

TIROFIBAN HYDROCHLORIDE - tirofiban injection, solution

Gland Pharma Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **TIROFIBAN HYDROCHLORIDE INJECTION** safely and effectively. See full prescribing information for **TIROFIBAN HYDROCHLORIDE INJECTION**.

TIROFIBAN HYDROCHLORIDE injection, for intravenous use

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Tirofiban hydrochloride injection is a platelet aggregation inhibitor indicated to reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with non-ST elevation acute coronary syndrome (NSTEMI/ACS). (1)

DOSAGE AND ADMINISTRATION

- Administer intravenously 25 mcg/kg within 5 minutes and then 0.15 mcg/kg/min for up to 18 hours. In patients with creatinine clearance ≤ 60 mL/min, give 25 mcg/kg within 5 minutes and then 0.075 mcg/kg/min. (2)

DOSAGE FORMS AND STRENGTHS

Injection: 12.5 mg/250 mL (50 mcg/mL) in 250 mL bag. (3) (3)

CONTRAINDICATIONS

- Known hypersensitivity to any component of tirofiban hydrochloride injection. (4)
- History of thrombocytopenia with prior exposure to tirofiban hydrochloride injection. (4)
- Active internal bleeding, or history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month. (4)

WARNINGS AND PRECAUTIONS

- Tirofiban hydrochloride injection can cause serious bleeding. If bleeding cannot be controlled discontinue tirofiban hydrochloride injection. (5.1)
- Thrombocytopenia: Discontinue tirofiban hydrochloride injection and heparin. (5.2)

ADVERSE REACTIONS

Bleeding is the most commonly reported adverse reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gland Pharma at 864-879-9994 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Coadministration of fibrinolytics, anticoagulants and antiplatelet agents, increases the risk of bleeding. (7)

USE IN SPECIFIC POPULATIONS

- Renal Insufficiency: Reduce the dose in patients with severe renal insufficiency. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tirofiban hydrochloride injection is indicated to reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with non-ST elevation acute coronary syndrome (NSTEMI/ACS).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is 25 mcg/kg administered intravenously within 5 minutes and then 0.15 mcg/kg/min for up to 18 hours.

2.2 Administration

For intravenous use only. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To open the 250 mL premixed bag, first tear off its foil overpouch. The plastic may be somewhat opaque because of moisture absorption during sterilization; the opacity will diminish gradually. Check for leaks by squeezing the inner bag firmly; if any leaks are found or sterility is suspect then the solution should be discarded. Do not use unless the

solution is clear and the seal is intact.

Administration Instructions

1. The bolus dose of tirofiban hydrochloride injection may be administered from the 250 mL premixed bag. Do not dilute. Administer the bolus dose within 5 minutes via an IV pump.
2. Immediately following the bolus dose administration, administer the maintenance infusion from the 250 mL premixed bag via an IV pump.
3. Discard any unused portion left in the bag.

The recommended bolus volume using 250 mL premixed bag can be calculated using the following equation:

$$\text{Bolus Volume (mL)} = \frac{25 \text{ mcg/kg} \times \text{body weight (kg)}}{50 \text{ mcg/mL}}$$

The recommended infusion rate for patients with CrCl (Creatinine Clearance) > 60 mL/min using the 250 mL premixed bags can be calculated using the following equation:

$$\text{Infusion Rate for CrCl} > 60 \text{ mL/min (mL/h)} = \frac{0.15 \text{ mcg/kg/min} \times \text{body weight (kg)} \times 60 \text{ min/h}}{50 \text{ mcg/mL}}$$

Example calculation of infusion rate for 60 kg patient with CrCl > 60 mL/min using the 250 mL premixed bag:

$$\text{Infusion Rate for CrCl} > 60 \text{ mL/min (mL/h)} = \frac{0.15 \text{ mcg/kg/min} \times 60 \text{ kg} \times 60 \text{ min/h}}{50 \text{ mcg/mL}} = 10.8 \text{ mL/h}$$

Drug Compatibilities

Tirofiban hydrochloride injection can be administered in the same intravenous line as heparin, atropine sulfate, dobutamine, dopamine, epinephrine hydrochloride (HCl), famotidine injection, furosemide, lidocaine, midazolam HCl, morphine sulfate, nitroglycerin, potassium chloride, and propranolol HCl. Do not administer tirofiban hydrochloride injection through the same IV line as diazepam. Do not add other drugs or remove solution directly from bag with a syringe.

