The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

18 June 1999
CPMP/990/99-EN

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

OPINION FOLLOWING AN ARTICLE 10 REFERRAL

AGGRASTAT

International Nonproprietary Name (INN): Tirofiban

BACKGROUND INFORMATION

On 18 June 1999, the European Commission issued a Decision valid throughout the European Union for the medicinal product AGGRASTAT/AGRASTAT, which contains Tirofiban. This decision was based on the arbitration assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 25 March 1999. The Marketing Authorisation Holder responsible for this medicinal product is MSD Sharp & Dohme GmbH.

The approved indication is for the prevention of early myocardial infarction in patients presenting with unstable angina (UA) or non-Q-wave myocardial infarction (NQMI) 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/AGRASTAT 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. AGGRASTAT/AGRASTAT is intended for use with acetylsalicylic acid (ASA) and unfractionated heparin.

In July 1998 MSD Sharp & Dohme GmbH, submitted applications for Mutual Recognition of the Marketing Authorisation granted by the German Competent Authority acting as Reference Member State, for Aggrastat solution for infusion and concentrate for solution for infusion. The Mutual Recognition procedure started on 05 August 1998. The Concerned Member States were Austria, Belgium, Denmark, Finland, France, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, United Kingdom, Spain and Sweden. The Concerned Member State, France not being able to agree with the Mutual Recognition of the Marketing Authorisation granted by the Reference Member State referred the reasons for disagreement to the EMEA on 30 October 1998.

The reasons concerned the enzymatic definition of the Myocardial Infarction component used for the combined endpoint in the PRISM PLUS study, which supported evidence of efficacy and safety of tirofiban at the proposed dosing regimen.

The Reference Member State sent its report to the EMEA on 11 November 1998. The matter was referred to the CPMP on 19 November 1998. The Marketing Authorisation Holder provided written explanations on 18 January and 11 March 1999, and an oral explanation at the March 1999 plenary meeting of the CPMP.

The CPMP adopted a positive opinion on 25 March 1999 recommending the granting of the Marketing Authorisation for Aggrastat with amendments to the Summary of Product Characteristics (SPC) of the Reference Member State. An overall summary of the scientific evaluation is provided, together with Annex I and Annex Ia of the opinion, which contain the amendments to the SPC and the amended SPC. The final Opinion was converted into a Decision by the European Commission on 18 June 1999.

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AGGRASTAT/AGRASTAT is supplied in two pharmaceutical forms; a concentrate for solution for infusion containing (0.25 mg/ml) and a solution for infusion (0.05 mg/ml).

The active substance of AGGRASTAT/AGRASTAT is tirofiban hydrochloride. Tirofiban 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.

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.

The clinical study PRISM-PLUS, which supported evidence of efficacy and safety of tirofiban at the proposed dosing regimen, investigated the efficacy of AGGRASTAT/AGRASTAT with unfractionated heparine versus unfractionated heparine in patients with unstable angina or acute non-Q-wave myocardial infarction. The combined primary study endpoint was the occurrence of refractory ischemia, myocardial infarction or death at *7* days after the start of tirofiban hydrochloride. 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 ischemic conditions. After 30 days the RR for the combined endpoint (death/myocardial infarction/refractory ischemic conditions/readmissions for unstable angina) was 22 % (18.5 % vs. 22.3 %; p=0.029).

The adverse events causally related to AGGRASTAT/AGRASTAT 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/AGRASTAT in combination with heparin was not significantly higher than in the control group (1.4 % for AGGRASTAT/AGRASTAT in combination with heparin and 0.8 % for the control group which received heparin). There were no reports of intracranial bleeding for AGGRASTAT/AGRASTAT in combination with heparin or in the control group. The incidence of retroperitoneal bleeding reported for AGGRASTAT/AGRASTAT 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/AGRASTAT and 2.8 % for the control group. 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/AGRASTAT in combination with heparin and 8 % for the control group.

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF AGGRASTAT

The basis for arbitration procedure was the enzymatic definition of the Myocardial Infarction (MI) component used for the combined endpoint in the PRISM PLUS study, which supported evidence of efficacy and safety of tirofiban at the proposed dosing regimen.

Concern has been expressed by the Concerned Member State France (FR), that the sponsor's definition used in the protocol – and consequently in the respective publication of the PRISM PLUS study – did not completely overlap with those used during the course of the study. Accordingly, FR raised doubts about the validity of the diagnosis 'new MI' in patients who presented with increased creatine kinase (CK) values (total activity) of less than twice the upper limit of normal.

