

1. NAME OF THE MEDICINAL PRODUCT

AGGRASTAT^{®*} 0.25 mg/mg concentrate, concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 0.281 mg of tirofiban hydrochloride monohydrate which is equivalent to 0.25 mg tirofiban

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colorless concentrated solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AGGRASTAT is indicated for the prevention of early myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 12 hours and with ECG changes and/or elevated cardiac enzymes.

Patients most likely to benefit from AGGRASTAT treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early PTCA (see also 4.2 Posology and method of administration and 5.1 Pharmacodynamic properties).

AGGRASTAT is intended for use with acetylsalicylic acid and unfractionated heparin.

4.2 Posology and method of administration

This product is for hospital use only, by specialist physicians experienced in the management of acute coronary syndromes.

AGGRASTAT concentrate for solution for infusion must be diluted before use.

AGGRASTAT is given intravenously at an initial infusion rate of 0.4 microgram/kg/min for 30 minutes. At the end of the initial infusion, AGGRASTAT should be continued at a maintenance infusion rate of 0.1 microgram/kg/min. AGGRASTAT should be given with unfractionated heparin (usually an intravenous bolus of 5000 units (U) simultaneously with the start of AGGRASTAT therapy, then approximately 1000 U per hour, titrated on the basis of the activated thromboplastin time (APTT), which

* in the following AGGRASTAT means AGGRASTAT concentrate for solution for infusion.

should be about twice the normal value) and ASA (see 5.1 Pharmacodynamic properties, PRISM-PLUS study), unless contraindicated.

No dosage adjustment is necessary for the elderly (see also 4.4 Special warnings and special precautions for use).

Patients with severe kidney failure

In severe kidney failure (creatinine clearance < 30 ml/min) the dosage of AGGRASTAT should be reduced by 50 % (see also 4.4 Special warnings and special precautions for use and 5.2 Pharmacokinetic properties).

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

AGGRASTAT Concentrate for Solution for Infusion must first be diluted to the same strength as AGGRASTAT Injection Premixed, as noted under *Instructions for Use*.

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

Start and duration of therapy with AGGRASTAT

AGGRASTAT optimally should be initiated within 12 hours after the last anginal episode. The recommended duration should be at least 48 hours. Infusion of AGGRASTAT and unfractionated heparin

may be continued during coronary angiography and should be maintained for at least 12 hours and not more than 24 hours after angioplasty/atherectomy. Once a patient is clinically stable and no coronary intervention procedure is planned by the treating physician, the infusion should be discontinued. The entire duration of treatment should not exceed 108 hours.

Concurrent therapy (unfractionated heparin, ASA)

Treatment with unfractionated heparin is initiated with an i.v. bolus of 5000 U and then continued with a maintenance infusion of 1000 U per hour. The heparin dosage is titrated to maintain an APTT of approximately twice the normal value.

Unless contraindicated, all patients should receive ASA orally before the start of AGGRASTAT (see 5.1 Pharmacodynamic properties, PRISM-PLUS study). This medication should be continued at least for the duration of the infusion of AGGRASTAT.

If angioplasty (PTCA) is required, heparin should be stopped after PTCA, and the sheaths should be withdrawn once coagulation has returned to normal, e.g., when the activated clotting time (ACT) is less than 180 seconds (usually 2-6 hours after discontinuation of heparin).

Instructions for use

AGGRASTAT Concentrate must be diluted before use:

1. Draw 50 ml from a 250 ml container of sterile 0.9 % saline or 5 % glucose in water and replace with 50 ml AGGRASTAT (from one 50 ml puncture vial) to make up a concentration of 50 microgram/ml. Mix well before use.
2. Use according to the dosage table above.

Where the solution and container permit, parenteral drugs should be inspected for visible particles or discolouration before use.

AGGRASTAT should only be given intravenously and may be administered with unfractionated heparin through the same infusion tube.

It is recommended that AGGRASTAT be administered with a calibrated infusion set using sterile equipment.