2.3 Dose Adjustment for Renal Impairment

The recommended dosage in patients with CrCl ≤ 60 mL/min (calculated using the Cockcroft-Gault equation with actual body weight) is 25 mcg/kg intravenously within 5 minutes and then 0.075 mcg/kg/min, for up to 18 hours.

The recommended infusion rate for patients with CrCl ≤ 60 mL/min using the 250 mL premixed bag can be calculated using the following equation:

$$\text{Infusion Rate for CrCl} \leq 60 \text{ mL/min (mL/h)} = \frac{0.075 \text{ mcg/kg/min} \times \text{body weight (kg)} \times 60 \text{ min/h}}{50 \text{ mcg/mL}}$$

3 DOSAGE FORMS AND STRENGTHS

Tirofiban hydrochloride injection 12.5 mg tirofiban per 250 mL (50 mcg/mL) is a clear, non-preserved, colorless, isosmotic, sterile premixed injection with sodium chloride for tonicity adjustment.

4 CONTRAINDICATIONS

Tirofiban hydrochloride injection is contraindicated in patients with:

- Severe hypersensitivity reaction to tirofiban hydrochloride injection (i.e., anaphylactic reactions) [see *Adverse Reactions* (6.2)].
- A history of thrombocytopenia following prior exposure to tirofiban hydrochloride injection [see *Adverse Reactions* (6.1)].
- Active internal bleeding or a history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month [see *Adverse Reactions* (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Bleeding is the most common complication encountered during therapy with tirofiban hydrochloride injection. Most bleeding associated with tirofiban hydrochloride injection occurs at the arterial access site for cardiac catheterization. Minimize the use of traumatic or potentially traumatic procedures such as arterial and venous punctures, intramuscular injections, nasotracheal intubation, etc.

Concomitant use of fibrinolytics, anticoagulants and antiplatelet drugs increases the risk of bleeding.

5.2 Thrombocytopenia

Profound thrombocytopenia has been reported with tirofiban hydrochloride injection. Monitor platelet counts beginning about 6 hours after treatment initiation and daily thereafter. If the platelet count decreases to < 90,000/mm³, monitor platelet counts to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, discontinue tirofiban hydrochloride injection and heparin. Previous exposure to a glycoprotein (GP) IIb/IIIa receptor antagonist may increase the risk of developing thrombocytopenia [see *Adverse Reactions* (6.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the PRISM (Platelet Receptor Inhibition for Ischemic Syndrome Management), PRISM-PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management — Patients Limited by Unstable Signs and Symptoms) and RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) trials, 1946 patients received tirofiban hydrochloride injection in combination with heparin and 2002 patients received tirofiban hydrochloride injection alone for about 3 days. Forty-three percent of the population was > 65 years of age and approximately 30% of patients were female. In clinical studies with the recommended regimen (25 mcg/kg bolus followed by a 0.15 mcg/kg/min maintenance infusion), tirofiban hydrochloride injection was administered in combination with aspirin, clopidogrel and heparin or bivalirudin to over 8000 patients for typically ≤ 24 hours. Approximately 30% of the population was > 65 years of age and approximately 25% were female.

Bleeding

PRISM-PLUS Regimen

The incidences of major and minor bleeding using the TIMI criteria in the PRISM-PLUS study are shown below.

Table 2 TIMI Major and Minor Bleeding in PRISM-PLUS

		PRISM-PLUS (NSTE-ACS)
Bleeding (TIMI Criteria)† §	Tirofiban Hydrochloride Injection * + Heparin (N=773)	Heparin alone (N=797)
Major Bleeding	1.4%	0.8%
Minor Bleeding	10.5%	8.0%
Transfusions	4.0%	2.8%

* 0.4 mcg/kg/min initial infusion; 0.10 mcg/kg/min maintenance infusion.
†Major = Hemoglobin drop of >5.0 g/dL with or without an identified site, intracranial hemorrhage, or cardiac tamponade.
§Minor = Hemoglobin drop of >3.0 g/dL with bleeding from a known site, spontaneous gross hematuria, hematemesis or hemoptysis.