The arbitration procedure resulted in the following conclusions:

- there was a change in methods used for adjudication of MI by the Endpoint Classification Committee (ECC) as compared to the protocol,

however:

- due to misclassifications recognised by the appplicant, the number of patients with endpoint MI out of the protocol definition dramatically decreased,
- furthermore the exclusion of these cases from the efficacy analysis did not change the results,
- based on clinical judgement, these cases actually represented real ischemic events,
- lastly, considering the definition of combined endpoint (e.g. including refractory ischemic conditions and hospital readmissions for MI or unstable angina), any potential underreporting of [0-2] MI was assumed to be quite low and in any case balanced between the two treatment groups,
- as events were not adjudicated by the ECC and not monitored by the sponsor, the 6-month analysis can be considered only as exploratory.

Following a CPMP ad-hoc breakout meeting and the oral explanation provided by the company a number of amendments were made to the SPC as detailed in Annex I. The proposed SPC is now considered to provide adequate information.

The CPMP having considered

- the written responses provided by the company,
- the Rapporteur/Co-Rapporteur's assessment reports and their addenda,
- comments from CPMP members,
- and the oral explanation by the company,

was of the opinion that the objections raised by FR have been solved. Since the risk/benefit ratio of tirofiban is considered to be positive for the claimed indication and posology, a marketing authorisation should be granted. However, the SPC should be amended as set out in Annex I of the CPMP Opinion.

ANNEX I

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS

➢ **In section 4.1: Therapeutic indications**

~~AGGRASTAT is indicated for unstable angina pectoris or acute non-Q-wave myocardial infarction (NQWMI) (documented by electrocardiogram [ECG] evidence of ischemia or elevated cardiac enzymes) in addition to unfractionated heparin and acetylsalicylic acid (ASA).~~

~~**Note**~~

~~After initiation of therapy in these patients AGGRASTAT may continue to be given through coronary angiography, coronary angioplasty, or atherectomy should these procedures be necessary (see also~~

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.

➢ **In section 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.

(...)

Start and duration of therapy with AGGRASTAT
(...)
Once a patient is clinically stable and no ~~further~~ coronary intervention procedure is planned by the treating physician, the infusion should be discontinued.
(...)

➢ **In section: 4.3 Contraindications**

AGGRASTAT is contraindicated in patients who are hypersensitive to one of the constituents 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:

- ~~Acute cerebrovascular disease (e.g. stroke, TIA) or cerebrovascular disease less than one year previously.~~ **History of stroke within 30 days or any history of haemorhagic stroke**.
- ~~Acute or a k~~**K**nown 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**~~90,000~~/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.

➢ **In section 4.4: Special warnings and special precautions for use**

(...)

- Concurrent use of drugs that increase the risk of bleeding to a relevant degree (e.g. coumarins, ~~abciximab,~~ **other parenteral GP IIb/IIIa inhibitors,** dextran solutions).

(...)

➢ **In section 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.

~~The table below shows the incidences of major and minor bleeding, differentiated on the basis of TIMI** criteria – for the two large-scale clinical studies in which AGGRASTAT was used in conjunction with unfractionated heparin and ASA, in comparison to treatment consisting of unfractionated heparin and ASA:~~

	~~PRISM PLUS[1]~~ ~~(study on unstable angina pectoris / non-Q-wave myocardial infarction)~~		~~RESTORE[1]~~ ~~(study on angioplasty / atherectomy)~~	
~~Bleeding~~	~~AGGRASTAT + heparin (n = 773) (%)~~	~~Heparin (n = 797) (%)~~	~~AGGRASTAT + heparin (n = 1071) (%)~~	~~Heparin (n = 1070) (%)~~
~~Major bleeding (TIMI criteria)[2]~~	~~1.4~~	~~0.8~~	~~2.2~~	~~1.6~~
~~Minor bleeding (TIMI criteria)[3]~~	~~10.5~~	~~8.0~~	~~12.0~~	~~6.3~~
~~Intracranial haemorrhage~~	~~0.0~~	~~0.0~~	~~0.1~~	~~0.3~~
~~Retroperitoneal bleeding~~	~~0.0~~	~~0.1~~	~~0.6~~	~~0.3~~
~~Transfusions~~	~~4.0~~	~~2.8~~	~~4.3~~	~~2.5~~

~~[1]. Patients received ASA unless contraindicated.~~
~~[2]. Haemoglobin fall by more than 50 g/l with or without identified site, intracranial haemorrhage or cardiac tamponade.~~
~~[3]. Haemoglobin fall by more than 30 g/l with bleeding from known site, spontaneous marked haematuria, haematemesis or haemoptysis.~~

** Bovill, E.G. et al: Annals of Internal Medicine, 115(4): 256-265, 1991.

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 % 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.**

- **In section 5.1: Pharmacodynamic properties**

(...)

