8024063-9093

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

AGGRITOR

Tirofiban Hydrochloride I.V. Injection 5mg/100ml

For Intravenous Infusion only, Single dose infusion

THERAPEUTIC CLASSIFICATION

Platelet Aggregation Inhibitor

Composition :

Each 100 ml contains :

Tirofiban Hydrochloride equivalent to

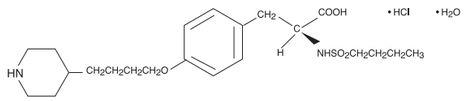
Tirofiban 5 mg

Sodium Chloride I.P. 0.9 % w/v

Water for Injections I.P. q.s.

Description

Tirofiban hydrochloride monohydrate, a non-peptide molecule, is chemically described as*N*-(butylsulfonyl)-*O*-[4-(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate. Its molecular formula is $C_{22}H_{36}N_2O_5S{\cdot}HCl{\cdot}H_2O$ and its structural formula is:



Tirofiban hydrochloride monohydrate is a white to off-white, non-hygroscopic, free-flowing powder, with a molecular weight of 495.08. It is very slightly soluble in water.

Mechanism of Action

AGGRITOR (Tirofiban Hydrochloride) is a reversible non-peptide antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation.

Pharmacodynamics

Tirofiban causes potent inhibition of platelet function as demonstrated by its ability to inhibit *ex vivo* Adenosine Phosphate (ADP)-induced platelet aggregation and prolong Bleeding Time (BT) in healthy subjects and patients with coronary artery disease. The time course of inhibition parallels the plasma concentration profile of the drug. Following discontinuation of an infusion of tirofiban, 0.1 µg/kg/min, *ex vivo* - platelet aggregation returns to near baseline in approximately 90% of patients with coronary artery disease in 4 to 8 hours. The addition of heparin to this regimen does not significantly alter the percentage of subjects with >70% Inhibition of Platelet Aggregation (IPA), but doesa increase the average bleeding time, as well as the number of patients with bleeding time prolonged to >30 minutes.

In patients with unstable angina, a two-staged intravenous infusion regimen of tirofiban (loading infusion of 0.4 µg/kg/min for 30 minutes followed by 0.1 µg/kg/min for up to 48 hours in the presence of heparin and Acetyl salicylic acid), produces approximately 90% inhibition of *ex vivo* ADP-induced platelet aggregation with a 2.9-fold prolongation of bleeding time during the infusion. Inhibition was achieved rapidly with the 30-minute loading infusion and was maintained over the duration of the infusion.

Pharmacokinetics

In healthy subjects, tirofiban is cleared from the plasma largely by renal excretion, with about 65% of a ^{14}C-labeled tirofiban dose appearing in the urine and about 25% in the feces, mainly as unchanged tirofiban. The metabolism of tirofiban appears to be limited.Tirofiban is not highly bound to plasma proteins and protein binding is concentration independent over the range of 0.01 to 25 µg/mL. Unbound fraction in human plasma is 35%. The steady state volume of distribution of tirofiban ranges from 22 to 42 liters. In healthy subjects, the plasma clearance of tirofiban ranges from 213 to 314 mL/min. Renal clearance accounts for 39 to 69% of plasma clearance. Half-life ranges from 1.4 to 1.8 hours.

In patients with coronary artery disease, the plasma clearance of tirofiban ranges from 152 to 267 mL/min. Renal clearance accounts for 39% of plasma clearance. Half-life ranges from 1.9 to 2.2 hours.

Special Populations

Gender

Plasma clearance of tirofiban in patients with coronary artery disease is similar in males and females.

Elderly

Plasma clearance of tirofiban is about 19 to 26% lower in elderly (>65 years) patients with coronary artery disease compared to younger (≤ 65 years) patients.

Race

No difference in plasma clearance was detected in patients of different races.

Hepatic Insufficiency

In patients with mild to moderate hepatic insufficiency, plasma clearance of tirofiban is not significantly different from clearance in healthy subjects.

Renal Insufficiency

Plasma clearance of tirofiban is lower to a clinically significant extent (>50%) in patients with creatinine clearance <30 mL/min, including patients requiring hemodialysis Tirofiban is removed by hemodialysis.

INDICATIONS AND CLINICAL USE

AGGRITOR (Tirofiban Hydrochloride), in combination with heparin and ASA is indicated in the management of patients with unstable angina or non-Q-wave myocardial infarction, including patients who may subsequently undergo PTCA, to decrease the rate of refractory ischemic conditions, new myocardial infarction and death.

