeezing inner bag firmly.

Preparation for administration:

1. Suspend container from eyelet support.

2. Remove plastic protector from outlet port at bottom of container.

3. Attach administration set. Refer to complete directions accompanying set.

4. Any unused intravenous solution should be discarded.

4.3. Contraindications

AGGRASTET 0,05 mg/ml is contraindicated in patients with:

- Hypersensitivity to tirofiban or to any of the excipients in AGGRASTET 0,05 mg/ml (see section 6.1).

- Active internal bleeding (e.g. gastrointestinal bleeding) or 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 AGGRASTET 0,05 mg/ml or other GP IIb/IIIa receptor antagonists.
- Thrombocytopenia (platelet count < 100,000/mm^3), disorders of platelet function.
- A history of major surgical procedure or severe physical trauma within the previous 6 weeks .
- A history of stroke within 30 days or any history of haemorrhagic stroke.
- Clotting disturbances (e.g. prothrombin time > 1,3 times normal or prolonged international normalised ratio (INR) > 1,5).
- Severe liver failure.
- Chronic haemodialysis.
- History, symptoms, or findings suggestive of aortic dissection.
- Severe hypertension (systolic blood pressure more than 180 mm Hg and/or diastolic blood pressure more than 110 mm Hg).
- Acute pericarditis.
- Concomitant use of another parenteral GP IIb/IIIa receptor antagonist.
- Recent epidural procedure (including lumbar puncture and spinal anaesthesia).
- Prolonged INR.

4.4. Special warnings and precautions for use

Heparin combinations

The administration of AGGRASTET 0,05 mg/ml alone without unfractionated heparin is not recommended.

There is limited experience with concomitant administration of AGGRASTET 0,05 mg/ml with enoxaparin. The concomitant administration of AGGRASTET 0,05 mg/ml with enoxaparin is associated with a higher frequency of cutaneous and oral bleeding events, but not in Thrombolysis in Myocardial Infarction (TIMI) bleeds**, when compared with the concomitant administration of AGGRASTET 0,05 mg/ml and unfractionated heparin. An increased risk of serious bleeding events associated with the concomitant administration of AGGRASTET 0,05 mg/ml and enoxaparin cannot be excluded, particularly in patients given additional unfractionated heparin in conjunction with angiography and/or percutaneous coronary intervention (PCI). The efficacy of AGGRASTET 0,05 mg/ml in combination with enoxaparin has not been established. The safety and efficacy of AGGRASTET 0,05 mg/ml with other low molecular weight heparins has not been investigated.

**TIMI major bleeds are defined as a haemoglobin drop of > 50 g/L with or without an identified site, intracranial haemorrhage, or cardiac tamponade. TIMI minor bleeds are defined as a haemoglobin drop of > 30 g/L but ≤ 50 g/L with bleeding from a known site or spontaneous gross haematuria, haematemesis, or haemoptysis. TIMI “loss no site” is defined as a haemoglobin drop > 40 g/L but < 50 g/L without an identified bleeding site.

Increased risk of bleeding

Bleeding is the most common complication encountered during therapy with AGGRASTET 0,05 mg/ml. Administration of AGGRASTET 0,05 mg/ml is associated with an increase in bleeding events classified as both major and minor bleeding events by criteria developed by the TIMI study group. Most major bleeding associated with AGGRASTET 0,05 mg/ml occurs at the arterial access site for cardiac catheterisation.

Because AGGRASTET 0,05 mg/ml inhibits platelet aggregation, caution should be employed when it is used with other medicines that affect haemostasis. The safety of AGGRASTET

0,05 mg/ml when used in combination with thrombolytic medicines has not been established.

During therapy with AGGRASTET 0,05 mg/ml, patients should be monitored for potential bleeding. When bleeding cannot be controlled with pressure, infusion of AGGRASTET 0,05 mg/ml and heparin should be discontinued.
When treatment of bleeding is required, discontinuation of AGGRASTET 0,05 mg/ml should be considered. Consideration may also be given to transfusions.

