SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AGGRASTAT®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for infusion contains 56 micrograms of tirofiban hydrochloride monohydrate which is equivalent to 50 micrograms tirofiban.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion (250 ml bag). A clear, colorless solution practically free from visible particulates.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aggrastat, in combination with heparin, is indicated for patients with unstable angina or non-Q-wave myocardial infarction to prevent cardiac ischemic events and is also indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy.
In this setting, Aggrastat has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure.

4.2 Posology and method of administration

Use with Aspirin and Heparin

In the clinical studies, patients received aspirin, unless it was contraindicated, and heparin. Aggrastat and heparin can be administered through the same intravenous catheter.

Precautions

Aggrastat is intended for intravenous delivery using sterile equipment and technique. Do not add other drugs or remove solution directly from the bag with a syringe. Do not use plastic containers in series connections; such use can result in air embolism by drawing air from the first container if it is empty of solution. Any unused solution should be discarded.

Directions for Use

Aggrastat is supplied as 250 mL of 0.9% sodium
chloride containing 50 mcg/ml tirofiban.
Check the expiry date. Check for leaks by squeezing the inner bag firmly; if any leaks are found, the sterility may be impaired and the solution should be discarded. Do not use unless the solution is clear and the seal is intact.
Do not add supplementary medication or withdraw solution directly from the bag with a syringe.

Aggrastat may be administered in the same intravenous line as dopamine, lidocaine, potassium chloride, and PEPCID* (famotidine) Injection. Aggrastat should not be administered in the same intravenous line as diazepam.
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 below.

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

In most patients, Aggrastat should be administered intravenously, at an initial rate of 0.4 mcg/kg/min for 30 minutes and then continued at 0.1 mcg/kg/min. Patients with severe renal insufficiency (creatinine clearance <30 mL/min) should receive half the usual rate of infusion (see section 4.8 and 5.2).

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

Patient Weight (kg)	Most Patients		Severe Renal Impairment	
	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

No dosage adjustment is recommended for elderly or female patients (see section 4.8). In PRISM-PLUS, AGGRASTAT was administered in combination with heparin for 48 to 108 hours. The infusion should be continued through angiography and for 12 to 24 hours after angioplasty or atherectomy.

4.3 Contraindications

Aggrastat is contra-indicated in patients who are hypersensitive to the active substance or to any of the excipients of the preparation listed in section 6.1 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. gastro-intestinal 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 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 two weeks
- Severe trauma or major surgery >6 weeks but <3 months previously
- Active peptic ulcer within the past three 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 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. Consequently, the use of tirofiban hydrochloride is not recommended in combination with thrombolytic therapy.

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

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

Paediatric 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 is 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 <60ml/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 GPIIb/IIIa receptor antagonists (cross reactivity can occur), the platelet count should be monitored immediately e.g. within the first hour of administration after re-exposure (see section 4.8). 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 GPIIb/IIIa receptor antagonists.

Sodium content
Aggrastat Solution
Aggrastat solution for infusion contains approximately 917 mg of sodium per 250 ml bag which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other 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 *ex vivo* APD-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
There are no or limited amount of data from the use of tirofiban hydrochloride in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Aggrastat is not recommended during pregnancy unless clearly necessary.

Breastfeeding
It is unknown whether tirofiban hydrochloride is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tirofiban hydrochloride in milk (for details see section 5.3). A risk to the newborn cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Aggrastat therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

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

a. Summary of safety profile
The most common adverse reaction reported during therapy with Aggrastat, when used concomitantly with heparin, aspirin and other oral anti-platelet agents, was bleeding, which usually involved mild mucocutaneous bleeding or mild catheterization-site bleeding.
Gastro-intestinal, retro-peritoneal, intracranial, haemorrhoidal and post-operative bleeding, epidural haematoma in the spinal region, haemopericardium and pulmonary (alveolar) haemorrhage have also been reported. Rates of TIMI major and intracranial bleeding in the pivotal Aggrastat studies were $\leq$2.2% and <0.1%, respectively. The most serious adverse reaction was fatal bleeding.
In the pivotal studies, administration of Aggrastat was associated with thrombocytopenia (platelet count <90,000/mm^3), occurring in 1.5% of patients treated with Aggrastat and heparin. The incidence of severe thrombocytopenia (platelet count <50,000/mm^3) was 0.3%. The most common non-bleeding adverse drug reactions associated with Aggrastat given concurrently with heparin were nausea (1.7%), fever (1.5%) and headache (1.1%).

b. Tabulated summary of adverse reactions

Table 2 lists the adverse reactions based on experience from six double-blind controlled clinical studies (including 1953 patients receiving Aggrastat plus heparin) 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.