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

Table 3 TIMI Major Bleeding Associated with Percutaneous Procedures in PRISM-PLUS

	Tirofiban Hydrochloride Injection + Heparin		Heparin alone	
	N	%	N	%
Prior to Procedures	773	0.3	797	0.1
Following Angiography	697	1.3	708	0.7
Following PTCA	239	2.5	236	2.2

The incidence rates of TIMI major bleeding in patients undergoing coronary artery bypass graft surgery (CABG) in PRISM-PLUS within one day of discontinuation of tirofiban hydrochloride injection were 17% on tirofiban hydrochloride injection plus heparin (N=29) and 35% on heparin alone (N=31).

Recommended ("High-Dose Bolus") Regimen

Rates of major bleeds (including any intracranial, intraocular or retroperitoneal hemorrhage, clinically overt signs of hemorrhage associated with a drop in hemoglobin of > 3 g/dL or any drop in hemoglobin by 4g/dL, bleeding requiring transfusion of \geq 2U blood products, bleeding directly resulting in death within 7 days or hemodynamic compromise requiring intervention) were consistent with the rates observed in subjects administered the PRISM-PLUS regimen of tirofiban hydrochloride injection. There was a trend toward greater bleeding in ST segment elevation myocardial infarction (STEMI) patients treated with fibrinolytics prior to administration of tirofiban hydrochloride injection using the recommended regimen during rescue PCI.

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:

Table 4 Non-bleeding Adverse Reactions in PRISM-PLUS

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

Thrombocytopenia

Patients treated with tirofiban hydrochloride injection plus heparin, were more likely to experience decreases in platelet counts than were those on heparin alone. These decreases were reversible upon discontinuation of tirofiban hydrochloride injection. The percentage of patients with a decrease of platelets to $< 90,000/\text{mm}^3$ was 1.5%, compared with 0.6% in the patients who received heparin alone. The percentage of patients with a decrease of platelets to $< 50,000/\text{mm}^3$ was 0.3%, compared with 0.1% of the patients who received heparin alone.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of tirofiban hydrochloride injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure.

Hypersensitivity: Severe allergic reactions including anaphylactic reactions have occurred during the first day of tirofiban hydrochloride injection infusion, during initial treatment, and during readministration of tirofiban hydrochloride injection. Some cases have been associated with severe thrombocytopenia (platelet counts $< 10,000/\text{mm}^3$). No information is available on the formation of antibodies to tirofiban.

7 DRUG INTERACTIONS

Concomitant use of fibrinolytics, anticoagulants and antiplatelet drugs increases the risk of bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

While published data cannot definitively establish the absence of risk, available published case reports have not established an association with tirofiban use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. Untreated myocardial infarction can be fatal to the pregnant women and fetus (see Clinical Considerations). Studies with tirofiban HCl 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.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Myocardial infarction is a medical emergency in pregnancy which can be fatal to the pregnant woman and fetus if left untreated.

Data

Animal Data

There was no evidence of maternal or developmental toxicity in any of the studies in Table 5.

Table 5 Developmental Toxicity Studies

Type of Study	Species	Dose/Exposure*	Duration/Timing Exposure
1) Range-finding	Rat (N=30)	1, 2, 5 mg/kg/day IV (N=10 per group)	Once daily from GD 6 through LD 20
2) Developmental Toxicity	Rat (N=66)	1, 2, 5 mg/kg/day IV (N=22 per group)	Once daily from GD 6 through GD 20
3) Developmental Toxicity with Postweaning Evaluation	Rat (N=66)	1, 2, 5 mg/kg/day IV (N=22 per group)	Once daily from GD 6 through LD 20
4) Range-finding (non-pregnant)	Rabbit (N=21)	1, 2, 5 mg/kg/day IV (N=7 per group)	Once daily for 14 days
5) Range-finding (pregnant)	Rabbit (N=30)	1, 2, 5 mg/kg/day IV (N=10 per group)	Once daily from GD 7 through GD 20
6) Developmental Toxicity	Rabbit (N=60)	1, 2, 5 mg/kg/day (N=20 per group) IV	Once daily from GD 7 through GD 20

*5 mg/kg/day is ~5 and 13 times the maximum recommended daily human dose for rat and rabbit, respectively, when compared on a body surface area basis.