Care should be taken to ensure that no prolongation of the infusion of the initial dose occurs and that miscalculation of the infusion rates for the maintenance dose on the basis of the patient's weight is avoided.

4.3 Contraindications

AGGRASTAT is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients of the preparation or who developed thrombocytopenia during earlier use of a GP IIb/IIIa receptor antagonist.

Since inhibition of platelet aggregation increases the bleeding risk, AGGRASTAT is contraindicated in patients with:

- History of stroke within 30 days or any history of haemorrhagic stroke.
- Known history of intracranial disease (e.g. neoplasm, arteriovenous malformation, aneurysm).

- Active or recent (within the previous 30 days of treatment) clinically relevant bleeding (e.g. gastrointestinal bleeding).
- Malignant hypertension.
- Relevant trauma or major surgical intervention within the past six weeks.
- Thrombocytopenia (platelet count < 100,000/mm³), disorders of platelet function.
- Clotting disturbances (e.g. prothrombin time > 1.3 times normal or INR (International Normalised Ratio) > 1.5).
- Severe liver failure.

4.4 Special warnings and special precautions for use

The administration of AGGRASTAT alone without unfractionated heparin is not recommended.

There is limited experience with concomitant administration of AGGRASTAT with enoxaparin (see also 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties). The concomitant administration of AGGRASTAT with enoxaparin is associated with a higher frequency of cutaneous and oral bleeding events, but not in TIMI bleeds**, when compared with the concomitant administration of AGGRASTAT and unfractionated heparin. An increased risk of serious bleeding events associated with the concomitant administration of AGGRASTAT and enoxaparin cannot be excluded, particularly in patients given additional unfractionated heparin in conjunction with angiography and/or PCI. The efficacy of AGGRASTAT in combination with enoxaparin has not been established. The safety and efficacy of AGGRASTAT with other low molecular weight heparins has not been investigated.

There is insufficient experience with the use of tirofiban hydrochloride in the following diseases and conditions, however, an increased risk of bleeding is suspected. Therefore, tirofiban hydrochloride is not recommended in:

- Traumatic or protracted cardiopulmonary resuscitation, organ biopsy or lithotripsy within the past 2 weeks
- Severe trauma or major surgery > 6 weeks but < 3 months previously
- Active peptic ulcer within the past 3 months
- Uncontrolled hypertension (> 180/110 mm Hg)
- Acute pericarditis
- Active or a known history of vasculitis
- Suspected aortic dissection
- Haemorrhagic retinopathy
- Occult blood in the stool or haematuria
- Thrombolytic therapy (see 4.5 Interaction with other medicinal products and other forms of interaction)

** 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, hematemesis, or hemoptysis. TIMI “loss no site” is defined as a haemoglobin drop > 40 g/l but < 50 g/l without an identified bleeding site.

- Concurrent use of drugs that increase the risk of bleeding to a relevant degree (see 4.5 Interaction with other medicinal products and other forms of interaction)

There is no therapeutic experience with tirofiban hydrochloride in patients for whom thrombolytic therapy is indicated (e.g. acute transmural myocardial infarction with new pathological Q-waves or elevated ST-segments or left bundle-branch block in the ECG). Consequently, the use of tirofiban hydrochloride is not recommended in these circumstances.

AGGRASTAT infusion should be stopped immediately if circumstances arise that necessitate thrombolytic therapy (including acute occlusion during PTCA) or if the patient must undergo an emergency coronary artery bypass graft (CABG) operation or requires an intra-aortic balloon pump.

There are limited efficacy data in patients immediately undergoing PTCA.

There is no therapeutic experience with AGGRASTAT in children, thus, the use of AGGRASTAT is not recommended in these patients.

Other precautionary notes and measures

There are insufficient data regarding the re-administration of AGGRASTAT.

Patients should be carefully monitored for bleeding during treatment with AGGRASTAT. If treatment of haemorrhage is necessary, discontinuation of AGGRASTAT should be considered (see also 4.9 Overdose). In cases of major or uncontrollable bleeding, tirofiban hydrochloride should be discontinued immediately.

