Xoforik
Tirofiban 50 mcg / ml
Solution for IV infusion

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xoforik 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 (NSTE-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 toadministration whenever solution and container permit.

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. Withdraw the bolus dose of Tirofiban 50 mcg/mL from the 15 mL premixed bolus vial into a syringe. Alternatively, the bolus dose of Tirofiban 50 mcg/mL may be administered from the 100 mL premixed vial or from the 100 mL bag. Do not dilute.Administer the bolus dose within 5 minutes via a syringe or IV pump. For patients ≥ 167 kg, it is recommended that the bolus dose be administered via syringe from the 15 mL premixed bolus vial, to ensure that delivery time does not exceed 5 minutes.
2. Immediately following the bolus dose administration, administer the maintenance infusion from the 100 mL bag via an IV pump.
3. Discard any unused portion left in the bag.

The recommended bolus volume using the 15 mL premixed bolus vial can be calculated using the following equation:

$$\text{Bolus Volume (mL)} = \frac{25\ \text{mcg/kg} \times \text{body weight (kg)}}{250\ \text{mcg/mL}}$$

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The recommended bolus volume using the 100 mL premixed vial, 100 mL 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 100 mL premixed vial, 100 mL bag 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 patients with CrCl > 60 mL/min using the 100 mL premixed vial, 100 mL 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 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 through the same IV line as diazepam. Do not add other drugs orremove solution directly from the 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 100 mL premixed vial, 100 mL 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

Xoforik is a clear, Colorless solution, free from any visible particles, available in the following presentations:

Table 1 Tirofiban Strength and Packaging

Strength	Volume – Packaging
50 mcg/mL	100 mL – bag

4 CONTRAINDICATIONS

Xoforik is contraindicated in patients with:
- Severe hypersensitivity reaction to Tirofiban (i.e., anaphylactic reactions) [see Adverse Reactions (6.2)].
- A history of thrombocytopenia following prior exposure to Tirofiban [see Adverse Reactions (6.1)].
- Active internal bleeding or a history of bleeding diathesis, major surgical procedure or severe physical trauma within the previousmonth [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. Most bleeding associated with Tirofiban 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. Monitor platelet counts beginning about 6 hours after treatmentinitiation and daily thereafter. If the platelet count decreases to < 90,000/mm^3, monitor platelet counts to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, discontinue Xoforik 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.

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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 Studyof Tirofiban for Outcomes and Restenosis) trials, 1946 patients received Tirofiban in combination with heparin and 2002 patients received Tirofiban 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 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 * + 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 + 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 were 17% on Tirofiban 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 4 g/dL, bleeding requiring transfusion of ≥ 2 U 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. There was a trend toward greater bleeding in ST segment elevation myocardial infarction (STEMI) patients treated with fibrinolytics prior to administration of Tirofiban 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 + Heparin (N=1953)%	Heparin alone (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

Thrombocytopenia

Patients treated with Tirofiban 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. The percentage of patients with a decrease ofplatelets to < 90,000/mm^3 was 1.5%, compared with 0.6% in the patients who received heparin alone. The percentage of patients witha decrease of platelets to < 50,000/mm^3 was 0.3%, compared with 0.1% of the patients who received heparin alone.

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6.2 Post-Marketing Experience

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

Hypersensitivity: Severe allergic reactions including anaphylactic reactions 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). No information is available on the formation of antibodies to tirofiban.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Egyptian pharmacovigilance center pv.followup@edaegypt.gov.eg

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. Untreatedmyocardial infarction can be fatal to the pregnant woman 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.

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 onhuman 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 and any potential adverse effects on the breastfed child from Tirofiban or from the underlying maternal condition.

8.3 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.4 Geriatric Use
Of the total number of patients in controlled clinical studies of Tirofiban, 43% were 65 years and over, while 12% were 75 yearsand over. With respect to efficacy, the effect of Tirofiban in the elderly (≥ 65 years) appeared similar to that seen in younger patients (< 65 years). Elderly patients receiving Tirofiban 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 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)]*.

8.5 Renal Insufficiency
Patients with moderate to severe renal insufficiency have decreased plasma clearance of Tirofiban. Reduce the dosage of Tirofiban in patients with severe renal insufficiency *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Safety and efficacy of Tirofiban has not been established in patients on hemodialysis.

9 OVERDOSAGE

In clinical trials, inadvertent overdosage with Tirofiban 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 minorbleeding at the sites of cardiac catheterization *[see Warnings and Precautions (5.1)]*.

Overdosage of Tirofiban should be treated by assessment of the patient's clinical condition and cessation or adjustment of thedrug infusion as appropriate.

Tirofiban can be removed by hemodialysis.

10 DESCRIPTION

Xoforik 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-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate.

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Each 100 mL of plastic polypropylene bag, contain 5.618 mg tirofiban hydrochloride monohydrate equivalent to 5 mg tirofiban (50 mcg/mL) and **the following inactive ingredients:** sodium chloride, sodium citrate dihydrate, citric acid anhydrous, Hydrochloric acid, Sodium hydroxide and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Tirofiban 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 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.

12.2 Pharmacodynamics
Tirofiban inhibits platelet function, as demonstrated by its ability to inhibit *ex vivo* adenosine phosphate (ADP)-induced plateletaggregation 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 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 recoveryrates 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 42liters.

In healthy subjects, the plasma clearance of tirofiban ranges from 213 to 314 mL/min. Renal clearance accounts for 39 to 69% ofplasma 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xoforik is supplied as a clear, Colorless solution, free from any visible particles.

Pack:
Carton box contains single use transparent plastic polypropylene bag with SFC system (SFC port and SFC cap assembled with rubber disc polyisoperene (type I)) of 100 ml solution containing tirofiban hydrochloride 50 mcg / ml with outer label.

Table 8 Xoforik Product Details

50 mcg/mL	5 mg/100 mL	bag	25208-002-01

FOR INTRAVENOUS USE ONLY

Store Xoforik at temperature not exceeding 30 °C, don't freeze. Keep the bag in the carton box to protect from light.

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 use.

MANUFACTURER
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