8.2 Lactation

Risk Summary

There is no data on the presence of tirofiban in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on human milk production. However, tirofiban is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tirofiban hydrochloride injection and any potential adverse effects on the breastfed child from tirofiban hydrochloride injection or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in controlled clinical studies of tirofiban hydrochloride injection, 43% were 65 years and over, while 12% were 75 years and over. With respect to efficacy, the effect of tirofiban hydrochloride injection in the elderly (≥ 65 years) appeared similar to that seen in younger patients (< 65 years). Elderly patients receiving tirofiban hydrochloride injection with heparin or heparin alone had a higher incidence of bleeding complications than did younger patients, but the incremental risk of bleeding in patients treated with tirofiban hydrochloride injection in combination with heparin compared to the risk in patients treated with heparin alone was similar regardless of age. No dose adjustment is recommended for the elderly population [see *Dosage and Administration* (2)].

8.6 Renal Insufficiency

Patients with moderate to severe renal insufficiency have decreased plasma clearance of

tirofiban hydrochloride injection. Reduce the dosage of tirofiban hydrochloride injection in patients with severe renal insufficiency [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

Safety and efficacy of tirofiban hydrochloride injection has not been established in patients on hemodialysis.

10 OVERDOSAGE

In clinical trials, inadvertent overdosage with tirofiban hydrochloride injection occurred in doses up to 2 times the recommended dose for initial infusion doses. Inadvertent overdosage occurred in doses up to 9.8 times the 0.15 mcg/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 [see *Warnings and Precautions (5.1)*].

Overdosage of tirofiban hydrochloride injection should be treated by assessment of the patient's clinical condition and cessation or adjustment of the drug infusion as appropriate.

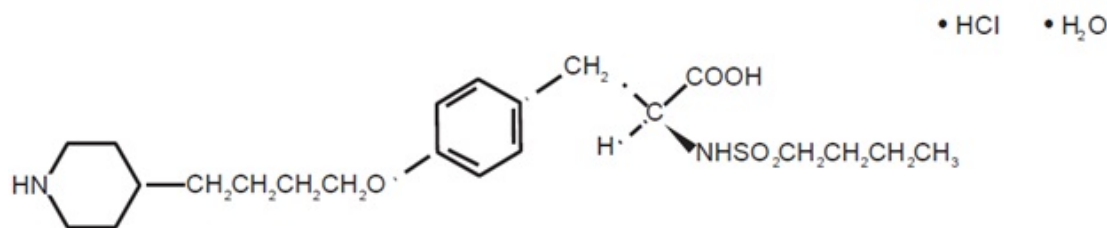
Tirofiban hydrochloride injection can be removed by hemodialysis.

11 DESCRIPTION

Tirofiban hydrochloride injection contains tirofiban hydrochloride, a non-peptide antagonist of the platelet GP IIb/IIIa receptor, which inhibits platelet aggregation.

Tirofiban hydrochloride monohydrate is chemically described as *N*-(butylsulfonyl)-*O*-[4-(4-piperidiny)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.

Tirofiban hydrochloride injection is supplied as a sterile solution in water for injection, for intravenous use. The pH of the solution ranges from 5.5 to 6.5 adjusted with hydrochloric acid and/or sodium hydroxide.

Each 250 mL of the premixed, isosmotic intravenous injection contains 14.045 mg tirofiban hydrochloride monohydrate equivalent to 12.5 mg tirofiban (50 mcg/mL) and the following inactive ingredients: 2.25 g sodium chloride, 135 mg sodium citrate

dihydrate, and 8 mg citric acid anhydrous.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tirofiban hydrochloride injection is a reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. When administered intravenously, tirofiban hydrochloride injection inhibits *ex vivo* platelet aggregation in a dose- and concentration-dependent manner.

When given according to the PRISM-PLUS regimen of 0.4 mcg/kg/min over 30 minutes followed by a 0.1 mcg/kg/min maintenance infusion, > 90% inhibition of platelet aggregation is attained by the end of the 30-minute infusion. When given according to the recommended regimen of 25 mcg/kg followed by a 0.15 mcg/kg/min maintenance infusion, > 90% inhibition of platelet aggregation is attained within 10 minutes. Platelet aggregation inhibition is reversible following cessation of the infusion of tirofiban hydrochloride injection.

