SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
AGREDUR READY 50 mcg/mL Solution For I.V. Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Substance:
Tirofiban hydrochloride…….5,62 mg/100 ml (equivalent to 5 mg tirofiban).
Excipients:
Sodium citrate dihydrate…….54 mg/100 ml
Sodium chloride……..0,9 g/100 ml
See: section 6.1 for excipients.

3. PHARMACEUTICAL FORM
Prefilled diluted solution for infusion.
Clear, colorless, prefilled solution for infusion.

4. CLINICAL PARTICULARS
4.1 Therapeutical indications
AGREDUR READY is indicated to prevent early myocardial infarction in patients presenting with unstable angina or non-Q wave myocardial infarction, who have experienced a chest pain attack within the past 12 hours, with ECG changes and/or elevated cardiac enzymes.

Patients who would benefit most from AGREDUR READY treatment are those at high risk of developing myocardial infarction within the first 3-4 days after the onset of acute angina symptoms. (example: patients likely to administer PTCA early) (see also sections 4.2 and 5.1).

AGREDUR READY is intended for use with acetyl salicylic acid or aspirin (ASA) and unfractionated heparin.

4.2 Posology and method of administration
This product should only be administered in a hospital by specialist physicians experienced in the treatment of acute coronary syndromes.

AGREDUR READY is developed in a ready-to-use dose, does not require dilution.

Posology

The table below is provided as a guide for dose adjustment based on body weight.

Table 1. Provided as a guide for dose adjustment based on body weight.

	0,4 mcg/kg/minute Loading Dose In Most Patients		**0,4 mcg/kg/minute Loading Dose Severe Renal Failure**		**25 mcg/kg Bolus Dose In Most Patients**		**25 mcg/kg Bolus Dose Severe Renal Failure**	
Patient Weight (kg)	30 minutes Loading Infusion Rate (ml/hour)	Maintanence Infusion Rate (ml/hour)	30 minutes Loading Infusion Rate (ml/hour)	Maintanence Infusion Rate (ml/hour)	Bolus (ml)	Maintanence Infusion Rate (ml/hour)	Bolus (ml)	Maintanence Infusion Rate (ml/hour)
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

Frequency and Duration of administration:

In patients who are treated for NSTE-ACS by an early invasive route and are not scheduled to have angiography for at least 4 to 48 hours after diagnosis, AGREDUR READY is administered intravenously for 30 minutes at an initial infusion rate of 0.4 micrograms (mcg)/kg/min. At the end of the initial infusion, AGREDUR READY should be continued at a maintenance infusion rate of 0.1 microgram (mcg)/kg/min. AGREDUR READY, unfractionated heparin (usually 50-60 units [U]/kg intravenously with the initiation of AGREDUR READY therapy, then titrated to keep the activated thromboplastin time (APTT) at approximately twice the normal value, approximately 1000 U/hour and should be given together with oral antiplatelet therapy, including, but not limited to, ASA, unless contraindicated.

In NSTE-ACS patients planned to undergo Percutaneous Coronary Intervention (PCI) in the first 4 hours of diagnosis or in patients who have had acute myocardial infarction and who are required to perform primary PCI; It should be administered as an initial bolus dose of 25 micrograms/kg over a 3-minute period followed by a continuous infusion of up to 48 hours at a rate of 0.15 micrograms/kg per minute for 12-24 hours. AGREDUR READY should be given in conjunction with unfractionated heparin (at the doses specified above) and oral antiplatelet therapy, including but not limited to ASA, unless contraindicated (see section 5.1).

Starting AGREDUR READY treatment and duration of treatment

In patients treated for NSTE-ACS by an early invasive route and for whom angiography is not planned for at least 4 to 48 hours after diagnosis, a loading dose of 0.4 micrograms/kg/min of AGREDUR READY should be initiated at the time of diagnosis. The 0.4 microgram/kg/min loading dose regimen should be initiated according to the diagnosis. The recommended time is at least 48 hours. The infusion of AGREDUR READY and unfractionated heparin can be continued during coronary angiography and should be maintained for a minimum of 12 hours

and a maximum of 24 hours after angioplasty/atherectomy. The infusion should be discontinued when the patient is clinically stabilized and no coronary intervention procedure is planned by the treating physician. The whole treatment period should not exceed 108 hours.

If angiography is performed within 4 hours after diagnosis in a patient diagnosed with NSTE-ACS and treated by an invasive way, a bolus dose of 25 micrograms/kg AGREDUR READY should be initiated at the beginning of PCI for 12-24 hours and up to 48 hours. In patients with acute myocardial infarction undergoing primary PCI, a bolus dose of 25 micrograms/kg should be initiated as soon as the diagnosis is made.

Concomitant therapy (oral antiplatelet therapy including unfractionated heparin, acetyl salicylic acid (ASA))
Unfractionated heparin treatment is started with 50-60 U/kg I.V. bolus and then continued with a 1000 U maintenance infusion per hour. The dose of heparin is titrated to maintain APTT approximately twice the normal value.