Fatal bleedings have been reported (see section 4.8).

Thrombolytic therapy
There is no therapeutic experience with AGGRASTET 0,05 mg/ml in patients for whom thrombolytic therapy is indicated. Consequently, the use of AGGRASTET 0,05 mg/ml is not recommended in combination with thrombolytic therapy.

AGGRASTET 0,05 mg/ml infusion should be stopped immediately if circumstances arise that necessitate thrombolytic therapy (including acute occlusion during PCI) or if the patient must undergo an emergency coronary artery bypass graft (CABG) operation or requires an intra-aortic balloon pump.

Other precautionary notes and measures
There are insufficient data regarding the re-administration of AGGRASTET 0,05 mg/ml.

Patients should be carefully monitored for bleeding during treatment with AGGRASTET 0,05 mg/ml. If treatment of haemorrhage is necessary, discontinuation of AGGRASTET

0,05 mg/ml should be considered (see section 4.9). In cases of major or uncontrollable bleeding, AGGRASTET 0,05 mg/ml should be discontinued immediately.

AGGRASTET 0,05 mg/ml should be used with caution in patients with:

- recent clinically relevant bleeding (< 1 year);
- puncture of a non-compressible vessel with 24 hours before administration of AGGRASTET 0,05 mg/ml;
- severe acute or chronic heart failure;
- cardiogenic shock;
- mild to moderate liver insufficiency;
- platelet count < 150,000/mm^3, known history of coagulopathy or platelet function disturbance or thrombocytopenia;
- haemoglobin concentration less than 11 g/dl or haematocrit less than 34 %.

Special caution should be used during concurrent administration of ticlopidine, clopidogrel, adenosine, dipyridamole, sulfinpyrazone and prostacyclin.

Impaired renal function

There is evidence that the risk of bleeding increases with decreasing creatinine clearance and hence also reduces plasma clearance of AGGRASTET 0,05 mg/ml. Patients with decreased renal function (creatinine clearance < 60 ml/min) should therefore be carefully monitored for bleeding during treatment with AGGRASTET 0,05 mg/ml and the heparin effect should be carefully monitored. In severe kidney failure (creatinine clearance < 30 ml/min), the AGGRASTET 0,05 mg/ml dosage should be reduced (see section 4.2).

Femoral artery access site

During treatment with AGGRASTET 0,05 mg/ml there is a significant increase 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. Arterial sheaths may be removed when coagulation has returned to normal, e.g. when activated clotting time (ACT) is less than 180 seconds, (usually 2 to 6 hours after discontinuation of heparin). Care should be taken to obtain proper haemostasis after removal of the sheaths followed by close observation.

General nursing care

The number of vascular punctures, and intramuscular injections should be minimised during the treatment with AGGRASTET 0,05 mg/ml. I.V. access should only be obtained at compressible sites of the body. All vascular puncture sites should be documented and closely monitored. The use of urinary catheters, nasotracheal intubation and nasogastric tubes should be critically considered.

Laboratory Monitoring

Platelet counts, haemoglobin and haematocrit levels should be monitored prior to treatment with AGGRASTET 0,05 mg/ml as well as within 2 to 6 hours following the bolus or loading infusion, and at least daily thereafter during therapy with AGGRASTET 0,05 mg/ml (or more frequently if there is evidence of significant decline).

In patients who have previously received GPIIb/IIIa receptor antagonists (cross reactivity can occur), the platelet count should be monitored immediately e.g. within the first hour of administration after re-exposure (see section 4.8).

AGGRASTET 0,05 mg/ml should be used with caution in patients with platelet count less

than 150 000 cells/mm^3 and in patients with haemorrhagic retinopathy.

If the patient experiences a platelet count decrease to less than 90 000 cells/mm^3, additional platelet counts should be performed to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, AGGRASTET 0,05 mg/ml 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 anticoagulant effects of heparin should be carefully monitored by repeated determinations of APTT and the dose should be adjusted accordingly (see section 4.2). Potentially life-threatening bleeding may occur especially when heparin is administered with other products affecting haemostasis, such as GP IIb/IIIa receptor antagonists.