12.2 Pharmacodynamics

Tirofiban hydrochloride injection inhibits platelet function, as demonstrated by its ability to inhibit *ex vivo* adenosine phosphate (ADP)-induced platelet aggregation and prolong bleeding time 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 hydrochloride injection 0.10 mcg/kg/min, *ex vivo* platelet aggregation returns to near baseline in 4 to 8 hours in approximately 90% of patients with coronary artery disease. The addition of heparin to this regimen does not significantly alter the percentage of subjects with > 70% inhibition of platelet aggregation (IPA), but does increase the average bleeding time, as well as the number of patients with bleeding times prolonged to > 30 minutes. Similar platelet aggregation recovery rates are observed following discontinuation of a 0.15 mcg/kg/min infusion.

12.3 Pharmacokinetics

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.

Tirofiban is not highly bound to plasma proteins and protein binding is concentration independent over the range of 0.01 to 25 mcg/mL. The 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.

Specific Populations

There is no effect on clearance of tirofiban by sex, race, age, or hepatic impairment.

Renal Insufficiency

Plasma clearance of tirofiban is decreased about 40% in subjects with creatinine clearance < 60 mL/min and > 50% in patients with creatinine clearance < 30 mL/min, including patients requiring hemodialysis [see *Dosage and Administration* (2.3)]. Tirofiban

is removed by hemodialysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of tirofiban hydrochloride injection 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 up to 5 mg/kg/day (about 5 times the maximum recommended daily human dose when compared on a body surface area basis).

14 CLINICAL STUDIES

Two large-scale clinical studies established the efficacy of tirofiban hydrochloride injection in the treatment of patients with NSTEMI-ACS (unstable angina/non-ST elevation MI). The two studies examined tirofiban hydrochloride injection alone and added to heparin, prior to and after percutaneous coronary revascularization (if indicated) (PRISM-PLUS) and in comparison to heparin in a similar population (PRISM). These trials are discussed in detail below.

PRISM-PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management — Patients Limited by Unstable Signs and Symptoms)

In the double-blind PRISM-PLUS trial, 1570 patients with documented NSTEMI-ACS within 12 hours of entry into the study were randomized to tirofiban hydrochloride injection (30 minute initial infusion of 0.4 mcg/kg/min followed by a maintenance infusion of 0.10 mcg/kg /min) in combination with heparin (bolus of 5,000 U followed by an infusion of 1,000 U/h titrated to maintain an activated partial thromboplastin time (APTT) of approximately 2 times control) or to heparin alone. All patients received concomitant aspirin unless contraindicated. Patients who were medically managed or who underwent revascularization procedures were studied. Patients underwent 48 hours of medical stabilization on study drug therapy, and they were to undergo angiography before 96 hours (and, if indicated, angioplasty/atherectomy, while continuing on tirofiban hydrochloride injection and heparin for 12-24 hours after the procedure). Tirofiban hydrochloride injection and heparin could be continued for up to 108 hours. Exclusions included contraindications to anticoagulation, decompensated heart failure, platelet count < 150,000/mm³, and serum creatinine > 2.5 mg/dL. The mean age of the population was 63 years; 32% of patients were female and approximately half of the population presented with non-ST elevation myocardial infarction. On average, patients received tirofiban hydrochloride injection for 71 hours.

A third group of patients was initially randomized to tirofiban hydrochloride injection alone (no heparin). This arm was stopped when the group was found, at an interim look, to have greater mortality than the other two groups.

The primary endpoint of the study was a composite of refractory ischemia, new MI and death within 7 days. There was a 32% risk reduction in the overall composite primary endpoint. The components of the composite were examined separately and the results

are shown in Table 6. Note that the sum of the individual components may be greater than the composite (if a patient experiences multiple component events only one event counts towards the composite).

Table 6 Primary Outcomes at 7 days in PRISM-PLUS

Endpoint	Tirofiban Hydrochloride Injection + Heparin(N=773)	Heparin(N=797)	Risk Reduction	p-value
Death, new MI, and refractory ischemia at 7 days	12.9%	17.9%	32%	0.004
Death	1.9 %	1.9%	---	---
MI	3.9%	7.0%	47%	0.006
Refractory Ischemia	9.3%	12.7%	30%	0.023

The benefit seen at 7 days was maintained over time. The risk reduction in the composite endpoint at 30 days and 6 months is shown in the Kaplan-Meier curve below.