CONTRAINDICATIONS

AGGRITOR (Tirofiban Hydrochloride) is contraindicated in patients with:

- known hypersensitivity to any component of the product
- active internal bleeding or a history of bleeding diathesis within the previous 30 days.
- a history of intracranial hemorrhage or noeplasm, anteriovenous malformation, or aneurysm
- who developed thrombocytopenia following prior exposure to AGGRITOR
- known coagulopathy, platelet disorder or history of thromobocytopenia
- stroke within 30 days prior to hospitalization or any history of hemorrhagic stroke
- major surgical procedure or severe physical trauma within the previous month
- history, symptoms or findings suggestive of aortic dissection
- severe uncontrolled hypertension (systollic blood pressure > 180 mm/Hg and/or diastolic blood pressure > 110 mm/Hg)
- concomitant use of another GP IIb/IIa inhibitor
- acute pericarditis
- cirrhosis or clinically significant liver disease
- angina precipitated by obvious provoking factors (e.g., arrhythmia, severe anemia, hyperthyroidism or hypotension)
- recent epidural procedure

WARNINGS

AGGRITOR(Tirofiban Hydrochloride) inhibits platelet aggregation and therefore caution should be employed when used with other drugs affecting hemostasis. AGGRITOR should be used with caution in the following patients:

- recent (<1year) bleeding, including a history of gastrointestinal bleeding, or genitourinary bleeding of clinical significance
- platelet count < 150,00 cells/mm³
- history of cerebrovascular disease within 1 year
- hemorrhagic retinopathy
- chronic hemodialysis

Use in Pregnancy

Tirofiban has been shown to cross the placenta in pregnant rats and rabbits. However, there are no adequate and well controlled studies in pregnant women. Tirofiban should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether AGGRITOR is excreted in human milk. However, significant levels of tirofiban are excreted in rat milk. Because many drugs are excreted in human milk, and 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.

Pediatric Use

Safety and effectiveness in Pediatric patients (<18 years old)have not been established.

Geriatric Use

The effect of Tirofiban hydrochloride in the elderly (≥65 years) appeared similar to that seen in younger patients (<65 years). Elderly patients receiving Tirofiban hydrochloride with heparin or heparin alone had a higher incidence of bleeding complications than younger patients, but the incremental risk of bleeding in patients treated with Tirofiban hydrochloride in combination with heparin compared to the risk in patients treated with heparin alone was similar regardless of age.

The overall incidence of non-bleeding adverse events was higher in older patients (compared to younger patients) but this was true both for Tirofiban hydrochloride with heparin and heparin alone. No dose adjustment is recommended for the elderly population.

PRECAUTIONS

Bleeding Precautions

AGGRITOR (Tirofiban Hydrochloride) inhibits platelet aggregation and therefore caution should be employed when it is used with other drugs that affect hemostasis (e.g., warfarin). The safety of AGGRITOR when used in combination with thrombolytic agents has not been established.

During therapy with AGGRITOR, patients should be monitored for potential bleeding. When bleeding cannot be controlled with pressure, infusion of AGGRITOR and heparin should be discontinued. Transfusions may be given if required.

Fatal bleedings have been reported (see ADVERSE REACTIONS).

Femoral Artery Access Site

AGGRITOR is associated with minor increases in bleeding rates particularly at the site of arterial access for femoral sheath placement. Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured [a Seldinger (through and through) technique for obtaining sheath access should be avoided]. Arterial sheaths should be removed when the patient's activated clotting time is <180 sec or 2 - 6 hours following cessation of heparin.

Laboratory Monitoring

Baseline evaluation: Should be performed on platelet count, hematocrit, hemoglobin and activated Partial Thromboplastin Time (aPTT) prior to treatment.

Following the loading infusion: Monitor platelet count within 6 hours following the loading infusion and at least daily thereafter (or more frequently if there is evidence of significant decline). Acute decrease in platelet count to <20,000 cells/mm³ within one day after start of therapy with AGGRITOR have been reported post-marketing.

In patients previously exposed to GP IIb/IIIa receptor antagonists: Monitor platelet count earlier and more often. Platelet decreases have been observed in patients with no prior history of thrombocytopenia upon re-administration of GP IIb/IIIa receptor antagonists.

If the platelet count decreases to <90,000 cells/mm³: Evaluate to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed discontinue AGGRITOR and heparin and treat appropriately.

Monitor aPTT: Monitor aPTT frequently and adjust the dose of heparin accordingly. Potentially lifethreatening bleeding may occur especially when heparin is administered with other products affecting hemostasis, such as GP IIb/IIIa receptor antagonists .

Renal Insufficiency

Patients with moderate (creatinine clearance <60 mL/min) and severe (creatinine clearance < 30mL/min) renal insufficiency should be monitored for bleeding complications. Since clinical studies showed a decreased plasma clearance of tirofiban in patients with severe renal insufficiency, the dosage should be reduced in these patients.

Drug Interactions

Tirofiban has been studied on a background of aspirin and heparin.

The use of Tirofiban, in combination with heparin and aspirin, has been associated with an increase in bleeding compared to heparin and aspirin alone. Caution should be employed when Tirofiban is used with other drugs that affect hemostasis (e.g., warfarin). No information is available about the concomitant use of Tirofiban with thrombolytic agents.

There were no clinically significant effects of co-administration 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, heparin, insulin, isosorbide, lorazepam, lovastatin, metoclopramide, metoprolol, morphine, nifedipine, nitrate preparations, oxazepam, potassium chloride, propranolol, ranitidine, simvastatin, sucralfate and temazepam. Patients who received levothyroxine or omeprazole along with Tirofiban had a higher rate of clearance of Tirofiban. The clinical significance of this is unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Tirofiban has not been evaluated.

Tirofiban HCl was negative in the *in vitro* microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays.

There was no induction of chromosomal aberrations in bone marrow cells of male mice after the administration of intravenous doses up to 5 mg tirofiban/kg (about 3 times the maximum recommended daily human dose when compared on a body surface area basis). Fertility and reproductive performance were not affected in studies with male and female rats given intravenous doses of tirofiban hydrochloride up to 5 mg/kg/day (about 5 times the maximum recommended daily human dose when compared on a body surface area basis).

ADVERSE REACTIONS

In clinical trials, 1946 patients received tirofiban hydrochloride in combination with heparin and 2002 patients received tirofiban hydrochloride alone. Duration of exposure was up to 116 hours. 43% of the population was >65 years of age and approximately 30% of patients were female.

BLEEDING

The most common drug-related adverse event reported during therapy with tirofiban hydrochloride when used concomitantly with heparin and aspirin, was bleeding (usually reported by the investigators as oozing or mild). The incidences of major and minor bleeding using the TIMI criteria in the PRISM-PLUS and RESTORE studies are shown below.

	PRISM-PLUS* (UAP/Non-Q-Wave MI Study)		RESTORE* (Angioplasty/Atherectomy Study)	
	TIROFIBAN HYDROCHLORIDE† + Heparin‡	Heparin‡	TIROFIBAN HYDROCHLORIDE§ + Heparin¶	Heparin¶
Bleeding	(n=773) %(n)	(n=797) %(n)	(n=1071) %(n)	(n=1070) %(n)
Major Bleeding (TIMI Criteria)#	1.4 (11)	0.8 (6)	2.2 (24)	1.6 (17)
Minor Bleeding (TIMI Criteria)Þ	10.5 (81)	8.0 (64)	12.0 (129)	6.3 (67)
Transfusions	4.0 (31)	2.8 (22)	4.3 (46)	2.5 (27)

* Patients received aspirin unless contraindicated.

† 0.4 mcg/kg/min loading infusion; 0.10 mcg/kg/min maintenance infusion.

‡ 5,000 U bolus followed by 1,000 U/hr titrated to maintain an APTT of approximately 2 times control.

§ 10 mcg/kg bolus followed by infusion of 0.15 mcg/kg/min.

¶ Bolus of 10,000 U or 150 U/kg for patients <70 kg followed by administration as necessary to maintain ACT in approximate range of 300 to 400 seconds during procedure.

Hemoglobin drop of >50g/L with or without an identified site, intracranial hemorrhage, or cardiac tamponade.

Þ Hemoglobin drop of >30 g/L with bleeding from a known site, spontaneous gross hematuria, hematemesis or hemoptysis.

There were no reports of intracranial bleeding in the PRISM-PLUS study for tirofiban hydrochloride in combination with heparin or in the heparin control group. The incidence of intracranial bleeding in the RESTORE study was 0.1% for tirofiban hydrochloride in combination with heparin and 0.3% for the control group (which received heparin). In the PRISM-PLUS study, the incidences of retroperitoneal bleeding reported for tirofiban hydrochloride in combination with heparin, and for the heparin control group were 0.0% and 0.1%, respectively.

In the RESTORE study, the incidences of retroperitoneal bleeding reported for tirofiban hydrochloride in combination with heparin, and the control group were 0.6% and 0.3%, respectively. The incidences of TIMI major gastrointestinal and genitourinary bleeding for tirofiban hydrochloride in combination with heparin in the PRISM-PLUS study were 0.1% and 0.1%, respectively; the incidences in the RESTORE study for tirofiban hydrochloride in combination with heparin were 0.2% and 0.0%, respectively.

The incidence rates of TIMI major bleeding in patients undergoing percutaneous procedures in PRISM-PLUS are shown below.

	Tirofiban Hydrochloride + Heparin		Heparin	
	n	%	n	%
Prior to Procedures	2/773	0.3	1/797	0.1
Following Angiography	9/697	1.3	5/708	0.7
Following PTCA	6/239	2.5	5/236	2.2

The incidence rates of TIMI major bleeding (in some cases possibly reflecting hemodilution rather than actual bleeding) in patients undergoing CABG in the PRISM-PLUS and RESTORE studies within one day of discontinuation of tirofiban hydrochloride are shown below.

	Tirofiban Hydrochloride + Heparin		Heparin	
	n	%	n	%
PRISM-PLUS	5/29	17.2	11/31	35.4
RESTORE	3/12	25.0	6/16	37.5

Female patients and elderly patients receiving tirofiban hydrochloride with heparin or heparin alone had a higher incidence of bleeding complications than male patients or younger patients. The incremental risk of bleeding in patients treated with tirofiban hydrochloride in combination with heparin over the risk in patients treated with heparin alone was comparable regardless of age or gender. No dose adjustment is recommended for these populations.

NON-BLEEDING

The incidences of non-bleeding adverse events that occurred at an incidence of >1% and numerically higher than control, regardless of drug relationship, are shown below:

	Tirofiban Hydrochloride + Heparin (n=1953) %	Heparin (n=1887) %
Body as a Whole		
Edema/swelling	2	1
Pain, pelvic	6	5
Reaction, vasovagal	2	1
Cardiovascular System		
Bradycardia	4	3
Dissection, coronary artery	5	4
Musculoskeletal System		
Pain, leg	3	2
Nervous System/Psychiatric		
Dizziness	3	2
Skin and Skin Appendage		
Sweating	2	1

Other non-bleeding side effects (considered at least possibly related to treatment) reported at a >1% rate with tirofiban hydrochloride administered concomitantly with heparin were nausea, fever, and headache; these side effects were reported at a similar rate in the heparin group.

In clinical studies, the incidences of adverse events were generally similar among different races, patients with or without hypertension, patients with or without diabetes mellitus, and patients with or without hypercholesteremia. The overall incidence of non-bleeding adverse events was higher in female patients (compared to male patients) and older patients (compared to younger patients). However, the incidences of non-bleeding adverse events in these patients were comparable between the tirofiban hydrochloride with heparin and the heparin alone groups.

Allergic Reactions/Readministration

Anaphylaxis has been reported in post-marketing experience. No information is available regarding the development of antibodies to tirofiban.

Laboratory Findings

The most frequently observed laboratory adverse events in patients receiving tirofiban hydrochloride concomitantly with heparin were related to bleeding. Decreases in hemoglobin (2.1%) and hematocrit (2.2%) were observed in the group receiving tirofiban hydrochloride compared to 3.1% and 2.6%, respectively, in the heparin group. Increases in the presence of urine and fecal occult blood were also observed (10.7% and 18.3%, respectively) in the group receiving tirofiban hydrochloride compared to 7.8% and 12.2%, respectively, in the heparin group. Patients treated with tirofiban hydrochloride, with heparin, were more likely to experience decreases in platelet counts than the control group. These decreases were reversible upon discontinuation of tirofiban hydrochloride. The percentage of patients with a decrease of platelets to < 90,000/mm^3 was 1.5%, compared with 0.6% in the patients who received heparin alone. The percentage of patients with a decrease of platelets to <50,000/mm^3 was 0.3%, compared with 0.1% of the patients who received heparin alone. Platelet decreases have been observed in patients with no prior history of thrombocytopenia upon readministration of GP IIb/IIIa receptor antagonists.

Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing experience: *Bleeding:* Intracranial bleeding, retroperitoneal bleeding, hemopericardium, pulmonary (alveolar) hemorrhage, and spinal-epidural hematoma. Fatal bleeding events have been reported; *Body as a Whole:* Acute and/or severe decreases in platelet counts which may be associated with chills, low-grade fever, or bleeding complications; *Hypersensitivity:* Severe allergic reactions including anaphylactic reactions. The reported cases have occurred during the first day of tirofiban infusion, during initial treatment, and during readministration of tirofiban. Some cases have been associated with severe thrombocytopenia (platelet counts <10,000/mm^3).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In clinical trials, inadvertent overdosage with Tirofiban Hydrochloride occurred in doses up to 5 times and 2 times the recommended dose for bolus administration and loading infusion, respectively. Inadvertent overdosage occurred in doses up to 9.8 times of the 0.15 µg/kg/min maintenance infusion rate. The most frequently reported manifestation of overdosage was bleeding, primarily minor mucocutaneous bleeding events and minor bleeding at the sites of cardiac catheterization. Overdosage of Tirofiban Hydrochloride should be treated by assessment of the patient's clinical condition and cessation or adjustment of the drug infusion as appropriate. Tirofiban Hydrochloride is dialyzable.

DOSAGE AND ADMINISTRATION

DOSAGE

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

Use with Aspirin and Heparin

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

STORAGE : Store below 25^{0}C. Do not freeze. Protect from light during storage.

Keep out of reach of children.

EXPIRY: Do not use later than the date of expiry.

PRESENTATION : 100ml Vial.

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