Unless contraindicated, all patients should take oral antiplatelet medications, including but not limited to ASA, before starting AGREDUR READY (see Section 5.1). These drugs should be continued for at least the duration of the AGREDUR READY infusion. Clopidegrel has been used as oral antiplatelet therapy with ASA in many studies investigating the use of AGREDUR READY as an adjunct to PCI treatment. The effectiveness of the combination of AGREDUR READY with prasurgel or ticagrelor has not been proven in randomized controlled studies.

If angioplasty (PTCA) is required, heparin should be discontinued after PTCA, and the sheaths should be removed as soon as clotting returns to normal, that is active clotting time (ACT) falls below 180 seconds (usually 2-6 hours after heparin discontinuation).

Method of administration:
AGREDUR READY is supplied ready-to-use; it does not need to be diluted before use.
Before parenteral drugs are used, the solution and bag, if appropriate, should be checked for visible particles or discoloration.

AGREDUR READY should only be administered intravenously and can be administered with heparin unfractionated from the same infusion tube.

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

Care should be taken not to prolong the initial dose infusion time and not to make errors in calculating maintenance dose infusion rates based on the patient's body weight.

Additional information on special populations:
Renal failure:
In severe renal impairment (creatinine clearance <30 ml/min) the dose of AGREDUR READY should be reduced by 50% (see also sections 4.4 and 5.2).

Liver failure:
There is no evidence of clinically significant reduction in plasma clearance of tirofiban in patients with mild to moderate hepatic impairment. It should not be used in patients with severe hepatic impairment.

Pediatric population:
There is no treatment experience with tirofiban in children under 18 years of age; therefore, the use of AGREDUR READY is not recommended in these patients.

Geriatric population:
No dose adjustment is required in the elderly (see also Section 4.4).

4.3. Contraindications
AGREDUR READY should not be used in patients with hypersensitivity to the active substance or any of the excipients in the preparation, or in patients who have had thrombocytopenia during previous use of a GP IIb/IIIa receptor antagonist.

As inhibition of platelet aggregation increases the risk of bleeding, AGREDUR READY is contraindicated in patients:

- History of stroke or any haemorrhagic stroke within the last 30 days,
- Known history of intracranial disease (e.g. neoplasm, arteriovenous malformation, aneurysm),
- Active or recent (within 30 days prior to treatment) clinically significant bleeding (e.g. gastrointestinal bleeding),
- Malignant hypertension,
- Significant trauma or major surgical intervention in the last six weeks,
- Thrombocytopenia (platelet count <100,000/mm^3), platelet function disorders,
- Coagulation disorders (e.g. prothrombin time > 1.3 times normal or INR (International Normalized Ratio) > 1,5),
- Severe liver failure.

4.4 Special warnings and precautions for use
AGREDUR READY alone is not recommended without unfractionated heparin.

Experience with the co-administration of AGREDUR READY with enoxaparin is limited (see Sections 5.1 and 5.2). Co-administration of AGREDUR READY with enoxaparin is associated with an increased frequency of cutaneous and oral bleeding events (excluding TIMI bleeding **) compared to the combination of AGREDUR READY and unfractionated heparin. The increased risk of serious bleeding events cannot be ruled out with the concomitant administration of AGREDUR READY and enoxaparin, especially in patients receiving additional unfractionated heparin with angiography and/or PCI. The efficacy of the combination of AGREDUR READY with enoxaparin has not been established. The safety and efficacy of AGREDUR READY with other low molecular weight heparins has not been investigated.

***TIMI major bleeding is defined as a defined or unspecified bleeding site, intracranial bleeding, or cardiac tamponade with a hemoglobin decrease of > 50 g/l. TIMI is defined as a hemoglobin drop of >30 g/l but ≤50 g/l, with bleeding from a known site of minor bleeding or spontaneous visible hematuria, hematemesis or hemoptysis. TIMI "Loss no site" bleeding is defined as a hemaglobin drop of >40 g/l but <50 g/l without the bleeding site being specified.*

Experience with the use of tirofiban in the following diseases and conditions is not sufficient, but an increased risk of bleeding is suspected. Therefore, AGREDUR READY is not recommended in the following situations:

- Traumatic or prolonged cardiopulmonary resuscitation, organ biopsy or lithotripsy within the past 2 weeks
- Severe trauma or major surgical intervention> 6 weeks but <3 months ago
- Active peptic ulcer in the last 3 months
- Uncontrolled hypertension (> 180/110 mm Hg)
- Acute pericarditis
- Active or known history of vasculitis
- Suspected aortic dissection
- Hemorrhagic retinopathy
- Occult blood or hematuria in the stool
- Thrombolytic therapy (see section 4.5)
- Concomitant use of drugs that significantly increase the risk of bleeding (see section 4.5).