Table 2: Undesirable effects in clinical studies and from post-marketing experience

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders				Acute and/or severe (<20,000/mm3) decreases in platelet counts
Immune System Disorders				Severe allergic reactions including anaphylactic reactions.
Nervous system disorders	Headache			Intracranial bleeding, spinal epidural haematoma
Cardiac disorders				Hemopericardium
Vascular disorders	Haematoma			
Respiratory, thoracic and mediastinal disorders		Haemoptysis, epistaxis		Pulmonary (alveolar) haemorrhage
Gastrointestinal disorders	Nausea	Oral haemorrhage gingival haemorrhage	GI haemorrhage, haematemesis	Retroperitoneal bleeding
Skin and subcutaneous tissue disorders	Ecchymosis			
Renal and urinary disorders		Haematuria		
General disorders and administration site conditions		Fever		
Injury, poisoning and procedural complications	Post-operative haemorrhage*	Vessel puncture site haemorrhage		
Investigations	Occult blood in stool or urine	Decreases in haematocrit and haemoglobin, platelet counts <90,000/mm^3	Platelet counts <50,000/mm^3	

***Primarily related to catheterization sites.**

c. Description of selected adverse reactions

Bleeding
Rates of major bleeding complications are low and not significantly increased with Aggrastat 0.4 microgram/kg/min infusion regimen.

In the PRISM-PLUS study, using the Aggrastat 0.4 microgram/kg/min infusion regimen, 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).

In the On-TIME 2 study, there were no significant differences in the incidence of TIMI major bleeding (3.4% vs. 2.9% p =0.58) and TIMI minor bleeding (5.9% vs. 4.4%; p=0.206) between the Aggrastat 25 microgram/kg dose bolus regimen and the control arm.
The rates of TIMI major (2.4% vs. 1.6%; p=0.44) or minor bleeding (4.8% vs. 6.2%; p=0.4) were also not significantly different between the Aggrastat 25 microgram/kg dose and the standard dose of abciximab, which were compared in the MULTISTRATEGY study.

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

Thrombocytopenia
During Aggrastat therapy, acute decreases in platelet count or thrombocytopenia occurred more frequently than in the placebo group. These decreases were reversible upon discontinuation of Aggrastat. Acute and severe platelet (platelet counts $<20,000/mm^3$) decreases have been observed in patients with no prior history of thrombocytopenia upon re-administration of GPIIb/IIIa receptor antagonists and may be associated with chills, low-grade fever or bleeding complications.

Analysis of the studies comparing the 25 microgram/kg dose bolus regimen against abciximab yielded a significantly lower rate of thrombocytopenia for Aggrastat (0.45% vs. 1.7%; OR=0.31; p=0.004).
Allergic reactions
Severe allergic reactions (e.g., bronchospasm, urticaria) including anaphylactic reactions have occurred during initial treatment (also on the first day) and during readministration of Aggrastat. Some cases have been associated with severe thrombocytopenia (platelet counts $<10,000/mm^3$).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/.
In addition, you may report by sending an e-mail message to safety@tzamal-medical.co.il.

4.9 Overdose

Inadvertent overdose with tirofiban hydrochloride occurred in the clinical studies, up to 50 microgram/kg as a three 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

Mechanism of action
Tirofiban hydrochloride (tirofiban) is a non-peptidal 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 eight hours after discontinuation.
The extent of this inhibition runs parallel to the tirofiban plasma concentration.

Pharmacodynamic effects
In the 0.4 microgram/kg/min infusion regimen of tirofiban, in the presence of unfractionated heparin and ASA, tirofiban 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 tirofiban 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).

Clinical efficacy and safety

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 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 units (U) followed by an infusion of 1,000 U/hr titrated to maintain an activated partial thromboplastin time (APTT) of approximately two 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 end-point was the occurrence of refractory ischaemia, myocardial infarction or death at seven days after the start of Aggrastat.
At 7 days, the primary end-point, there was a 32% risk reduction (RR) (12.9% vs. 17.9%) in the Aggrastat group for the combined end-point (p=0.004): this represents approximately 50 events avoided for 1,000 patients treated. After 30 days the RR for the composite end-point of death, MI, refractory ischaemic conditions, or readmissions for UA was 22% (18.5% vs. 22.3%; p=0.029). After six months the relative risk of 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 seven 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 randomised 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 section 4.4) in either group. The efficacy of Aggrastat in combination with enoxaparin has not been established.

PRISM PLUS trial was conducted at a time when the standard of care of managing acute coronary syndromes was different from that of present times in terms of oral platelet ADP receptor (P2Y12) antagonists use and the routine use of intracoronary stents.