AGGRASTAT should be used with special caution in the following conditions and patient groups:

- Recent clinically relevant bleeding (less than one year)
- Puncture of a non-compressible vessel within 24 hours before administration of AGGRASTAT
- Recent epidural procedure (including lumbar puncture and spinal anaesthesia)
- Severe acute or chronic heart failure
- Cardiogenic shock
- Mild to moderate liver insufficiency
- Platelet count $< 150,000/\text{mm}^3$, known history of coagulopathy or platelet function disturbance or thrombocytopenia
- Haemoglobin concentration less than 11 g/dl or haematocrit $< 34 \%$

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

Elderly patients, female patients, and patients with low body weight

Elderly and/or female patients 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 AGGRASTAT should be used with caution in these patients and the heparin effect should be carefully monitored.

Impaired Renal Function

There is evidence from clinical studies that the risk of bleeding increases with decreasing creatinine clearance and hence also reduced plasma clearance of tirofiban. Patients with decreased renal function (creatinine clearance $< 60 \text{ ml/min}$) should therefore be carefully monitored for bleeding during treatment

with AGGRASTAT and the heparin effect should be carefully monitored. In severe kidney failure the AGGRASTAT dosage should be reduced (see also 4.2 Posology and method of administration).

Femoral artery line

During treatment with AGGRASTAT there is a significant increase in bleeding rates, especially in the femoral artery area, where the catheter sheath is introduced. Care should be taken to ensure that only the anterior wall of the femoral artery is punctured. Arterial sheaths may be removed when coagulation has returned to normal, e.g., when activated clotting time (ACT) is less than 180 seconds, (usually 2–6 hours after discontinuation of heparin).

After removal of the introducer sheath, careful haemostasis should be ensured under close observation.

General nursing care

The number of vascular punctures and intramuscular injections should be minimised during the treatment with AGGRASTAT. 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.

Monitoring of laboratory values

Platelet count, haemoglobin and haematocrit levels should be determined before treatment with AGGRASTAT as well as within 2-6 hours after start of therapy with AGGRASTAT and at least once daily thereafter while on therapy (or more often if there is evidence of a marked decrease). In patients who have previously received GP IIb/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 also 4.8 Undesirable effects). If the platelet count falls below 90,000/mm³, further platelet counts should be carried out in order to rule out pseudothrombocytopenia. If thrombocytopenia is confirmed, AGGRASTAT and heparin should be discontinued. Patients should be monitored for bleeding and treated if necessary (see also 4.9 Overdose).

In addition, activated 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 4.2 Posology and method of administration). Potentially life-threatening bleeding may occur especially when heparin is administered with other products affecting haemostasis, such as GP IIb/IIIa receptor antagonists.

4.5 Interaction with other medicinal products and other forms of interaction

The use of several platelet aggregation inhibitors increases the risk of bleeding, likewise their combination with heparin, warfarin and thrombolytics. Clinical and biological parameters of haemostasis should be regularly monitored.

The concomitant administration of AGGRASTAT and ASA (acetylsalicylic acid or aspirin) increases the inhibition of platelet aggregation to a greater extent than aspirin alone, as measured by the *ex vivo* ADP-induced platelet aggregation test. The concomitant administration of AGGRASTAT 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 AGGRASTAT and unfractionated heparin and ASA there was a higher incidence of bleeding than when only unfractionated heparin and ASA were used together (see also 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

AGGRASTAT prolonged bleeding time, however, the combined administration of AGGRASTAT and ticlopidine did not additionally affect bleeding time.

Concomitant use of warfarin with AGGRASTAT plus heparin was associated with an increased risk of bleeding.

AGGRASTAT is not recommended in thrombolytic therapy - concurrent or less than 48 hours before administration of tirofiban hydrochloride 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 tirofiban hydrochloride in these conditions; however, an increased risk of bleeding is suspected.