There is no treatment experience with tirofiban in patients for whom thrombolytic therapy is indicated (eg, new pathological Q waves on ECG or raised ST segments or acute transmural myocardial infarction with left bundle branch block). Therefore, the use of AGREDUR READY is not recommended in these cases.

When situations requiring thrombolytic therapy arise (including acute occlusion during PTCA) or if the patient needs urgent coronary artery bypass graft (CABG) surgery, or if the patient needs an intraaortic balloon pump, the AGREDUR READY infusion should be stopped immediately. Efficacy data are limited in patients undergoing emergency PTCA.

There is no treatment experience with tirofiban in children; therefore, the use of AGREDUR READY is not recommended in these patients.

Other considerations and measurements
Data on repeated applications of tirofiban are insufficient.

Patients should be carefully monitored for bleeding during treatment with AGREDUR READY. If treatment of haemorrhage is required, discontinuation of AGREDUR READY should be considered (see also Section 4.9). In cases of major or uncontrolled bleeding, AGREDUR READY should be discontinued immediately.

AGREDUR READY should be used with extreme caution in the following situations and groups of patients:

- Recent clinically significant bleeding (less than 1 year),
- Entry into a vein that cannot be compressed within 24 hours prior to AGREDUR READY application,
- Recent epidural procedure (including lumbar puncture and spinal anesthesia),
- Severe acute or chronic heart failure,
- Cardiogenic shock
- Mild to moderate liver failure,
- Platelet count <150,000 mm^3, known history of coagulopathy, platelet dysfunction or thrombocytopenia,

- Hemoglobin concentration <11 g/dl or hematocrit <34%.
- Caution should be exercised when concomitantly using ticlopidine, clopidogrel, adenosine, dipyridamole, sulfinpyrazone and prostacyclin.

Dose dependent efficacy
Administration of the 10 microgram/kg bolus dose of AGREDUR READY failed to show that it was not worse at clinically relevant endpoints at 30 days compared with abciximab (see Section 5.1).

Elderly patients, female patients and patients with low body weight
The incidence of bleeding complications in elderly and/or female patients is higher than in young or male patients, respectively. Patients with low body weight have a higher incidence of bleeding than patients with higher body weight. For these reasons, AGREDUR READY should be used with caution in these patients and the heparin effect should be carefully monitored.

Kidney dysfunction
According to clinical study findings, the risk of bleeding increases as creatinine clearance decreases and hence tirofiban clearance from plasma decreases. Consequently, patients with reduced renal function (creatinine clearance <60 ml/min) should be carefully monitored for bleeding during AGREDUR READY therapy and the heparin effect should be carefully monitored. In severe renal failure the dose of AGREDUR READY should be reduced (see also section 4.2).

Access to the femoral artery
Bleeding rates increase significantly during treatment with AGREDUR READY; This increase occurs especially in the femoral artery region where the catheter sheath enters. When entering the vein, attention should be paid to puncturing only the anterior wall of the femoral artery. Arterial sheaths can be removed as soon as coagulation returns to normal, ie active clotting time (ACT) falls below 180 seconds (usually 2-6 hours after heparin cessation).
After removal of the inlet sheath, hemostasis should be achieved carefully under close supervision.

General nursing care
Vascular access and intramuscular injections should be minimized during treatment with AGREDUR READY. Intravenous access should only be done in compressible areas of the body. All venipuncture sites must be documented and closely monitored. The use of urinary catheters, nasotracheal intubation and nasogastric tubes should be carefully considered.

Follow-up of laboratory values
Platelet count, hemoglobin and hematocrit levels should be checked before starting AGREDUR READY treatment. These checks should then be performed 2-6 hours after the start of treatment and then at least daily during treatment (or more frequently if there is evidence of significant reduction). In patients who previously received GP IIb/IIIa receptor antagonists (cross-reactivity may occur), the platelet count should be measured immediately (eg within the first hour of administration after re-use) (see also section 4.8). If the platelet count falls below 90,000/mm^3, additional platelet count should be performed to exclude pseudotrombocytopenia. If thrombocytopenia is confirmed, AGREDUR READY and heparin should be discontinued. Patients should be monitored for bleeding and treated if necessary (see also Section 4.9).

In addition, the active thromboplastin time (APTT) should be determined prior to treatment and the anticoagulant effects of heparin should be carefully controlled by repeat APTT measurements and the dose adjusted accordingly (see also section 4.2). There is a potential for life-threatening bleeding when heparin is administered with other preparations that affect hemostasis, such as GP IIb/IIIa receptor antagonists.

This medicinal product contains less than 1 mmol (23 mg) sodium in each 100 ml portion; so essentially "does not contain sodium".

4.5 Interactions with other medical products and other forms of interaction

The use of many platelet aggregation inhibitors and their combination with heparin, warfarin and thrombolytic agents increases the risk of bleeding. Clinical and biological parameters of hemostasis should be monitored regularly.