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 post-procedural 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).

On-Time 2 study
The On-TIME 2 trial was a multi-centre, prospective, randomised, controlled clinical trial which was designed to assess the effect of early upfront Aggrastat administration using the 25 microgram/kg dose bolus regimen in patients with STEMI planned for primary PCI. All patients received ASA, a 600 mg loading dose of clopidogrel, and unfractionated heparin. The use of bail-out Aggrastat was allowed according to pre-specified criteria. The study was accomplished in two phases: a pilot, open label phase (n=414) followed by a larger double-blind phase (n=984). A pooled analysis of data from both phases was pre-specified to evaluate the effect of the 25 microgram/kg dose bolus regimen compared to control as measured by a primary endpoint defined as the 30-day MACE rate (death, recurrent MI and uTVR).
In this pooled analysis, MACE at 30 days was significantly reduced by early upfront initiation of Aggrastat compared to control (5.8% vs. 8.6%; p=0.043). In addition, there was a strong trend toward a significant decrease in mortality with Aggrastat with respect to all-cause death (2.2% in the Aggrastat arm vs. 4.1% in the control arm; p=0.051). This mortality benefit was mainly due to a reduction of cardiac death (2.1% vs. 3.6%; p=0.086). At 1-year follow-up (the secondary endpoint), the mortality difference was maintained (3.7% vs. 5.8%; p=0.078 for all-cause mortality and 2.5% vs. 4.4% for cardiac mortality; p=0.061).
Patients who underwent primary PCI (86% of study population of pooled analysis) demonstrated a significant reduction in mortality both at 30 days (1.0% in the Aggrastat group vs. 3.9% in the control group; p=0.001) and at 1 year (2.4% for Aggrastat vs. 5.5% for control; p=0.007).

MULTISTRATEGY study
The MULTISTRATEGY study was an open-label, 2X2 factorial, multinational trial which compared the Aggrastat (n=372) with abciximab (n=372) when used in conjunction with either a sirolimus-eluting (SES) or bare metal stent (BMS), in patients with STEMI. Either Aggrastat (bolus of 25 microgram/kg, followed by an infusion at 0.15 microgram/kg/min continued for 18 to 24 hours) or abciximab (bolus of 0.25 mg/kg, followed by a 12-hour infusion at 0.125 microgram/kg/min) was initiated before arterial sheath insertion during the angiography. All patients received unfractionated heparin, ASA and clopidogrel.
The primary endpoint for the drug comparison was cumulative ST-segment resolution expressed as the proportion of patients who achieve at least 50% recovery within 90 minutes after the last balloon inflation and tested the hypothesis that Aggrastat is noninferior to abciximab with respect to this endpoint.In the intention-to-treat population, the percentage of patients with at least 50% recovery from ST-segment elevation was not significantly different between Aggrastat (85.3%) and abciximab (83.6%), demonstrating the non-inferiority of Aggrastat to abciximab (RR for Aggrastat vs. abciximab, 1.020; 97.5% CI, 0.958- 1.086; p<0.001 for non-inferiority). At 30 days, the rates of major adverse cardiac events (MACE) were similar for abciximab and Aggrastat (4.3% vs. 4.0%, respectively; p=0.85) with these results maintained at 8 months (12.4% vs. 9.9%, respectively; p=0.30).

In On-TIME 2 and MULTISTRATEGY, patients were treated with dual oral antiplatelet therapy consisting of ASA and high-dose clopidogrel. The efficacy of Aggrastat in combination with either prasugrel or ticagrelor has not been established in randomised controlled trials.

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

TARGET study
In one study using a 10 microgram/kg bolus followed by a 0.15 microgram/kg/min infusion of Aggrastat , 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-labelled 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-labelled 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 two 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 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 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, 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, paracetamol, 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

Non-clinical 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 injection, 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.

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, propanolol HCl and famotidine injection.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Protect from light during storage.

6.5 Nature and contents of container

Aggrastat Solution:
250 ml plastic bag (non-PVC plastic) with 2 port tubes (Freeflex®), non-PVC, multilayer polyolefin plastic film with polyolefin plastic tubes. Tubes closure with Polyisoprene plastic stoppers.

Pack size: 1 plastic bag with 250 ml solution for infusion.

6.6 Special precautions for disposal

Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

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

7 MANUFACTURER

Correvio International Sarl, Geneva, Switzerland

8 REGISTRATION HOLDER

Tzamal Bio-Pharma Ltd., 20 Ha'Magshimim St., Petah-Tikva 4934829, Israel

9 DRUG REGISTRATION NUMBER

116-15-29580-00

Revised in February 2025.

AGG_SPC_TZ022025