1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

AGGRASTET 0,05 mg/ml (solution for infusion)

COMPOSITION

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

Excipients:

Sodium chloride, water for injection

Sugar free

CATEGORY AND CLASS

A 8.2 Medicines acting on blood and haemopoietic system; Anticoagulants

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 subjects and patients with coronary artery disease. The time course of inhibition parallels the plasma concentration profile of the medicine. 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 AGGRASTET 0,05 mg/ml is initiated in the setting of coronary angioplasty, a two-staged intravenous infusion regimen of AGGRASTET 0,05 mg/ml (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 AGGRASTET 0,05 mg/ml, platelet function rapidly returns to near baseline in approximately 90 % of patients with coronary artery disease in 4 to 8 hours.

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.

Metabolism

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.

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 and is also indicated for 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 DOSAGE AND DIRECTIONS FOR USE).

CONTRAINDICATIONS

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

- Known hypersensitivity to any component of the product;
- active internal 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;
- major surgical procedure or severe physical trauma within the previous month;
- history of stroke within 30 days or any history of haemorrhagic stroke;
- history, symptoms, or findings suggestive of aortic dissection;
- severe hypertension (systolic blood pressure more than 180 mmHg and/or diastolic blood pressure more than 110 mmHg);
- acute pericarditis;
- concomitant use of another parenteral GP IIb/IIIa;
- recent epidural procedure;
- chronic haemodialysis;
- prolonged INR.

Paediatric use

Safety and effectiveness in children have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

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 Thrombolysis in Myocardial Infarction Study group (TIMI). 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 agents 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 SIDE EFFECTS).

Femoral artery access site: AGGRASTET 0,05 mg/ml is associated with minor increases in bleeding rates particularly at the site of arterial access for femoral sheath placement. Care

should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Care should be taken to obtain proper haemostasis after removal of the sheaths followed by close observation.

Laboratory Monitoring:

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

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 DOSAGE AND DIRECTIONS FOR USE). 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

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 receiving AGGRASTET 0,05 mg/ml with heparin or heparin alone had a higher incidence of bleeding complications than younger patients. 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 DOSAGE AND DIRECTIONS FOR USE, Other Patient Populations).

INTERACTIONS

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, has been associated with an increase in bleeding compared to heparin and aspirin alone (see SIDE EFFECTS).

Caution should be employed when AGGRASTET 0,05 mg/ml is used with other medicines that affect haemostasis (e.g. warfarin) (see WARNINGS AND SPECIAL PRECAUTIONS, Bleeding).

AGGRASTET 0,05 mg/ml has been used concomitantly in clinical studies with beta-blockers, calcium channel blockers, non-steroidal anti-inflammatory agents (NSAIDs) and nitrate preparations without evidence of clinically significant adverse interactions.

In a sub-set of patients (n=762) in the PRISM study (Platelet Receptor Inhibition for

Ischaemic Syndrome Management), the plasma clearance of tirofiban 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: acebutolol, paracetamol, alprazolam, amlodipine, aspirin preparations, atenolol, bromazepam, captopril, diazepam, digoxin, diltiazem, docusate sodium, enalapril, furosemide, glyburide, heparin, insulin, isosorbide, levothyroxine, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, omeprazole, oxazepam, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam.

HUMAN REPRODUCTION

Pregnancy

Safety and efficacy in pregnancy and lactation has not been established.

Lactation

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

DOSAGE AND DIRECTIONS FOR USE

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 (ml/hr)	Maintenance Infusion Rate (ml/hr)	30 Min Loading Infusion Rate (ml/hr)	Maintenance Infusion Rate (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.

Other Patient Populations

No dosage adjustment is recommended for elderly patients (see SPECIAL PRECAUTIONS, Use in the Elderly) or female patients.

Directions for use

Parenteral medicine products should be inspected visually for particulate matter and

discolouration prior to use, whenever solution and container permit.

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.

Check the expiry date.

Do not withdraw solution directly from the container with a syringe.