Co-administration of AGREDUR READY and ASA increases the inhibition of platelet aggregation more than aspirin alone, as shown in the *ex vivo* adenosindiphosphate (ADP) induced platelet aggregation test. Combination of AGREDUR READY with unfractionated heparin prolongs bleeding time more than using unfractionated heparin alone.

There is a similar incidence of bleeding when AGREDUR READY is used concurrently with unfractionated heparin, ASA and clopidogrel, and combined use of only unfractionated heparin, ASA, and clopidogrel. (See also sections 4.4 and 4.8).

AGREDUR READY prolonged bleeding time, but co-administration of AGREDUR READY and ticlopidine did not affect bleeding time additionally.

Co-administration of warfarin with AGREDUR READY and heparin is associated with an increased risk of bleeding.

AGREDUR READY is not recommended for thrombolytic therapy [<48 hours prior to or concomitant administration of AGREDUR READY or concomitant use with drugs that significantly increase the risk of bleeding (eg, oral anticoagulants, other parenteral GP IIb/IIIa inhibitors, dextran solutions)]. There is insufficient experience with the use of tirofiban in these situations, but an increased risk of bleeding is suspected.

Additional information on special populations:
Pediatric population:
No interaction studies have been conducted.

4.6 Pregnancy and lactation
General advice
Pregnancy category is B.

Women with childbearing potential/Contraception
No data on women of childbearing potential and contraception are available for AGREDUR READY.

Pregnancy
For tirofiban, clinical data on exposure to pregnancies are not available. Studies in animals have provided limited information on pregnancy, embryo/fetal development, birth and effects on postnatal development. AGREDUR READY should not be used during pregnancy unless absolutely necessary.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and/or embryonal/fetal development and/or birth and/or postnatal development. (see section 5.3)

Lactation
Although it is not known whether tirofiban passes into breast milk, it is known to pass into rat milk. Since there is a potential for side effects in a breastfed baby, it should be decided whether to discontinue breastfeeding or drug use, considering the importance of the drug for the mother.

The reproductive capability/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 not sufficient to come to a conclusion regarding reproductive toxicity in humans.

4.7 Effects on ability to drive and use machines
There are no data on the effects of tirofiban on the ability to drive or use machines.

4.8 Undesirable effects
a. Security profile summary
The most common adverse reaction reported when tirofiban was used in combination with heparin, aspirin, and other oral anti-platelet agents was bleeding, usually including mild mucocutaneous or catheterization site bleeding. Gastrointestinal, retroperitoneal, intracranial, hemorrhoidal bleeding, epidural hematoma bleeding in the spinal region, hemopericardium, and pulmonary (alveolar) hemorrhage have also been reported. In the pivotal studies of tirofiban, TIMI major and intracranial bleeding was <2.2% and <0.1%, respectively. The most serious adverse reaction was fatal bleeding. Thrombocytopenia (thrombocyte count <90.000 mm^3) developed in 1.5% of patients treated with heparin and tirofiban in pivotal studies where tirofiban was applied. The incidence of severe thrombocytopenia (platelet count <50,000 mm^3) has been reported as 0.3%. The most common non-bleeding adverse drug reactions associated with tirofiban and heparin are (incidence> 1%), nausea (1.7%), fever (1.5%), and headache (1.1%).

b. Tabulated summary of adverse reactions
Table 2 provides a list of adverse reactions reported in post-marketing experience, as well as six double-blind controlled clinical trials (including 1953 patients who received heparin in combination with tirofiban). Within organ system classes, side effects are listed under the headings of frequency using the following categories:

Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (cannot be estimated from the available data). As post-marketing cases are derived from spontaneous reports from a

population of uncertain size, it is not possible to determine accurate incidences. Therefore, the frequency of these side effects is classified as unknown.

Table 2: Undesirable effects in clinical trials and post marketing

System Organ Classification	Very Common	Common	Rare	Unknown
Blood and lymphatic system diseases				Acute and/or severe reduction in platelet count <20,000 mm^3
Immun system diseases				Severe allergic reactions, including anaphylactic reactions
Nervous system diseases	Headache			Intracranial hemorrhage, spinal epidural hematoma
Cardiac diseases				Hemopericardium
Vascular diseases	Hematoma			
Respiratory, chest disorders and mediastinal diseases		Hemoptysis, epistaxis		Pulmonary (alveolar) hemorrhage
Gastrointestinal diseases	Nausea	Oral hemorrhage, gingival hemorrhage	GI hemorrhage, hematomatosis	Retroperitoneal bleeding
Skin and subcutaneous tissue diseases	Ecchymosis			
Kidney and urinary tract diseases		Hematuria		
General disorders and administration site diseases		Fever		
Injury, poisoning, and procedural complications	Postoperative hemorrhage*	Hemorrhage at the intravascular access site		
Research findings	Occult blood in stool or urine	Decrease in hematocrit and hemoglobin, TS <90.000 mm^3	TS <50.000 mm^3	

*Primarily associated with the catheter

c. Description of selected adverse reactions

Bleeding

The rate of major bleeding complications is low and not significantly increased with the tirofiban 0.4 microgram/kg/min infusion regimen and the 25 microgram/kg dose bolus regimen.

