AGGRASTAT®

Tirofiban hydrochloride
Concentrate solution for I.V. infusion equivalent to 0.25 mg/mL Tirofiban base.

1. NAME OF THE MEDICINAL PRODUCT
AGGRASTAT®* concentrate solution for I V. infusion equivalent to 0 25 mg/mL Tirofiban base

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 mL of concentrate solution for I.V. infusion contains 0.281 mg of tirofiban hydrochloride monohydrate which is equivalent to 0.25 mg tirofiban.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate solution for I.V. infusion (50 ml vial).
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 section 4.2 and 5.1).
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 must be diluted before use.

• Posology
In patients who are managed with an early invasive strategy for NSTE-ACS and not planned to undergo angiography for at least 4 hours and up to 48 hours after diagnosis, 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 should be about twice the normal value), and oral antiplatelet therapy, including but not limited to acetylsalicylic acid (ASA) (see section 5.1), unless contraindicated.

Patients undergoing PCI demonstrated clinical efficacy with treatment with AGGRASTAT utilizing an initial bolus of 25 microgram/kg given over a 3 minute period, followed by a continuous infusion at a rate of 0.15 microgram/kg/min for 18-24, and up to 48 hours. AGGRASTAT should be administered with unfractionated heparin and oral antiplatelet therapy, including but not limited to ASA (see section 5.1), unless contra-indicated

No dosage adjustment is necessary for the elderly (see section 4.4).

• Patients with severe kidney failure:
In severe kidney failure (creatinine clearance <30 mL/min) the dosage of AGGRASTAT should be reduced by 50% (see sections 4.4 and 5.2).

• Pediatric population
The safety and efficacy of Aggrastat in children have not been established.
No data are available.

The following table is provided as a guide to dosage adjustment by weight
AGGRASTAT Concentrate must first be diluted to the same strength as AGGRASTAT Solntion as noted under Instructions for Use.

Patient Weight (kg)	0.4 microgram/kg/min Loading Dose Regimen Most Patients		0.4 microgram/kg/min Loading Dose Regimen Severe Renal Insufficiency		25 microgram/kg Dose Bolus Regimen Most Patients		25 microgram/kg Dose Bolus Regimen Severe Renal Insufficiency	
	30 Min Loading Infusion Rate (mL/hr)	Maintenance Infusion Rate (mL/hr)	30 Min Loading Infusion Rate (mL/hr)	Maintenance Infusion Rate (mL/hr)	Bolus (ml)	Maintenance Infusion Rate (mL/hr)	Bolus (ml)	Maintenance Infusion Rate (mL/hr)
30 37	16	4	8	2	17	6	8	3
38-45	20	5	10	3	21	7	10	4
46-54	24	6	12	3	25	9	13	5
55-62	28	7	14	4	29	11	15	5
63-70	32	8	16	4	33	12	17	6
71-79	36	9	18	5	38	14	19	7
80-87	40	10	20	5	42	15	21	8
88-95	44	11	22	6	46	16	23	8
96-104	48	12	24	6	50	18	25	9
105-112	52	13	26	7	54	20	27	10
113-120	56	14	28	7	58	21	29	10
121-128	60	15	30	8	62	22	31	11
129-137	64	16	32	8	67	24	33	12
138-145	68	17	34	9	71	25	35	13
146-153	72	18	36	9	75	27	37	13

• Start and duration of therapy with AGGRASTAT:
In patients who are managed with an early invasive strategy for NSTE-ACS and not planned to undergo angiography for at least 4 hours and up to 48 hours after diagnosis, the AGGRASTAT 0.4 microgram/kg/min loading dose regimen should be initiated upon diagnosis. 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.
If the patient diagnosed with NSTE ACS and managed with an invasive strategy undergoes angiography within 4 hours after the diagnosis, the AGGRASTAT 25 microgram/kg dose bolus regimen should be initiated at the start of PCI with the infusion continued for 18-24 hours and up to 48 hours.

• Concurrent therapy (unfractionated heparin, oral antiplatelet therapy):
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 oral antiplatelet agents, including but not limited to ASA, before the start of AGGRASTAT (see section 5.1). 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).