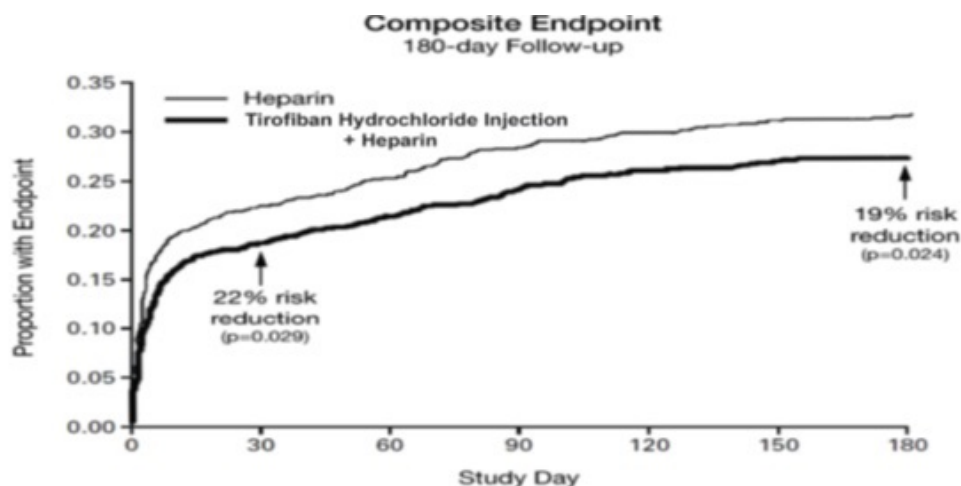


Figure 1. Time to first event of death, new MI, or refractory ischemia in PRISM-PLUS

An analysis of the results by sex suggests that women who are medically managed or who undergo subsequent percutaneous transluminal coronary angioplasty (PTCA)/atherectomy may receive less benefit from tirofiban hydrochloride injection (95% confidence limits for relative risk of 0.61-1.74) than do men (0.43-0.89) ($p=0.11$). This difference may be a true treatment difference, the effect of other differences in these subgroups, or a chance occurrence.

Approximately 90% of patients in the PRISM-PLUS study underwent coronary angiography and 30% underwent angioplasty/atherectomy during the first 30 days of the study.

The majority of these patients continued on study drug throughout these procedures. Tirofiban hydrochloride injection was continued for 12-24 hours (average 15 hours) after angioplasty/atherectomy. The effects of tirofiban hydrochloride injection at Day 30 did not appear to differ among sub-populations that did or did not receive PTCA or CABG, both prior to and after the procedure.

PRISM (Platelet Receptor Inhibition for Ischemic Syndrome Management)

In the PRISM study, a randomized, parallel, double-blind study, 3232 patients with NSTEMI/ACS intended to be managed without coronary intervention were randomized to tirofiban hydrochloride injection (initial dose of 0.6 mcg/kg/min for 30 minutes followed by 0.15 mcg/kg/min for 47.5 hours) or heparin (5000-unit intravenous bolus followed by an infusion of 1000 U/h for 48 hours). The mean age of the population was 62 years; 32% of the population was female and 25% had non-ST elevation MI on presentation. Thirty percent had no ECG evidence of cardiac ischemia. Exclusion criteria were similar to PRISM-PLUS. The primary endpoint was the composite endpoint of refractory ischemia, MI or death at the end of the 48-hour drug infusion. The results are shown in Table 7.

Table 7 Primary Outcomes in PRISM - Cardiac Ischemia Events

Composite Endpoint (death, MI, or refractory ischemia)	Tirofiban Hydrochloride Injection (N=1616)	Heparin (N=1616)	Risk Reduction	p-value
2 Days (end of drug infusion)	3.8%	5.6%	33%	0.015
7 Days	10.3%	11.3%	10%	0.33

In the PRISM study, no adverse effect of tirofiban hydrochloride injection on mortality at either 7 or 30 days was detected. This result is different from that in the PRISM-PLUS study, where the arm that included tirofiban hydrochloride injection without heparin (N=345) was dropped at an interim analysis by the Data Safety Monitoring Committee for increased mortality at 7 days.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tirofiban hydrochloride injection 12.5 mg/250 mL (50 mcg/mL) is supplied as a clear, non-preserved, colorless, isosmotic, sterile premixed solution with sodium chloride for tonicity adjustment and is supplied as follows:
NDC 68083-145-01, 250 mL single-dose bag

FOR INTRAVENOUS USE ONLY

Store tirofiban hydrochloride injection at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F) (see USP Controlled Room Temperature). Do not freeze. Protect from light during storage.