4.6 Pregnancy and lactation

Pregnancy

For tirofiban hydrochloride, no clinical data on exposed pregnancies are available. Animal studies provide limited information with respect to effects on pregnancy, embryonal/fetal development, parturition, and postnatal development. AGGRASTAT should not be used during pregnancy unless clearly necessary.

Lactation

It is not known whether AGGRASTAT is excreted in human milk but it is known to be excreted in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

No data are available on whether AGGRASTAT impairs the ability to drive or operate machinery.

4.8 Undesirable effects

Bleeding

The adverse event causally related to AGGRASTAT therapy (used concurrently with unfractionated heparin and ASA) most commonly reported was bleeding, which was usually of a milder nature.

In the PRISM-PLUS study, the overall incidence of major bleeding using the TIMI criteria (defined as a haemoglobin drop of >50 g/l with or without an identified site, intracranial haemorrhage, or cardiac tamponade) in patients treated with AGGRASTAT in combination with heparin was not significantly higher than in the control group. The incidence of major bleeding using the TIMI criteria was 1.4 % for AGGRASTAT in combination with heparin and 0.8 % for the control group (which received heparin). The incidence of minor bleeding using the TIMI criteria (defined as a haemoglobin drop of > 30 g/l with bleeding from a known site, spontaneous gross haematuria, haematemesis or haemoptysis) was 10.5 % for AGGRASTAT in combination with heparin and 8.0 % for the control group. There were no reports of intracranial bleeding for AGGRASTAT in combination with heparin or in the control group. The incidence of retroperitoneal bleeding reported for AGGRASTAT in combination with heparin was 0.0 % and 0.1 % for the control group. The percentage of patients who received a transfusion (including packed red blood cells, fresh frozen plasma, whole blood cryoprecipitates and platelets) was 4.0 % for AGGRASTAT and 2.8 % for the control group.

AGGRASTAT given with unfractionated heparin and ASA was associated with gastrointestinal, haemorrhoidal and postoperative bleeding, epistaxis, gum bleeds and surface dermatorrhagia as well as

oozing haemorrhage (haematoma) in the area of intravascular puncture sites (e.g. in cardiac catheter examinations) significantly more often than was unfractionated heparin and ASA alone.

Non-bleeding-associated adverse reactions

The most common adverse drug reactions (incidence over 1 %) associated with AGGRASTAT given concurrently with heparin, apart from bleeding, were nausea (1.7 %), fever (1.5 %) and headache (1.1 %); nausea, fever and headache occurred with incidences of 1.4 %, 1.1 % and 1.2 %, respectively, in the control group.

The incidence of adverse non-bleeding-related events was higher in women (compared to men) and older patients (compared to younger patients). However, the incidences of non-bleeding-related adverse events in these patients were comparable for the “AGGRASTAT with heparin” group and the “heparin alone” group.

[Common: (>1/100, <1/10)]

Nervous system and psychiatric disorders:

Common: headache

Gastrointestinal disorders:

Common: nausea

General disorders and administration site conditions:

Common: fever

Investigations

The most common changes of laboratory parameters associated with AGGRASTAT related to bleeding: reduction of haemoglobin and haematocrit levels and an increased occurrence of occult blood in urine and faeces.

Occasionally during AGGRASTAT therapy an acute fall in the platelet count or thrombocytopenia occurred. The percentage of patients in whom the platelet count fell to below 90,000/mm³ was 1.5 %. The percentage of patients in whom the platelet count fell to less than 50,000/mm³ was 0.3 %. These decreases were reversible upon discontinuation of AGGRASTAT. Acute and severe platelet decreases have been observed in patients with no prior history of thrombocytopenia upon readministration of GP IIb/IIIa receptor antagonists.

The following additional adverse reactions have been reported infrequently in post-marketing experience; they are derived from spontaneous reports for which precise incidences cannot be determined:

Blood and lymphatic system disorders:

Intracranial bleeding, retroperitoneal bleeding, haemopericardium, pulmonary (alveolar) haemorrhage, and epidural haematoma in the spinal region. Fatal bleedings have been reported rarely.