• Method of administration
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/mm^3), 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 sections 5.1 and 5.2). 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 mmHg); Acute pericarditis; Active or a known history of vasculitis; Suspected aortic dissection; Haemorrhagic retinopathy; Occult blood in the stool or haematuria; Thrombolytic therapy (see section 4.5); Concurrent use of drugs that increase the risk of bleeding to a relevant degree (see section 4.5).
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.

• Pediatric population
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 section 4.9). 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/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.

• Efficacy with regard to dose
The administration of a 10 microgram/kg bolus regimen of tirofiban failed to show noninferiority in clinically relevant endpoints at 30 days compared to abciximab (see section 5.1)

• 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 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 section 4.2).

• 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 section 4.8). If the platelet count falls below 90,000/mm^3, 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 section 4.9).
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 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.

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 increases the inhibition of platelet aggregation to a greater extent than ASA 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, 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).
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 Fertility, 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.

• Breastfeeding: 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.

• Fertility: Fertility and reproductive performance were not affected in studies with male and female rats treated with different doses of tirofiban hydrochloride (see section 5.3)
However, animal studies are insufficient to draw conclusions with respect to reproductive toxicity in humans.

4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
Table 1 lists the adverse reactions based on experience from clinical studies as well as adverse reactions reported from post-marketing experience. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Because post-marketing events are derived from spontaneous reports from a population of uncertain size, it is not possible to determine their exact incidence. Therefore, the frequency of these adverse reactions is categorised as not known.

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders				Acute and/or severe (<20,000/mm^3) decreases in platelet counts
Immune System Disorders				Severe allergic reactions including anaphylactic reactions.
Nervous system disorders				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 administration site conditions		Fever		
Injury, poisoning and procedural complications	Post-operative haemorrhage*	Vessel puncture site haemorrhage		
Investigations	Occultblood in stool or urine	Decreases in haematocrit and haemoglobin, PLC <90,000/mm^3	PLC <50,000/mm^3	

*Primarily related to catheterization sites.

Experience in clinical studies
• Bleeding: The adverse event causally related to AGGRASTAT therapy (used concurrently with unfractionated heparin, ASA, and oral antiplatelet therapy) most commonly reported was bleeding, which was usually of a milder nature.
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 unfractionated heparin and ASA alone.
With the 0.4 microgram/kg/min infusion regimen, the rate of major bleeding complications is low and not significantly increased. In the PRISM-PLUS study, the incidence of TIMI major bleeding was 1.4% for AGGRASTAT in combination with heparin and 0.8% for heparin alone. The incidence of TIMI minor bleeding was 10.5% for AGGRASTAT in combination with heparin and 8.0% for heparin alone. The percentage of patients who received a transfusion was 4.0% for AGGRASTAT in combination with heparin and 2.8% for heparin alone.
With the AGGRASTAT 25 microgram/kg dose bolus regimen, data from the ADVANCE study suggest that the number of bleeding events is low and does not seem to be significantly increased compared to placebo. There were no TIMI major bleedings and no transfusions in either group. TIMI minor bleeding with the AGGRASTAT 25 microgram/kg dose bolus regimen was 4% as compared with 1% in the placebo arm (p=0.19). There were no cases of severe thrombocytopenia and the rate of mild thrombocytopenia was 1% with the tirofiban 25 microgram/kg dose bolus regimen and 1% with placebo. Compared with abciximab, various studies involving over 1200 patients showed comparable bleeding incidences ranging from 0% to 0.5% with AGGRASTAT vs. 0% to 3.2% for abciximab for TIMI major bleedings, and no incidence of thrombocytopenia.

• 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.

• 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. During AGGRASTAT therapy acute decreases in platelet count or thrombocytopenia occurred more frequently than in the placebo group. The percentage of patients in whom the platelet count fell to below 90,000/mm^3 was 1.5%. The percentage of patients in whom the platelet count fell to less than 50,000/mm^3 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.

Experience in post-marketing
The following additional adverse reactions have been reported infrequently in postmarketing 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/mm^3) 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 re-administration of tirofiban. Some cases have been associated with severe thrombocytopenia (platelet counts < 10,000/mm^3).