~~Clinical studies~~ **PRISM-PLUS study**

The double-blind, multicenter, controlled PRISM PLUS study ~~demonstrated~~**compared** the efficacy of tirofiban and unfractionated heparin (n=773) ~~compared to~~**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 ³ 0.1 mV; T-wave inversions ³ 0.3 mV) or elevated cardiac enzymes (total CPK ³ 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 mg/kg/min followed by a maintenance infusion of 0.10 mg/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 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 ischemia, myocardial infarction or death at ***7***~~seven~~ days after the start of tirofiban hydrochloride.

The mean age of the population was 63 years; 32 % of patients were female. Approximately at baseline 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; ~~approximately~~ 30 % underwent early angioplasty and 23 % 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 ischemic conditions. ~~with a 47 % RR (3.9 % vs. 7.0 %) for myocardial infarction (p=0.006), and a 43 % RR (4.9 % vs. 8.3 %) for "myocardial infarction or death" (p=0.006).~~

After 30 days the RR for the combined endpoint **(death/myocardial infarction/refractory ischemic conditions/readmissions for unstable angina)** was 22 % (**18.5 % vs. 22.3 %;** p=0.0~~39~~**29**). ~~The risk of "myocardial infarction or death" was reduced by 30 % (p=0.031).~~

After **6**~~six~~ months the risk of the combined endpoint **(death/myocardial infarction/refractory ischemic conditions/readmissions for unstable angina)** was reduced by 19 % (**27.7 % vs. 32.1 %;** p=0.024). ~~and the RR for "myocardial infarction or death" was 23 % (p=0.063).~~

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".

~~The RESTORE trial (n=2141) studied patients undergoing PTCA or atherectomy within 72 hours of presentation with unstable angina or acute myocardial infarction. Tirofiban was initiated immediately prior to the procedure as a bolus of 10 µg/kg for 3 minutes followed by a maintenance infusion of 0.15 µg/kg/min for 36 hours. All patients received ASA and unfractionated heparin. At 2 and 7 days after angioplasty the RR for the combined endpoint (occurrence of all deaths, non-fatal myocardial infarctions, or all repeat revascularisations) was 38 % (5.4 % vs. 8.7 %) (p = 0.004) and 28 % (7.6 % vs. 10.4 %) (p=0.023), respectively. At 30 days there was a 17 % RR (10.3 % vs. 12.2 %) (p=0.169).~~

~~A further study (PRISM, n=3232) and a treatment group of another study (PRISM PLUS) (n=345) did not include the concomitant administration of tirofiban with unfractionated heparin. Since this is not the recommended dosing regimen, the respective results are not reported here.~~

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
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 ischemic cardiac pain, marked ECG changes (in particular ST- segment abnormalities), raised cardiac enzymes or markers (e.g. CK-MB, tropinins) and heart failure.

(...)

ANNEX Ia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AGGRASTAT/AGRASTAT* 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.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

AGGRASTAT/AGRASTAT is given intravenously at an initial infusion rate of 0.4 μg/kg/min for 30 minutes. At the end of the initial infusion, AGGRASTAT/AGRASTAT should be continued at a maintenance infusion rate of 0.1 μg/kg/min. AGGRASTAT/AGRASTAT should be given with unfractionated heparin (usually an intravenous bolus of 5000 units (U) simultaneously with the start of AGGRASTAT/AGRASTAT 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 ASA (see 5.1 Pharmacodynamic properties, Clinical studies), 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/AGRASTAT 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.

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

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/AGRASTAT

AGGRASTAT/AGRASTAT optimally should be initiated within 12 hours after the last anginal episode. The recommended duration should be at least 48 hours. Infusion of AGGRASTAT/AGRASTAT 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/AGRASTAT (see 5.1 Pharmacodynamic properties, Clinical studies). This medication should be continued at least for the duration of the infusion of AGGRASTAT/AGRASTAT.

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/AGRASTAT 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/AGRASTAT (from one 50 ml puncture vial) to make up a concentration of 50 µg/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/AGRASTAT should only be given intravenously and may be administered with unfractionated heparin through the same infusion tube.

It is recommended that AGGRASTAT/AGRASTAT 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/AGRASTAT is contraindicated in patients who are hypersensitive to one of the constituents 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/AGRASTAT is contraindicated in patients with:

- History of stroke within 30 days or any history of haemorhagic 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/AGRASTAT alone without unfractionated heparin is not recommended.