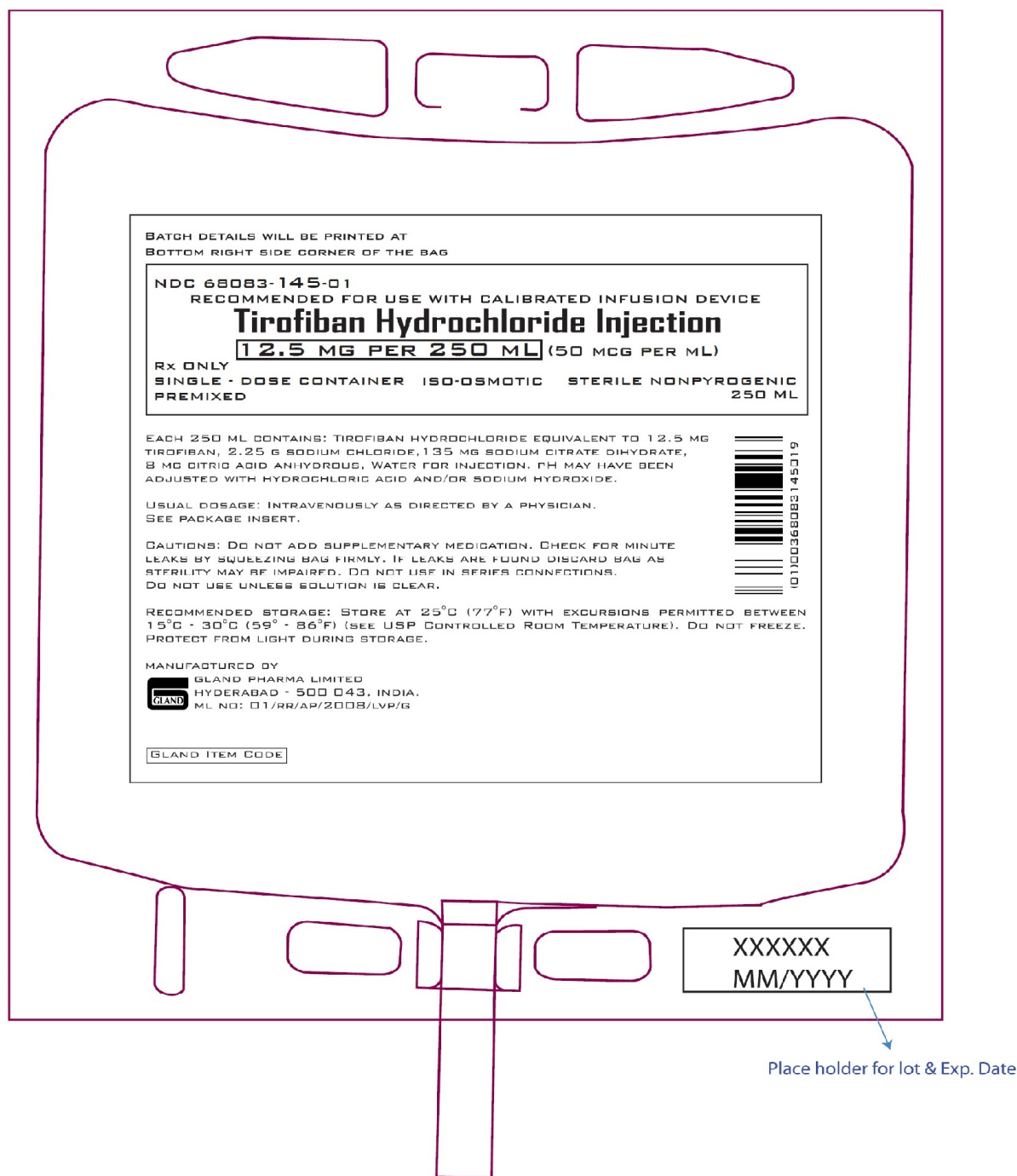
17 PATIENT COUNSELING INFORMATION

Advise patients to watch closely for any signs of bleeding or bruising and to report these to their health care provider when they occur.