Use in the elderly, female patients and patients with low body weight

In clinical studies the efficacy of AGGRASTET 0,05 mg/ml in the elderly (65 years and older) was comparable to that seen in younger patients (younger than 65 years). Elderly patients and/or female patients receiving AGGRASTET 0,05 mg/ml with heparin or heparin alone had a higher incidence of bleeding complications than younger or male patients, respectively. Patients with a low body weight had a higher incidence of bleeding than patients with a higher body weight. For these reasons AGGRASTET 0,05 mg/ml should be used with caution in these patients and the heparin effect should be carefully monitored. The incremental risk of bleeding in patients treated with AGGRASTET 0,05 mg/ml 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 AGGRASTET 0,05 mg/ml with heparin and the heparin alone groups. No dose adjustment is recommended (see section 4.2).

Paediatric population

There is no therapeutic experience with AGGRASTET 0,05 mg/ml in children, thus, the use of AGGRASTET 0,05 mg/ml is not recommended in these patients.

Excipients

AGGRASTET 0,05 mg/ml contains sodium

AGGRASTET 0,05 mg/ml product contains approximately 40,10 mmol (approximately 992,07 mg) of sodium per 250 ml bag which should be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicines and other forms of interaction

AGGRASTET 0,05 mg/ml has been studied on a background of aspirin and heparin.

The use of AGGRASTET 0,05 mg/ml, in combination with heparin and aspirin (acetylsalicylic acid) (ASA), has been associated with an increase in bleeding and increases the inhibition of platelet aggregation to a greater extent than aspirin alone, as measured by *ex vivo* APD-induced platelet aggregation test compared to heparin and aspirin alone (see section 4.8).

The concomitant administration of AGGRASTET 0,05 mg/ml and unfractionated heparin increases the prolongation of the bleeding time to a greater extent as compared to unfractionated heparin alone.

With the concurrent use of AGGRASTET 0,05 mg/ml, unfractionated heparin, ASA, and clopidogrel there was a comparable incidence of bleeding than when only unfractionated heparin, ASA, and clopidogrel were used together (see sections 4.4 and 4.8).

AGGRASTET 0,05 mg/ml prolonged bleeding time; however, the combined administration of AGGRASTET 0,05 mg/ml and ticlopidine did not additionally affect bleeding time.

Caution should be employed when AGGRASTET 0,05 mg/ml is used with other medicines that affect haemostasis (e.g. warfarin) as concomitant use with AGGRASTET 0,05 mg/ml and heparin is associated with an increased risk of bleeding (see section 4.4).

AGGRASTET 0,05 mg/ml is not recommended in thrombolytic therapy - concurrent or less than 48 hours before administration of AGGRASTET 0,05 mg/ml or concurrent use of medicines 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 AGGRASTET 0,05 mg/ml in these conditions; however, an increased risk of bleeding is suspected.

AGGRASTET 0,05 mg/ml 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 (Platelet Receptor Inhibition for Ischaemic Syndrome Management), the plasma clearance of AGGRASTET 0,05 mg/ml in patients receiving one of the following medicines was compared to that in patients not receiving that medicine.

There were no clinically significant interactions of these medicines on the plasma clearance of tirofiban, as in AGGRASTET 0,05 mg/ml: acebutolol, paracetamol, alprazolam, amlodipine, medicines containing aspirin , 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.

4.6. Fertility, pregnancy, lactation

The safety of AGGRASTET 0,05 mg/ml in pregnancy and lactation has not been established.

Pregnancy

There are no or limited amount of data from the use of AGGRASTET 0,05 mg/ml in pregnant women. AGGRASTET 0,05 mg/ml is not recommended during pregnancy.

Breastfeeding

AGGRASTET 0,05 mg/ml should not be used during lactation.