4.9 Overdose
Inadvertent overdose 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. Overdose with up to 1.47 microgram/kg/min as a maintenance infusion rate has also occurred.
a) Symptoms of overdose: The symptom of overdose 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 sections 4.4 and 5.1).
b) Measures: Overdose 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
Pharmacotherapeutic group: Blood and blood forming organs – antithrombotic agents antithrombotic agents -- Platelet aggregation inhibitors excl. heparin
ATC-Code: B01A C17
Tirofiban hydrochloride (tirofiban) is a nonpeptidal antagonist of the GP IIb/IIIa receptor, an important platelet surface receptor involved in platelet aggregation. Tirofiban prevents fibrinogen from binding to the GP IIb/IIIa receptor, thus blocking platelet aggregation.
Tirofiban 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 plasma concentration.
In the 0.4 microgram/kg/min infusion regimen of AGGRASTAT, in the presence of unfractionated heparin and ASA, AGGRASTAT 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.
The AGGRASTAT 25 microgram/kg dose bolus regimen (followed by 18-24 hour maintenance infusion of 0.15 microgram/kg/min), in the presence of unfractionated heparin and oral antiplatelet therapy, produced an average ADP-induced inhibition of maximal aggregation 15 to 60 minutes after onset of treatment of 92% to 95% as measured with light transmission aggregometry (LTA)

PRISM-PLUS study
The double-blind, multicentre, controlled PRISM-PLUS study compared the efficacy of AGGRASTAT and unfractionated heparin (n=773) versus unfractionated heparin (n=797) in patients with unstable angina (UA) or acute non-Q-wave myocardial infarction (NQWMI) with prolonged repetitive anginal pain or post infarction angina, accompanied by new transient or persistent ST-T wave changes or elevated cardiac enzymes.
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]).
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

All patients received ASA unless contraindicated. 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 AGGRASTAT was continued. AGGRASTAT 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 AGGRASTAT.
At 7 days, the primary endpoint, there was a 32% risk reduction (RR) (12.9% vs. 17.9%) in the AGGRASTAT group for the combined endpoint (p=0.004): this represents approximately 50 events avoided for 1,000 patients treated. After 30 days the RR for the composite endpoint of death, MI, refractory ischaemic conditions, or readmissions for UA was 22% (18.5% vs. 22.3%; p=0.029). After 6 months the relative risk of the composite of death, MI, refractory ischaemic conditions, or readmissions for UA was reduced by 19% (27.7% vs. 32.1%; p 0.024). Regarding the composite of death or MI, at 7 days for the AGGRASTAT 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 of MI in patients receiving AGGRASTAT appeared early during treatment (within the first 48 hours) and was maintained through 6 months.
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 composite endpoint at 30 days as well as a 43% RR (5.9% vs. 10.2%) for death or MI.

Based on a safety study, the concomitant administration of AGGRASTAT (30 minute loading dose of 0.4 microgram/kg/min followed by a maintenance infusion of 0.1 microgram/kg/min for up to 108 hours) with enoxaparin (n=315) was compared to the concomitant administration of AGGRASTAT with unfractionated heparin (n 210) in patients presenting with UA and NQWMI. Patients in the enoxaparin group received a 1.0 milligram/kg subcutaneous injection every 12 hours for a period of at least 24 hours and a maximum duration of 96 hours. Patients randomized to unfractionated heparin received a 5000-unit intravenous bolus 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 AGGRASTAT/enoxaparin group and 4.8% for the AGGRASTAT/unfractionated heparin group. 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 section 4.4) in either group. The efficacy of AGGRASTAT in combination with enoxaparin has not been established.

ADVANCE study
The ADVANCE study determined the safety and efficacy of the AGGRASTAT 25 microgram/kg dose bolus regimen as compared with placebo in patients undergoing elective or urgent PCI who exhibit high-risk characteristics including the presence of at least one coronary narrowing ≥70% and diabetes, need for multi-vessel intervention, or NSTE-ACS. All patients received unfractionated heparin, acetylsalicylic acid (ASA) and a thienopyridine loading dose followed by maintenance therapy. A total of 202 patients were randomised to either AGGRASTAT (25 microgram/kg bolus IV over 3 minutes followed by a continuous IV infusion of 0.15 microgram/kg/minute for 24-48 hours) or Placebo given immediately before PCI.
The primary endpoint was a composite of death, nonfatal MI, urgent target vessel revascularization (uTVR), or thrombotic bailout GP IIb/IIIa inhibitor therapy within a median follow-up of 180 days after the index procedure. The safety endpoints of major and minor bleeding were defined according to the TIMI criteria.
In the intent to-treat population, the cumulative incidence of the primary end point was 35% and 20% in placebo and AGGRASTAT groups, respectively (hazard ratio [HR] 0.51 [95% confidence interval (CI), 0.29 to 0.88]; p=0.01). As compared with placebo, there was a significant reduction in the composite of death, MI, or u TVR in the AGGRASTAT group ([31% vs. 20%, HR 0.57, 95% CI, 0.99--0.33]; p=0.048).