Acute and/or severe (< 20,000/mm³) decreases in platelet counts which may be associated with chills, low-grade fever or bleeding complications (see Investigations above).

Immune system disorders:

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

cases have occurred during initial treatment (also on the first day) and during readministration of tirofiban. Some cases have been associated with severe thrombocytopenia (platelet counts $<10,000/\text{mm}^3$).

4.9 Overdose

Inadvertent overdosage with tirofiban hydrochloride occurred in the clinical studies, up to 50 microgram/kg as a 3 minute bolus or 1.2 microgram/kg/min as an initial infusion. Overdosage with up to 1.47 microgram/kg/min as a maintenance infusion rate has also occurred.

a) Symptoms of overdosage

The symptom of overdosage most commonly reported was bleeding, usually mucosal bleeding and localised bleeding at the arterial puncture site for cardiac catheterisation but also single cases of intracranial haemorrhages and retroperitoneal bleedings (see also 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties, PRISM-PLUS study).

b) Measures

Overdosage with tirofiban hydrochloride 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: B01A C17

Tirofiban hydrochloride is a nonpeptidal antagonist of the GP IIb/IIIa receptor, an important platelet surface receptor involved in platelet aggregation. Tirofiban hydrochloride prevents fibrinogen from binding to the GP IIb/IIIa receptor, thus blocking platelet aggregation.

Tirofiban hydrochloride leads to inhibition of platelet function, evidenced by its ability to inhibit *ex vivo* ADP-induced platelet aggregation and to prolong bleeding time (BT). Platelet function returns to baseline within 8 hours after discontinuation.

The extent of this inhibition runs parallel to the tirofiban hydrochloride plasma concentration.

In the target population the recommended dosage of AGGRASTAT, in the presence of unfractionated heparin and ASA, produced a more than 70 % (median 89 %) inhibition of *ex vivo* ADP-induced platelet aggregation in 93 % of the patients, and a prolongation of the bleeding time by a factor of 2.9 during infusion. Inhibition was achieved rapidly with the 30-minute loading infusion and was maintained over the duration of the infusion.

PRISM-PLUS study

The double-blind, multicentre, controlled PRISM-PLUS study compared the efficacy of tirofiban and unfractionated heparin (n=773) versus unfractionated heparin (n=797) in patients with unstable angina or acute non-Q-wave myocardial infarction (NQWMI).

Patients had to have prolonged, repetitive anginal pain, or postinfarction angina within 12 hours prior to randomisation, accompanied by new transient or persistent ST-T wave changes (ST depression or elevation ≥ 0.1 mV; T-wave inversions ≥ 0.3 mV) or elevated cardiac enzymes (total CPK ≥ 2 times upper limit of normal, or CK-MB fraction elevated at the time of enrollment [> 5 % or greater than upper limit of normal]).

In this study, patients were randomised to

- either AGGRASTAT (30 minute loading infusion of 0.4 microgram/kg/min followed by a maintenance infusion of 0.10 microgram/kg/min) and heparin (bolus of 5,000 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 ASA unless contraindicated; 300-325 mg orally per day were recommended for the first 48 hours and thereafter 80-325 mg orally per day (as determined by the physician). Study drug was initiated within 12 hours after the last anginal episode. Patients were treated for 48 hours, after which they underwent angiography and possibly angioplasty/atherectomy, if indicated, while tirofiban hydrochloride was continued. Tirofiban hydrochloride was infused for a mean period of 71.3 hours.

The combined primary study endpoint was the occurrence of refractory ischaemia, myocardial infarction or death at 7 days after the start of tirofiban hydrochloride.

The mean age of the population was 63 years; 32 % of patients were female. At baseline approximately 58 % of patients had ST segment depression; 53 % had T-wave inversions; 46 % of patients presented with elevated cardiac enzymes. During the study approximately 90 % of patients underwent coronary angiography; 30 % underwent early angioplasty and 23 % underwent early coronary artery bypass surgery.

At the primary endpoint, there was a 32 % risk reduction (RR) (12.9 % vs. 17.9 %) in the tirofiban hydrochloride group for the combined endpoint ($p=0.004$): this represents approximately 50 events avoided for 1,000 patients treated. Results of the primary endpoint were principally attributed to the occurrence of myocardial infarction and refractory ischaemic conditions.

After 30 days the RR for the combined endpoint (death/myocardial infarction/refractory ischaemic conditions/readmissions for unstable angina) was 22 % (18.5 % vs. 22.3 %; $p=0.029$).

After 6 months the risk of the combined endpoint (death/myocardial infarction/refractory ischaemic conditions/readmissions for unstable angina) was reduced by 19 % (27.7 % vs. 32.1 %; $p=0.024$).

Regarding the most commonly used double combined endpoint, death or myocardial infarction, the results at 7 days, 30 days and 6 months were as follows: at 7 days for the tirofiban group there was a 43 % RR (4.9 % vs. 8.3 %; $p=0.006$); at 30 days the RR was 30 % (8.7 % vs. 11.9 %; $p=0.027$) and at 6 months the RR was 23 % (12.3 % vs. 15.3 %; $p=0.063$).

The reduction in the incidence of myocardial infarctions in patients receiving AGGRASTAT appeared early during treatment (within the first 48 hours) and this reduction was maintained through 6 months, without significant effect on mortality.

In the 30 % of patients who underwent angioplasty/atherectomy during initial hospitalisation, there was a 46 % RR (8.8 % vs. 15.2 %) for the primary combined endpoint at 30 days as well as a 43 % RR (5.9 % vs. 10.2 %) for “myocardial infarction or death”.

Based on a safety study, the concomitant administration of AGGRASTAT with enoxaparin ($n=315$) was compared to the concomitant administration of AGGRASTAT with unfractionated heparin ($n=210$) in patients presenting with unstable angina and non-Q wave myocardial infarction. A 30 minute loading dose of tirofiban (0.4 microgram/kg/min) was followed by a maintenance infusion of 0.1 microgram/kg/min for up to 108 hours. Patients randomized to the enoxaparin group received a 1.0 mg/kg subcutaneous injection of enoxaparin every 12 hours for a period of at least 24 hours and a maximum duration of 96 hours. Patients randomized to the unfractionated heparin group received a 5000-unit intravenous bolus of

unfractionated heparin followed by a maintenance infusion of 1000 units per hour for at least 24 hours and a maximum duration of 108 hours. The total TIMI bleed rate was 3.5% for the tirofiban/enoxaparin group and 4.8% for the tirofiban/unfractionated heparin group. Cutaneous bleeds and oral bleeds occurred significantly more frequently in patients randomized to the enoxaparin group versus the unfractionated heparin group. Catheter site bleeds were more common in the enoxaparin group as compared to the unfractionated heparin group. Patients randomized to the enoxaparin group who subsequently required PCI were switched to unfractionated heparin periprocedurally with the dose titrated to maintain an ACT of 250 seconds or higher. Although there was a significant difference in the rates of cutaneous bleeds between the two groups (29.2% in the enoxaparin converted to unfractionated heparin group and 15.2% in the unfractionated heparin group), there were no TIMI major bleeds (see also 4.4 Special warnings and special precautions for use) in either group. The efficacy of AGGRASTAT in combination with enoxaparin has not been established.

Patients most likely to benefit from AGGRASTAT treatment are those at high risk of developing myocardial infarction within the 3-4 days after onset of acute angina symptoms. According to epidemiological findings, a higher incidence of cardiovascular events has been associated with certain indicators, for instance: age, elevated heart rate or blood pressure, persistent or recurrent ischaemic cardiac pain, marked ECG changes (in particular ST-segment abnormalities), raised cardiac enzymes or markers (e.g. CK-MB, troponins) and heart failure.

5.2 Pharmacokinetic properties

Distribution

Tirofiban is not strongly bound to plasma protein, and protein binding is concentration-independent in the range of 0.01–25 microgram/ml. The unbound fraction in human plasma is 35 %.