It is not known whether AGGRASTET 0,05 mg/ml is excreted in human milk.

Fertility

No human fertility data available.

4.7. Effects on ability to drive and use machines

AGGRASTET 0,05 mg/ml has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

a) Summary of the safety profile

Bleeding

The most common adverse event reported during therapy with AGGRASTET 0,05 mg/ml when used concomitantly with heparin, aspirin and other oral anti-platelet medicines, was bleeding (usually reported by the investigators as oozing or mild, or usually involved mild mucocutaneous bleeding or mild catheterization-site bleeding). Gastrointestinal, retro-

peritoneal, intracranial, haemorrhoidal and post-operative bleeding, epidural haematoma in the spinal region, hemopericardium and pulmonary (alveolar) haemorrhage have also been reported. Rates of TIMI major and intracranial bleeding in the pivotal AGGRASTET 0,05 mg/ml studies were < 2,2 % and < 0,1%, respectively. The most serious adverse reaction was fatal bleeding.

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:

	PRISM PLUS† (UAP/Non-Q-Wave MI Study)		**RESTORE† (Angioplasty/Atherectomy Study)**	
Bleeding	**AGGRASTET+ Heparin (n=773) %**	**Heparin (n=797) %**	**AGGRASTET + Heparin (n=1071) %**	**Heparin (n=1 070) %**
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.

‡ Haemoglobin drop of more than 50 g/l with or without an identified site, intracranial haemorrhage, or cardiac tamponade.

§ Haemoglobin drop of more than 30 g/l with bleeding from a known site, spontaneous gross haematuria, hematemesis or haemoptysis.

There were no reports of intracranial bleeding in the PRISM PLUS study for AGGRASTET

0,05 mg/ml 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 AGGRASTET 0,05 mg/ml in combination with heparin and 0,3 % for control group (which received heparin). In the PRISM PLUS Study, the incidences of retroperitoneal bleeding reported for AGGRASTET 0,05 mg/ml 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 AGGRASTET 0,05 mg/ml in combination with heparin, and the control group were 0,6 % and 0,3 %, respectively.

Thrombocytopenia

Patients treated with AGGRASTET 0,05 mg/ml, and heparin, were more likely to experience decreases in platelet counts than the control group. These decreases were reversible upon discontinuation of AGGRASTET 0,05 mg/ml. The percentage of patients with a decrease of platelets to less than 90 000 cells/mm^3 was 1,5 %. The percentage of patients with a decrease of platelets to less than 50 000 cells/mm^3 was 0,3 %. Platelet decreases have been observed in patients with no prior history of thrombocytopenia upon re-administration of GP IIb/IIIa receptor antagonists and may be associated with chills, low-grade fever or bleeding complications.

Non-bleeding-associated side effects

The most frequent non-bleeding side effects reported with AGGRASTET 0,05 mg/ml, administered concomitantly with heparin, occurring at an incidence of more than 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.

Allergic reactions

Severe allergic reactions (e.g., bronchospasm, urticaria) including anaphylactic reactions

have occurred during initial treatment (also on the first day) and during readministration of AGGRASTET 0,05 mg/ml. Some cases have been associated with severe thrombocytopenia (platelet counts < 10,000/mm^3).

b) Tabulated summary of adverse reactions

Very common (greater than or equal to 1/10), common (greater than or equal to 1/100, less than 1/10), uncommon (greater than or equal to 1/1 000, less than 1/100), rare (greater than or equal to 1/10 000, less than 1/1 000), very rare (less than 1/10 000 including isolated cases).