In the PRISM-PLUS study using tirofiban 0.4 microgram/kg infusion regimen, the incidence of major bleeding according to TIMI criteria was 1.4% for tirofiban given with heparin and 0.8% for heparin alone. The incidence of TIMI minor bleeding is 10.5% for tirofiban given with heparin and 8% for heparin alone. The percentage of patients who received blood transfusions was 4% for tirofiban given with heparin and 2.8% for heparin alone.

Data from the ADVANCE study suggest that the number of bleeding cases was low with a bolus dose of 25 micrograms/kg of tirofiban and did not significantly increase compared to placebo. There was no TIMI major bleeding and blood transfusion in either group. TIMI minor bleeding seen with a bolus dose of 25 micrograms/kg of tirofiban was reported as 4% compared to 1% in the placebo arm ($p = 0.19$).

In the On-TIME 2 study, between the tirofiban 25 microgram/kg bolus dose regimen and the control group, there was no significant change in the incidence of TIMI major bleeding (3.4% versus 2.9%, $p = 0.58$) and TIMI minor bleeding (4.4% versus 5.9%, $p = 0.206$).

In the MULTISTRATEGY study, when the standard dose of abciximab was compared with tirofiban at a dose of 25 micrograms/kg, there was no significant difference between bleeding rates of TIMI major (2.4% vs 1.6%, $p = 0.44$) and minor (4.8% vs 6.2%), $p = 0.4$).

Considering the meta-analysis of haemorrhagic complications (n = 4076 ACS patients), it was observed that the 25 microgram/kg tirofiban bolus dose regimen did not significantly increase the incidence of major bleeding or thrombocytopenia compared to placebo. In clinical trials, individual study results showed no significant difference in major bleeding rates between these two treatments when the 25 microgram/kg bolus dose regimen was compared with abciximab.

Thrombocytopenia

Acute decrease in platelet count or thrombocytopenia was observed more frequently during tirofiban treatment than in the placebo group. These decreases returned to normal after tirofiban was discontinued. Acute and severe reductions in platelets (platelet count $<20,000/mm^3$) have been observed in patients who have not experienced thrombocytopenia after re-administering GP IIb/IIIa receptor antagonists. It may be associated with chills, low-grade fever or bleeding complications.

A significantly lower rate of thrombocytopenia was shown for tirofiban in the analysis of studies comparing abciximab with 25 microgram/kg bolus dose regimens. (0.45% vs 1.7%; OR = 0.31; $p = 0.004$).

Allergic reactions

Severe allergic reactions (eg bronchospasm, urticaria), including anaphylactic reactions, occurred at the initiation of tirofiban treatment (also observed on the first day) and when reapplied. Severe thrombocytopenia (platelet count $<10,000/mm^3$) has been observed in some cases.

4.9. Overdose and therapy
In clinical studies, unintentional overdose with tirofiban hydrochloride has been observed in doses up to 50 micrograms/kg as a 3-minute bolus or as an initial infusion of 1.2 micrograms/kg/min. Overdose was also observed at a maintenance infusion rate of up to 1.47 microgram/kg/min.

Overdose symptoms
The most commonly reported symptom of overdose is bleeding. Generally, mucosal bleeding and localized bleeding in the arterial area entered for cardiac catheterization were observed. Single cases of intracranial hemorrhage and retroperitoneal hemorrhage have also been reported. (see sections 4.4 and 5.1)

Treatment
Tirofiban overdose should be treated according to the patient's condition and the physician's evaluation. If treatment of haemorrhage is required, the AGREDUR READY infusion should be discontinued. Blood and/or platelet transfusions should also be considered. AGREDUR READY can be removed by hemodialysis.

5. PHARMACOLOGIC PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic class: Blood and blood forming organs - antithrombotic agents - antithrombotic agents - Platelet aggregation inhibitors except heparin
ATC code: B01AC17

Effect mechanism
Tirofiban hydrochloride is a non-peptide antagonist of the GP IIb/IIIa receptor, which is the major platelet surface receptor involved in platelet aggregation. Tirofiban hydrochloride blocks the binding of fibrinogen to the GP IIb/IIIa receptor and blocks the aggregation of platelets.

Tirofiban hydrochloride leads to inhibition of platelet function; this has been demonstrated in its ability to inhibit *ex vivo* ADP-induced platelet aggregation and prolong bleeding time (BT). Platelet function returns to baseline within 8 hours after drug withdrawal.

The degree of this inhibition parallels the concentration of tirofiban hydrochloride in plasma.

Pharmacodynamic effects
Tirofiban; with 0.4 microgram/kg/min infusion, together with unfractionated heparin and ASA, *ex vivo* ADP-induced inhibition of platelet aggregation by more than 70% (median 89%) was achieved in 93% of patients and the bleeding time was 2.9-fold during infusion. extended. Inhibition was achieved rapidly with a 30-minute loading infusion and continued throughout the infusion.