The distribution volume of tirofiban in the steady state is about 30 litres.

Biotransformation

Experiments with ¹⁴C-labeled tirofiban showed the radioactivity in urine and faeces to be emitted chiefly by unchanged tirofiban. The radioactivity in circulating plasma originates mainly from unchanged tirofiban (up to 10 hours after administration). These data suggested limited metabolisation of tirofiban.

Elimination

After intravenous administration of ¹⁴C-labeled tirofiban to healthy subjects, 66 % of the radioactivity was recovered in the urine, 23 % in the faeces. The total recovery of radioactivity was 91 %. Renal and biliary excretion contribute significantly to the elimination of tirofiban.

In healthy subjects the plasma clearance of tirofiban is about 250 ml/min. Renal clearance is 39–69 % of plasma clearance. The half-life is about 1.5 hours.

Gender

The plasma clearance of tirofiban in patients with coronary heart disease is similar in men and women.

Elderly patients

The plasma clearance of tirofiban is about 25 % less in elderly (> 65 years) patients with coronary heart disease in comparison to younger (≤ 65 years) patients.

Ethnic groups

No difference was found in the plasma clearance between patients of different ethnic groups.

Coronary Artery Disease

In patients with unstable angina pectoris or NQWMI the plasma clearance was about 200 ml/min, the renal clearance 39 % of the plasma clearance. The half-life is about 2 hours.

Impaired renal function

In clinical studies patients with decreased renal function showed a reduced plasma clearance of tirofiban depending on the degree of impairment of creatinine clearance. In patients with a creatinine clearance of less than 30 ml/min, including haemodialysis patients, the plasma clearance of tirofiban is reduced to a clinically relevant extent (over 50 %) (see also 4.2 Posology and method of administration). Tirofiban is removed by haemodialysis.

Liver failure

There is no evidence of a clinically significant reduction of the plasma clearance of tirofiban in patients with mild to moderate liver failure. No data are available on patients with severe liver failure.

Effects of other drugs

The plasma clearance of tirofiban in patients receiving one of the following drugs was compared to that in patients not receiving that drug in a sub-set of patients (n=762) in the PRISM study. There were no substantial (> 15 %) effects of these drugs on the plasma clearance of tirofiban: acebutolol, paracetamol, alprazolam, amlodipine, aspirin preparations, atenolol, bromazepam, captopril, diazepam, digoxin, diltiazem, docusate sodium, enalapril, furosemide, glibenclamide, unfractionated heparin, insulin, isosorbide, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, oxazepam, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam.

The pharmacokinetics and pharmacodynamics of AGGRASTAT were investigated when concomitantly administered with enoxaparin (1 mg/kg subcutaneously every 12 hours) and compared with the combination of AGGRASTAT and unfractionated heparin. There was no difference in the clearance of AGGRASTAT between the two groups.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Tirofiban crosses the placenta in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium citrate dihydrate, citric acid anhydrous, water for injections, hydrochloric acid and/or sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

Incompatibility has been found with diazepam. Therefore, AGGRASTAT and diazepam should not be administered in the same intravenous line.

6.3 Shelf life

3 years.

From a microbiological point of view the diluted solution for infusion should be used immediately. If not used immediately, in use storage conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

Do not freeze. Keep container in outer carton to protect from light.

6.5 Nature and contents of container

50 ml Type I glass vial

6.6 Instructions for use and handling

No incompatibilities have been found with AGGRASTAT and the following intravenous formulations: atropine sulfate, dobutamine, dopamine, epinephrine HCl, furosemide, heparin, lidocaine, midazolam HCl, morphine sulfate, nitroglycerin, potassium chloride, propranolol HCl, and famotidine injection.

AGGRASTAT concentrate for solution for infusion must be diluted before use. See 4.2 Posology and method of administration.

Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Haarlem

8. MARKETING AUTHORISATION NUMBER

Entered in the register under RVG23380.

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

7 July 1999/14 May 2003

10. DATE OF REVISION OF THE TEXT

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