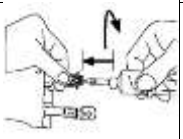
To open: Tear foil over pouch (250 ml Solution for Infusion) at notch and remove inner container. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

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

Do not add supplementary medication 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.

SIDE EFFECTS

Bleeding

The most common adverse event reported during therapy with AGGRASTET 0,05 mg/ml

when used concomitantly with heparin and aspirin, was bleeding (usually reported by the investigators as oozing or mild). The incidences of major and minor bleeding using the TIMI Criteria in the PRISM PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management - Patients Limited by Unstable Signs and Symptoms) and RESTORE (Randomized Efficacy Study of Tirofiban for outcomes and Restenosis) studies are shown below:

	PRISM PLUS† **(UAP/Non-Q-Wave MI Study)**		**RESTORE†** **(Angioplasty/Atherectomy Study)**	
Bleeding	AGGRASTET+ Heparin (n=773) %	Heparin (n=797) %	AGGRASTET+ Heparin (n=1 071) %	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 hematuria, hematemesis or hemoptysis.

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.

Female patients and elderly patients receiving AGGRASTET 0,05 mg/ml with heparin or heparin alone had a higher incidence of bleeding complications than male patients or younger patients, respectively. The incremental risk of bleeding in patients treated with AGGRASTET 0,05 mg/ml in combination with heparin over the risk in patients treated with heparin alone was comparable regardless of age or gender. No dose adjustment is recommended for these populations (see DOSAGE AND DIRECTIONS FOR USE, Other Patient Populations).

Patients treated with AGGRASTET 0,05 mg/ml, with 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.

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.

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).

Nervous system and psychiatric disorders:

Common: Headache

Gastrointestinal disorders:

Common: Nausea

General disorders and administration site conditions:

Common: Fever

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).

The following additional adverse reactions have been reported:

Blood and the lymphatic system disorders:

Intracranial bleeding, retroperitoneal bleeding and haemopericardium. Pulmonary (alveolar) haemorrhage and spinal-epidural haematoma. Fatal bleedings have been reported rarely. Acute and/or severe decreases in platelet counts which may be associated with chills, low-grade fever or bleeding complications (see above).

Immune system disorders:

Severe allergic reactions including anaphylactic reactions. The reported cases have occurred during the first day of AGGRASTET 0,05 mg/ml infusion, during initial treatment, and during re-administration of AGGRASTET 0,05 mg/ml.

Some cases have been associated with severe thrombocytopenia (platelet counts less than 10 000/mm^3).

Investigations:

The most frequently observed laboratory adverse events in patients receiving AGGRASTET 0,05 mg/ml concomitantly with heparin were related to bleeding. Decreases in haemoglobin (2,1 %) and haematocrit (2,2 %) were observed in the group receiving AGGRASTET 0,05 mg/ml compared to 3,1 % and 2,6 %, respectively, in the heparin group. Increases in the presence of urine and faecal occult blood were also observed (10,7 % and 18,3 %, respectively) in the group receiving AGGRASTET 0,05 mg/ml compared to 7,8 % and 12,2 %, respectively, in the heparin group.

Patients treated with AGGRASTET 0,05 mg/ml, with 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 %, compared with 0,6 % in the patients who received heparin alone. The percentage of patients with a decrease of platelets to less than 50 000 cells/mm^3 was 0,3 %, compared with 0,1 % or the patients who received heparin alone.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

In clinical trials, inadvertent overdosage with tirofiban occurred in doses up to 5 times and 2 times the recommended dose for bolus administration and loading infusion, respectively. Inadvertent overdosage occurred in doses up to 9,8 times the 0,15 microgram/kg/min maintenance infusion rate.

The most frequently reported manifestation of overdosage was bleeding, primarily minor mucocutaneous bleeding events and minor bleeding at the sites of cardiac catheterisation (see WARNINGS AND SPECIAL PRECAUTIONS, Bleeding).

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.

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

IDENTIFICATION

Clear, colourless solution essentially free from visible particles.

PRESENTATION

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.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Do not freeze.

Protect from light during storage.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

34/8.2/0481

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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