EVEREST study
The randomised open-label EVEREST trial compared the upstream 0.4 microgram/kg/min loading dose regimen initiated in the coronary care unit with the AGGRASTAT 25 microgram/kg dose bolus regimen or abciximab 0.25 milligram/kg initiated 10 minutes prior to PCI. All patients additionally received ASA and a thienopyridine. The 93 enrolled NSTE-ACS patients underwent angiography and PCI as appropriate, within 24-48 hours of admission.
With respect to the primary endpoints of tissue level perfusion and troponin I release, the results of EVEREST determined significantly lower rates of post-PCI TMPG 0/1 (6.2% vs. 20% vs. 35.5%, respectively; p=0.015), and improved post-PCI MCE score index (0.88 ± 0.18 vs. 0.77 ± 0.32 vs. 0.71 ± 0.30, respectively; p<0.05).
The incidence of postprocedural cardiac Troponin I (cTnI) elevation was significantly reduced in patients treated with the upstream AGGRASTAT regimen compared with PCI 25 microgram/kg dose bolus AGGRASTAT or abciximab (9.4% vs. 30% vs. 38.7%, respectively; p=0.018). The cTnI levels post-PCI were also significantly decreased with the upstream regimen of AGGRASTAT compared with PCI AGGRASTAT (3.8 ± 4.1 vs. 7.2 ± 12; p=0.015) and abciximab (3.8 ± 4.1 vs. 9 ± 13.8; p=0.0002). The comparison between the PCI AGGRASTAT 25 microgram/kg dose bolus and abciximab regimens indicated no significant differences in the rate of TMPG 0/1 post-PCI (20% vs. 35%; p=NS).

Several further trials were conducted comparing the 25 microgram/kg dose bolus regimen with abciximab involving over 1100 NSTE-ACS patients which showed non-significant differences with respect to the composite primary endpoint of MACE at 30 days ranging from 5.8% to 6.9% for AGGRASTAT and 7.1% to 8.8% for abciximab

In the TARGET study using a 10 microgram/kg bolus of AGGRASTAT followed by a 0.15 microgram/kg/min infusion, AGGRASTAT failed to demonstrate noninferiority to abciximab: the incidence of the composite primary endpoint (death, MI, or uTVR at 30 days) showed that abciximab was significantly more effective on clinically relevant endpoints, with 7.6% in the AGGRASTAT and 6.0% in the abciximab group (p=0.038), which was mainly due to a significant increase in the incidence of MI at 30 days (respectively 6.9% vs. 5.4%; p=0.04).

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 ^{14}C-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 ^{14}C-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 section 4.2). 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 subset 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 milligram/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.

Fertility and reproductive performance were not affected in studies with male and female rats given intravenous doses of tirofiban hydrochloride up to 5 mg/kg/day. These dosages are approximately 22-fold higher than the maximum recommended daily dose in humans.
However, animal studies are insufficient to draw conclusions with respect to reproductive toxicity in humans.

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 store above 30°C. Do not freeze. Keep container in outer carton to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container: 50 mL Type I glass vial

6.6 Special precautions for disposal and other 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 section 4.2
Any unused product or waste material should be disposed of in accordance with local requirements.

KEEP MEDICAMENT OUT OF REACH OF CHILDREN.

Do not exceed the prescribed dose.

Do not use after expiry date.

7. Marketing Anthorisation Holder
ALGORITHM S.A.L

Manufactured by Patheon Manufacturing Services LLC, North Carolina, U.S.A.
Packaged in Zouk Mosbeh, Lebanon, by ALGORITHM S.A.L.

*In the following AGGRASTAT means AGGRASTAT concentrate solution for I.V. infusion.
** 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 haemoglobin drop > 40 g/L but < 50 g/L without an identified bleeding site.

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