The efficacy and safety of AGGRASTAT/AGRASTAT has not been investigated in combination with low molecular weight heparins.

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 - concurrent or less than 48 hours before administration of tirofiban hydrochloride
- Concurrent use of drugs that increase the risk of bleeding to a relevant degree (e.g. coumarins, other parenteral GP IIb/IIIa inhibitors, dextran solutions).

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/AGRASTAT 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/AGRASTAT in children, thus, the use of AGGRASTAT/AGRASTAT is not recommended in these patients.

Other precautionary notes and measures

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

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

AGGRASTAT/AGRASTAT 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/AGRASTAT
- Severe acute or chronic heart failure
- Cardiogenic shock
- Mild to moderate liver insufficiency
- Platelet count < 150,000/mm³, 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/AGRASTAT 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/AGRASTAT and the heparin effect should be carefully monitored. In severe kidney failure the AGGRASTAT/AGRASTAT dosage should be reduced (see also 4.2 Posology and method of administration).

Femoral artery line

During treatment with AGGRASTAT/AGRASTAT 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/AGRASTAT. 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/AGRASTAT as well as within 2-6 hours after start of therapy with AGGRASTAT/AGRASTAT and at least once daily thereafter while on therapy (or more often if there is evidence of a marked decrease). 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/AGRASTAT and heparin should be discontinued. Patients should be monitored for bleeding and treated if necessary (see also 4.9 Overdosage).

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant administration of AGGRASTAT/AGRASTAT and ASA increases the inhibition of *ex vivo* adenosine diphosphate (ADP)-induced platelet aggregation to a greater extent as compared to ASA alone. The concomitant administration of AGGRASTAT/AGRASTAT 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/AGRASTAT 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).

The concomitant administration of AGGRASTAT/AGRASTAT (at approximately one-half the recommended dose) and ticlopidine significantly enhanced the inhibition of platelet aggregation induced by both ADP and collagen. AGGRASTAT/AGRASTAT prolonged bleeding time, however, the combined administration of AGGRASTAT/AGRASTAT and ticlopidine did not additionally affect bleeding time. Simultaneous ticlopidine administration did not alter the pharmacokinetics of tirofiban hydrochloride.

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

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/AGRASTAT should not be used during pregnancy unless clearly necessary**.**

Lactation

It is not known whether AGGRASTAT/AGRASTAT 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/AGRASTAT impairs the ability to drive or operate machinery.

4.8 Undesirable effects

Bleeding

The adverse event causally related to AGGRASTAT/AGRASTAT 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/AGRASTAT 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/AGRASTAT 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/AGRASTAT in combination with heparin and 8;0 % for the control group. There were no reports of intracranial bleeding for AGGRASTAT/AGRASTAT in combination with heparin or in the control group. The incidence of retroperitoneal bleeding reported for AGGRASTAT/AGRASTAT 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/AGRASTAT and 2.8 % for the control group.

AGGRASTAT/AGRASTAT 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 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/AGRASTAT 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/AGRASTAT with heparin" group and the "heparin alone" group.

Laboratory parameters

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

Occasionally during AGGRASTAT/AGRASTAT 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/AGRASTAT.

4.9 Overdose

Inadvertent overdosage with tirofiban hydrochloride occurred in the clinical studies, up to 50 µg/kg as a 3 minute bolus or 1.2 µg/kg/min as an initial infusion. Overdosage with up to 1.47 µg/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, Clinical Studies).

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/AGRASTAT infusion should be discontinued. Transfusions of blood and/or thrombocytes should also be considered. AGGRASTAT/AGRASTAT 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/AGRASTAT, 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 enrolment [> 5 % or greater than upper limit of normal]).

In this study, patients were randomised to

– either AGGRASTAT/AGRASTAT (30 minute loading infusion of 0.4 µg/kg/min followed by a maintenance infusion of 0.10 µg/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 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/AGRASTAT 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".

Patients most likely to benefit from AGGRASTAT/AGRASTAT 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 µg/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 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, acetaminophen, alprazolam, amlodipine, aspirin preparations, atenolol, bromazepam, captopril, diazepam, digoxin, diltiazem, docusate sodium, enalapril, furosemide, glyburide, unfractionated heparin, insulin, isosorbide, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, oxazepam, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam.

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

Compatibility of AGGRASTAT/AGRASTAT and the following intravenous formulations has been evaluated: heparin, dopamine, lidocaine, potassium chloride, and famotidine injection. No incompatibilities have been found with these agents.

6.3 Shelf life

2 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.

6.5 Nature and contents of container

50 ml Type I glass vial

6.6 Instructions for use and handling

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

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT