SBiocon

Tirofiban Injection



Composition :

Each mL contains Tirofiban hydrochloride equivalent to Tirofiban 50µg Water for Injection IP q.s

DESCRIPTION:

Tirofiban hydrochloride a non-peptide antagonist of the platelet glycoprotein (GP) llb/lla receptor, inhibits platelet aggregation. Tirofiban a white to off-white, non-hygroscopic, free-flowing powder, with a molecular weight of 495.08. It is very slightly soluble in water.

Tirofiban hydrochloride is chemically described as N-(butylsulfonyl)-O-[4-(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate. Its molecular formula is ${}_{c2}C_{HB}6_{N}2_{o}55$ -HCl- ${}_{H}2O$.

Mechanism of action:

Tirofiban inhibits platelet aggregation by reversibly binding to the receptor glycoprotein (GP) llb/lla of human platelets, thus preventing the binding of fibrinogen. Inhibition of platelet aggregation occurs in a dose- and concentrationdependent manner.

Pharmacokinetics:

When given according to the recommended regimen, >90% of platelet inhibition is attained by the end of the 30-minute infusion.

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.

Tirofiban has a half-life of approximately 2 hours. It is cleared from the plasma largely by renal excretion, with about 65% of an administered dose appearing in urine and about 25% in feces, both largely as unchanged Tirofiban. Metabolism appears to be limited.

Renal clearance accounts for 39 to 69% of plasma clearance. The recommended regimen of a loading infusion followed by a maintenance infusion produces a peak Tirofiban plasma concentration that is similar to the steady state concentration during the infusion. In patients with coronary artery disease, the plasma clearance of Tirofiban ranges from 152 to 267 mL/min.

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 than in 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 significantly decreased (>50%) in patients with creatinine clearance <30 mL/min, including patients requiring hemodialysis Tirofiban is removed by hemodialysis.

Pregnancy:

Pregnancy Category B

Tirofiban has been shown to cross the placenta in pregnant rats and rabbits. Studies with Tirofiban HCI at intravenous doses up to 5 mg/kg/day (about 5 and 13 times the maximum recommended daily human dose for rat and rabbit, respectively, when compared on a body surface area basis) have revealed no harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.



Nursing Mothers:

It is not known whether Tirofiban is excreted in human milk. However, significant levels of Tirofiban were shown to be present 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.

Indications:

Tirofiban, in combination with Heparin, is indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy.

Contraindications:

Tirofiban 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, intracranial neoplasm, arteriovenous malformation, or aneurysm
- a history of thrombocytopenia following prior exposure to Tirofiban
- history of stroke within 30 days 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 hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure>110 mmHq)
- concomitant use of another parenteral GP llb/llla inhibitor
- acute pericarditis

Warnings:

Bleeding is the most common complication encountered during therapy with Tirofiban. Administration of Tirofiban is associated with an increase in bleeding events classified as both major and minor bleeding events by criteria developed by the Thrombolysis in Myccardial Infarction Study group (TIMI).

Most major bleeding associated with Tirofiban occurs at the arterial access site for cardiac catheterization. Tirofiban should be used with caution in patients with platelet count <150,000/mm3 and in patients with hemorrhagic retinopathy. Because Tirofiban inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis. The safety of Tirofiban when used in combination with thrombolytic agents has not been established.

During therapy with Tirofiban, patients should be monitored for potential bleeding. When bleeding cannot be controlled with pressure, infusion of Tirofiban and Heparin should be discontinued.

Precautions:

Bleeding Precautions Percutaneous Coronary Intervention – Care of the femoral artery access site:

Therapy with Tirofiban is associated with increases in bleeding rates particularly at the site of arterial access for femoral sheath placement. Care should be taken when attempting vacular access that only the anterior wall of the femoral artery is punctured. Prior to pulling the sheath, Heparin should be discontinued for 3-4 hours and activated clotting time (ACT) <180 seconds or APTT <45 seconds should be documented. Care should be taken to obtain proper hemostasis after removal of the sheaths using standard compressive techniques followed by close observation. While the vascular sheath is in place, patients should be affected limb restrained in a straight position. Sheath hemostasis should be achieved at least 4 hours before hospital discharge.

Minimize Vascular and Other Trauma:

Other arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation and nasogastric tubes should be minimized. When obtaining intravenous access, non-compressible sites (e.g., subclavian or jugular veins) should be avoided.

Laboratory Monitoring:

Platelet counts, and hemoglobin and hematocrit should be monitored prior to treatment, within 6 hours following the loading infusion, and at least daily thereafter during therapy with Tirofiban (or more frequently if there is evidence of significant decline). If the patient experiences a platelet decrease to <90,000/mm³, additional platelet counts should be performed to exclude pseudo thrombocytopenia. If thrombocytopenia is confirmed, Tirofiban and Heparin should be discontinued and the condition appropriately monitored and treated.

To monitor unfractionated Heparin, APTT should be monitored 6 hours after the start of the Heparin infusion; Heparin should be adjusted to maintain APTT at approximately 2 times control.

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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.

In a sub-set of patients (n=762) in the PRISM study, the plasma clearance of Tirofiban in patients receiving one of the following drugs was compared to that in patients not receiving that drug.

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, Dilitazem, Docusate Sodium, Enalapril, Furosemide, Glyburide, Heparin, Insulin, Isosorbide, Lorazepam, Lovastatin, Metoclopramide, Metoprolol, Morphine, Nifedipine, Nitrat, Preparations, Oxazepam. Potassium Chloride, Propranolol, Ranitidine, Simwastatin, 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 HCI 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 in combination with Heparin and 2002 patients received Tirofiban 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 when used concomitantly with Heparin and Aspirin, was bleeding (usually reported by the investigators as oozing or mild).

There were no reports of intracranial bleeding in the PRISM-PLUS study for Tirofiban in combination with Heparin or in the Heparin control group.

In the PRISM-PLUS study, the incidences of retroperitoneal bleeding reported for Tirofiban 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 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 in combination with Heparin in the PRISM-PLUS study were 0.1% and 0.1%, respectively; the incidences in the RESTORE study for Tirofiban in combination with Heparin were 0.2% and 0.0%, respectively.

Female patients and elderly patients receiving Tirofiban with Heparin or Heparin alone had a higher incidence of bleeding complications than male patients or younger patients. No dose adjustment is recommended for these populations.

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

Allergic Reactions/Readministration

No patients in the clinical database developed anaphylaxis and/or hives requiring discontinuation of the infusion of Tirofiban. No information is available regarding the development of antibodies to Tirofiban; very few patients received Tirofiban twice.

Laboratory Findings

The most frequently observed laboratory adverse events in patients receiving Tirofiban concomitantly with Heparin were related to bleeding. Decreases in hemoglobin (2.1%) and hematocrit (2.2%) were observed in the group receiving Tirofibian 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 compared to 7.8% and 12.2%, respectively, in the Heparin group.

Patients treated with Tirofiban, with Heparin, were more likely to experience decreases in platelet counts than the control group. These decreases were reversible upon discontinuation of Tirofiban. The percentage of patients with a decrease of platelets to <90,000/mm³ 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/mm³ was 0.3%, compared with 0.1% of the patients who received Heparin alone.

Overdosage:

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In clinical trials, inadvertent overdosage with Tirofiban 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 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 should be treated by assessment of the patient's clinical condition and cessation or adjustment of the drug infusion as appropriate. Tirofiban can be removed by hemodialysis.

Use with Aspirin and Heparin

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

Precautions

Tirofiban is intended for intravenous delivery using sterile equipment and technique. Do not add other drugs or remove solution directly from the bag with a syringe. Do not use plastic containers in series connections; such use can result in air embolism by drawing air from the first container if it is empty of solution. Discard unused solution 24 hours following the start of infusion.

Recommended Dosage

In most patients, Tirofiban 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 The table below is provided as a guide to dosage adjustment by weight.

Storage

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

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