A bolus dose of 25 micrograms/kg of tirofiban (followed by a maintenance infusion of 0.15 micrograms/kg/min for 18-24 hours), in the presence of unfractionated heparin and oral antiplatelet therapy, as measured by light transmission aggregometry (LTA), provides ADP-induced inhibition of an average maximum aggregation of 92% to 95% after 15 to 60 minutes from the start of treatment.

Clinical efficacy and safety
PRISM-PLUS Study
Double blind, multicenter, controlled PRISM-PLUS study; Patients with unstable angina (UA) or acute non-Q wave myocardial infarction (NQWMI) with prolonged recurrent angina pain or post-infarct angina accompanied by new transient or permanent ST-T wave changes or elevated cardiac enzymes; compared the efficacy of tirofiban and unfractionated heparin (n=773) with unfractionated heparin (n=797).

Patients were randomized to the following treatments:
- Tirofiban (30 minutes loading infusion 0.4 microgram/kg/min followed by 0.10 microgram/kg/min maintenance infusion per minute) and heparin (5,000 units (U) bolus followed by activated partial thromboplastin time (APTT) value is normal 1000 U/hour infusion maintenance dose)
- or heparin alone

All patients received ASA, unless contraindicated. Study drug was started 12 hours after the last angina attack. After the patients were treated for 48 hours, angiography and, if indicated, angioplasty/atherectomy were performed and tirofibana was continued at this time. Tirofiban was infused for an average of 71.3 hours.

The combined primary study endpoint was the occurrence of refractory ischaemia, myocardial infarction, or death on day 7 after starting tirofiban.

On day 7, the primary endpoint was a 32% risk reduction (RR) for the combined endpoint in the tirofiban group (17.9% versus 12.9%) (p = 0,004). This represents approximately 50 cases avoided in 1.000 patients treated. The RR of death, MI, mixed endpoint of refractory ischemic conditions or re-hospitalization for UA after 30 days was 22% (18,5% versus 22,3%; p = 0,029). After 6 months, the relative risk of death, MI, mix of refractory ischemic conditions, or rehospitalization for UA decreased by 19% (27,7% versus 32,1%; p = 0,024).

Regarding the karma of death or MI, the results on day 7, day 30 and month 6 are as follows: On day 7 there was a 43% (RR) for the tirofiban group (1,3% versus 4,9%; p = 0.006); On day 30 (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 tirofiban occurred in the early period of the treatment (within the first 48 hours) and continued for 6 months without any significant effect on mortality.

In 30% of patients who underwent angioplasty/atherectomy at first hospitalization, a RR of 43% for death or MI for the primary mixed endpoint on day 30 (5,9% vs 10,2%) as well as 46% one (RR) (15,2% versus 8,8%).

Based on a safety study, concurrent administration of tirofiban (a 30-minute loading dose of 0,4 microgram/kg/min followed by a maintenance dose of 0.1 microgram/kg/min for up to 108 hours) with enoxaparin (n=315) was compared with co-administration of tirofiban with unfractionated heparin (n = 210) in patients with UA (unstable angina) and NQWMI (non-Q wave myocardial infarction). Patients in the enoxaparin group received a subcutaneous injection of 1,0 mg/kg every 12 hours for a minimum of 24 hours and a maximum of 96 hours. Patients randomized to the unfractionated heparin group were given an intravenous bolus of 5000 units followed by a maintenance infusion of 1000 units per hour over a period

of at least 24 hours and a maximum of 108 hours. The total TIMI bleeding rate was 3,5% for the tirofiban/enoxaparin group and 4,8% for the tirofiban/unfractionated heparin group.

Although there was a significant difference in rates of subcutaneous bleeding between the two groups (29,2% in the enoxaparin group converting to unfractionated heparin and 15,2% in the unfractionated heparin group), neither group had TIMI major bleeding (see section 4.4). The efficacy of tirofiban given with enoxaparin has not been established.

The PRISM PLUS study was conducted at a time when the standard of care for the management of acute coronary syndromes was different from the present in terms of the routine use of intracoronary stents and the use of oral thrombocyte ADP receptor (P2Y12) antagonists.

ADVANCE study
The ADVANCE study determined the safety and efficacy of the tirofiban 25 micrograms/kg bolus dose compared to placebo in patients undergoing voluntary or emergency PCI who showed high risk characteristics, including the presence of greater than 70% stenosis in at least one coronary vessel and diabetes, presence of NSTE-ACS, the need for multi-vessel intervention. All patients received a loading dose of unfractionated heparin, acetyl salicylic acid (ASA), and thienopyridine followed by a maintenance dose. A total of 202 patients were randomized to either tirofiban given just before PCI (25 microgram/kg bolus IV over 3 minutes followed by 0,15 microgram/kg/min continuous IV infusion for 24-48 hours) or placebo.