System organ class	**Very common**	**Common**	**Uncommon**	**Not known**
Blood and the lymphatic system disorders				Acute and/or severe (< 20 000/mm^3) decreases in platelet count
Immune system disorders				Severe allergic reactions including anaphylactic reactions
Nervous system disorders	Headache			Intracranial bleeding, spinal epidural haematoma
Cardiac disorders				Hemopericardium
Vascular disorders	Haematoma			
Respiratory , thoracic and mediastinal disorders		Haemoptysis, epistaxis		Pulmonary (alveolar) haemorrhage
Gastrointestinal disorders	Nausea	Oral haemorrhage, gingival haemorrhage	GI haemorrhage, haematemesis	Retroperitoneal bleeding
Skin and subcutaneous tissue disorders	Ecchymosis			
Renal and urinary disorders		Haematuria		

General disorders and administrative site conditions		Fever		
Investigations	Occult blood in stool or urine	Decreases in haematocrit and haemoglobin platelet counts < 90 000/mm^3	Platelet counts < 50 000/mm^3	
Injury and poisoning	Post-operative haemorrhage	Vessel puncture site haemorrhage		

c) Description of selected adverse reactions

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 hypercholesterolaemia.

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 AGGRASTET 0,05 mg/ml with heparin and the heparin alone groups (see above for bleeding adverse events).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

In clinical trials, inadvertent overdosage with tirofiban, as in AGGRASTET 0,05 mg/ml, 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 catheterisation but also single cases of intracranial haemorrhages and retroperitoneal bleedings (see section 4.4).

Treatment

Overdosage of AGGRASTET 0,05 mg/ml should be treated by assessment of the patient's clinical condition and cessation or adjustment of the AGGRASTET 0,05 mg/ml infusion as appropriate. If treatment of haemorrhage is necessary, the AGGRASTET 0,05 mg/ml infusion should be discontinued. Transfusions of blood and/or thrombocytes should also be considered.

AGGRASTET 0,05 mg/ml can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

CATEGORY AND CLASS A 8.2 Medicines acting on blood and haemopoietic system; Anticoagulants

Pharmacotherapeutic group: Blood and blood forming organs – antithrombotic agents – platelet aggregation inhibitors excl. heparin.

ATC Code: B01AC17.

Mechanism of action

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

Tirofiban causes 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 patients and patients with coronary artery disease. The time course of inhibition parallels the plasma concentration profile of the medicine. Following discontinuation of an infusion of tirofiban, platelet function rapidly returns to baseline.

In patients with unstable angina, a two-staged intravenous infusion regimen of AGGRASTET 0,05 mg/ml (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 tirofiban is initiated in the setting of coronary angioplasty, a two-staged intravenous infusion regimen of tirofiban (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 more than

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 tirofiban, platelet function rapidly returns to near baseline in approximately 90 % of patients with coronary artery disease in 4 to 8 hours.

5.2. Pharmacokinetic properties

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 litres. Tirofiban crosses the placenta in rats and rabbits.

Biotransformation

Profiling of ^{14}C-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 ^{14}C-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.

Significant levels of tirofiban are excreted in rat milk. Excretion into milk has not been studied in humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid anhydrous (for pH adjustment), hydrochloric acid (for pH adjustment), sodium chloride, sodium citrate dihydrate (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection.

6.2. Incompatibilities

AGGRASTET 0,05 mg/ml may be administered in the same intravenous line as atropine sulphate, dobutamine, dopamine, epinephrine HCl, furosemide, lidocaine, midazolam HCl, morphine sulphate, nitroglycerin, potassium chloride, propranolol HCl and famotidine injection.

AGGRASTET 0,05 mg/ml should not be administered in the same intravenous line as diazepam.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Protect from light during storage.

Keep in original packaging until required for use

6.5. Nature and contents of the container

250 ml solution is packed in a colourless (non-PVC plastic) container, multilayer polyolefin film with polyolefin injection moulded tubes. The units are packed in a preprinted foil overpouch, in an outer cardboard carton together with a leaflet.

6.6. Special precautions for disposal and other handling

Check for minute leaks by squeezing inner bag firmly.

If leaks are found, discard solution as sterility may be impaired. Do not use unless solution is clear and seal is intact.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

34/8.2/0481

9. DATE OF FIRST AUTHORISATION

07 August 2002

10. DATE OF REVISION OF THE TEXT

23 May 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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