Advise patients to discuss with their health care provider their use of any other medications, including over-the-counter or herbal products prior to tirofiban hydrochloride injection use.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Insert
Tirofiban Hydrochloride Injection
Single-Dose Container
Sterile Non Pyrogenic
Rx Only



Container
Tirofiban Hydrochloride Injection
Single-Dose Container
Sterile Non Pyrogenic
Rx Only

NDC 68083-145-01

PROTECT FROM LIGHT DURING STORAGE

RECOMMENDED FOR USE WITH CALIBRATED INFUSION DEVICE PREMIXED INJECTION

Tirofiban Hydrochloride Injection

12.5 mg per 250 mL (50 mcg per mL)

Rx Only

Single-Dose Container

Iso-osmotic

**Sterile Nonpyrogenic
250 mL**

Each 250 mL contains: Tirofiban hydrochloride equivalent to 12.5 mg tirofiban, 2.25 g sodium chloride, 135 mg sodium citrate dihydrate, 8 mg citric acid anhydrous, water for injection. pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

Usual Dosage: Intravenously as directed by a physician. See package insert.

Cautions: Do not add supplementary medication. Check for minute leaks by squeezing bag firmly. If leaks are found discard bag as sterility may be impaired. Do not use in series connections. Do not use unless solution is clear.

Recommended storage: Store at 25°C (77°F) with excursions permitted between 15°C - 30°C (59° - 86°F) (see USP Controlled Room Temperature). Do not freeze. Protect from light during storage.

Manufactured by:



GLAND PHARMA LIMITED

Hyderabad - 500043, INDIA.

ML No: 01/RR/AP/2008/LVP/G



Lot:

Exp:

Un Varnished area for
Batch details & 2D Barcode
60 x 40 mm

Gland Item Code

Tirofiban Hydrochloride Injection
12.5 mg per 250 mL
(50 mcg per mL)
250 mL

Carton
Tirofiban Hydrochloride Injection
Single-Dose Container

NDC 68083-145-01

PROTECT FROM LIGHT DURING STORAGE

RECOMMENDED FOR USE WITH CALIBRATED INFUSION DEVICE PREMIXED INJECTION

Tirofiban Hydrochloride Injection

Rx Only

12.5 mg per 250 mL (50 mcg per mL)

Single-Dose Container

Iso-osmotic

Sterile Nonpyrogenic
250 mL

Each 250 mL contains: Tirofiban hydrochloride equivalent to 12.5 mg tirofiban, 2.25 g sodium chloride, 135 mg sodium citrate dihydrate, 8 mg citric acid anhydrous, Water for Injection. pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

Usual Dosage: Intravenously as directed by a physician. See package insert.

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Recommended storage: Store at 25°C (77°F) with excursions permitted between 15°C - 30°C (59 - 86°F) (see USP Controlled Room Temperature). Do not freeze. Protect from light during storage.

Manufactured by:



GLAND PHARMA LIMITED
Hyderabad - 500043, INDIA,
ML No.: 01/RR/AP/2008/LVP/G

Gland Item Code

Un Varnished area for
Batch details & 2D Barcode
50 x 25 mm

Lot:

Exp:

Sterile Non Pyrogenic
Rx Only**TIROFIBAN HYDROCHLORIDE**

tirofiban injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68083-145
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TIROFIBAN HYDROCHLORIDE (UNII: 6H925F8O5J) (TIROFIBAN - UNII:GGX234S15H)	TIROFIBAN	12.5 mg in 250 mL

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	8 mg in 250 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.25 g in 250 mL
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	135 mg in 250 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68083-145-01	1 in 1 CARTON	04/15/2021	
1		250 mL in 1 CONTAINER; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206888	04/15/2021	

Labeler - Gland Pharma Limited (918601238)

Establishment

Name	Address	ID/FEI	Business Operations
Gland Pharma Limited		918601238	ANALYSIS(68083-145) , MANUFACTURE(68083-145)

Revised: 5/2021

Gland Pharma Limited