Primary endpoint; Death is non-fatal MI, a mix of immediate target vessel re-vascularization (uTVR), or thrombotic rescue GP IIb/IIIa inhibitor therapy with an average follow-up of 180 days after the index procedure. Safety endpoints for major and minor bleeds were defined according to TIMI criteria.

In the therapeutic intent population, the cumulative incidence of the primary endpoint was 35% and 20% in the placebo and tirofiban groups, respectively (hazard ratio [HR] 0,51 [95% confidence interval (CI), 0,29 to 0.88]; p = 0.01). Compared with placebo, there was a significant reduction in the mix of death, MI, or uTVR in the tirofiban group (31% vs. 20% HR, 0.57 95% CI, 0.99-0.33; p = 0.048).

EVEREST study
The randomized open EVEREST study compared the upstream 0.4 microgram/kg/min dose of tirofiban initiated in the coronary care unit with a bolus dose of 25 micrograms/kg or with 0.25 mg/kg abciximab initiated 10 minutes before PCI. All patients were additionally given ASA and thienopyridine. In the study, n = 93 NSTE-ACS patients enrolled in the study underwent angiography and PCI as deemed appropriate within 24-28 hours after admission to the hospital.

Regarding the primary endpoints of tissue-level perfusion and troponin I release, the results of EVEREST indicated that the PCI TIMI myocardial perfusion grade (TMPG) was significantly lower after 0/1 (6.2% versus 20% versus 35.5% respectively; p = 0,015) and score index after PCI myocardial contrast echocardiography (TCI) (0,88 ± 0,18 versus 0,77 ± 0,32 versus 0,71 ± 0,30, respectively; p <0.05).

Incidence of cardiac Troponin I (cTnI) rise after the procedure; PCI was significantly reduced in patients treated with the upstream tirofiban regimen compared to a bolus dose of 25 micrograms/kg tirofiban or abciximab (30% versus 38,8% versus 9,4%, respectively; p = 0.018). When PCI compared with tirofiban (3,8 ± 4,1 vs. 7.2 ± 12; p = 0.015) and abciximab (3.8 ± 4.1 vs. 9 ± 13.8; p = 0.0002), after PCI, cTnI levels also decreased significantly with continued administration of tirofiban. Comparison of PCI, tirofiban 25 microgram/kg bolus dose and abciximab regimens showed that there was no significant difference in TMPG 0/1 ratio after PCI (20% versus 35%; p = NS).

On-Time 2 study
The On-Time 2 study is a multi-center, prospective, randomized, controlled clinical study designed to see early results of tirofiban administration with 25 microgram/kg bolus dose regimen in STEMI patients scheduled for primary PCI. All patients received ASA, 600 mg clopidogrel loading dose and unfractionated heparin. Tirofiban was allowed to be discontinued in line with predetermined criteria. The study was carried out in two phases; open-ended pilot study (n=414) followed by a larger double-blind phase (n=984). A combined analysis of data from both phases was predetermined to evaluate the effect of the 25 microgram/kg dose bolus regimen compared to the control measured with a primary endpoint defined as the 30-day MACE ratio (death, recurrent MI and uTVR).

In these combined analyzes, a significant decrease in the 30-day MACE rate was observed with the application of tirofiban in the first stage compared to the control group. (5.8% versus 8.6%, p = 0.043) Also, considering all causes of death, a serious trend in mortality was observed with tirofiban administration. (2.2% versus 4.1% control arm side for the tirofiban arm, p = 0.051) This benefit is mainly due to the decrease in cardiac deaths (2.1% vs 3.6%, p = 0.086). At 1-year follow-up (secondary endpoint), mortality difference (for all causes of mortality; 3.7% versus 5.8%, p = 0.078, and 2.5% versus 4.4% for cardiac mortality, p = 0.061) was measured.

In patients who underwent primary PCI (86% of the population in the pooled analyzes), a significant decrease was shown in mortality at both 30 days (1,0% in the Tirofiban group versus 3,9% in the control group, p = 0.001) and 1 year (2,4% for Tirofiban versus 5,5% for the control group, p = 0,007).

MULTISTRATEGY
The MULTISTRATEGY study was performed to compare the tirofiban bolus dosing regimen (n=372) and abciximab (n=372) in STEMI patients with either sirolimus-elution (SES) or bare metal stent (BMS), it is an open-ended, 2x2 factorial, multinational study. During angiography, tirofiban (25 microgram/kg bolus followed by 0,15 microgram/kg/min infusion over 18 to 24 hours) or abciximab (0.25 mg/kg bolus followed by 0,125 microgram/kg/min for 12 hours) infusion) started prior to arterial sheath addition. All patients received ASA, unfractionated heparin, and clopidogrel.

The primary endpoint for this drug comparison was the cumulative ST segment resolution, expressed as the proportion of patients with 50% improvement after 90 minutes of balloon inflation, and the hypothesis that tirofiban was equally effective with abciximab was tested according to this endpoint.

In the population to be treated, there was no significant difference between the administration of tirofiban (85.3%) and abciximab (83.6%) in patients with at least 50% improvement in ST

segment elevation, showing that tirofiban was not less effective than abciximab. (RR 1.020 for abciximab versus Tirofiban; for equal efficacy; 97.5% CI, 0.958 - 1.086; p <0.001)

At 30 days, the rate of major cardiac adverse events (MACE) was similar for abciximab and tirofiban (4.3% versus 4.0% relative; p = 0.85), and these results at 8 months (12.4% versus 9.9%, p = 0.30 respectively) continued in the same way.

Meta-analysis of randomized clinical trials of the 25 microgram/kg tirofiban bolus dose regimen:
Meta-analysis results evaluating the effectiveness of the tirofiban 25 mcg/kg bolus dose regimen against abciximab could not reveal a significant difference between the two agents in terms of 30-day death and MI. Similarly, there was no significant difference in 30-day mortality between tirofiban and abciximab (OR, 0.73 [0.36-1.47]; p = 0.38). In addition, in the longest follow-up study, there was no significant difference between tirofiban and abciximab for death and MI. (OR, 0.84 [0.59-1.21], p = 0.35).

Target study
In a study (TARGET) in which tirofiban was infused at a dose of 0.15 micrograms/kg/min followed by a bolus dose of 10 micrograms/kg, superiority of abciximab could not be demonstrated. The incidence of the composite primary endpoint (immediate target vessel revascularization, MI, and death at 30 days) was 7.6% in the tirofiban group compared with 6% (p = 0.038) in the abciximab group, with abciximab to be more effective in terms of clinically relevant endpoints. This difference is mainly due to the significant increase (p = 0.04) in the incidence of MI in the tirofiban group (6.9%) compared to the abciximab group (5.4%).

5.2 Pharmacokinetic properties
General properties:
Absorption:

Distribution:

Biotransformation:

Elimination:

Characteristics of patients
Gender:
The plasma clearance of tirofiban is similar in male and female patients with coronary heart disease.

Elderly patients:
Elderly patients (65 years and older) with coronary heart disease had approximately 25% lower plasma clearance of tirofiban than younger patients (65 years).

Race:
There was no difference in plasma clearance in patients of different ethnicities.

Liver Failure:
There is no evidence of clinically significant reduction in plasma clearance of tirofiban in patients with mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment.

Kidney Failure:
Clinical studies conducted in patients with reduced renal function have shown a decrease in plasma clearance of tirofiban due to the degree of decrease in creatinine clearance. In patients with creatinine clearance below 30 ml/min (including hemodialysis patients), the plasma clearance of tirofiban is clinically significantly reduced (> 50%) (see section 4.2). Tirofiban can be removed by hemodialysis.

Coronary artery disease:
In patients with unstable angina pectoris or non-Q wave myocardial infarction, the plasma clearance is about 200 ml / min and the renal clearance is 39% of the plasma clearance. Its half-life is about 2 hours.

Effects of other drugs
The plasma clearance of tirofiban in patients receiving one of the following drugs was compared in the PRISM study with a subgroup of patients (n=762) not taking that drug. These drugs had no significant effects (> 15%) on the plasma clearance of tirofiban. These drugs; acebutolol, paracetamol, alprazolam, amlodipine, aspirin preparations, atenolol, bromozepam, captoril, diazepam, digoxin, diltiazem, docusate sodium, enalapril, furosemide, glibenclamide, unfractionated heparidine, insulin, isosorbide, lovaclothine, nitrate preparations, oxazepam, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam.

The pharmacokinetics and pharmacodynamics of tirofiban have been studied when administered with enoxaparin (1 mg/kg; subcutaneously every 12 hours) and compared with a combination of tirofiban and unfractionated heparin. There was no difference in the clearance of tirofiban between the two groups.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on repeated dose toxicity and genotoxicity studies based on conventional studies of safety pharmacology. In studies, it has been shown that fertility and reproductive ability are not affected by giving intravenous infusion doses of tirofiban up to 5 mg/kg/day in female and male rats. These doses are approximately 22 times higher than the maximum recommended daily dose in humans.

However, animal studies are not sufficient to gain an idea of reproductive toxicity in humans. Tirofiban crossed the placenta in rabbits and rats.

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, AGREDUR READY and diazepam should not be administered in the same intravenous line.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature below 25°C.
Do not freeze the product. Store in the original packaging to protect from ligth.

6.5. Nature and contents of container
AGREDUR READY is presented in 100 and 250 ml ready-to-use PP bags in a box.

6.6 Special precautions for and other handling
Unused products or waste materials must be disposed of in accordance with the "Regulation Related to the Control of Medical Wastes" and "Regulation Related to the Control of Packaging Materials and Packaging Waste".

7. MARKETING AUTHORIZATION HOLDER
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