TIROCIP Injection (Tirofiban hydrochloride)

Composition

TIROCIP Injection 50 mcg/ml
Each ml contains
Tirofiban...... 50 mcg
Water for injection IP...... qs

Dosage Form

Solution for infusion

Pharmacology

Mechanism of Action
Tirofiban is a reversible antagonist of fibrinogen binding to the glycoprotein (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 recommended regimen, >90% inhibition is attained by the end of the 30-minute infusion. Platelet aggregation inhibition is reversible following cessation of the infusion of tirofiban.

Inhibition of Platelet Aggregation
Tirofiban 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, 0.10 mcg/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 does increase the average bleeding time, as well as the number of patients with bleeding times prolonged to >30 minutes.

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

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. 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. 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; renal clearance accounts for 39% of plasma clearance.

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

### 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 percutaneous transluminal coronary angioplasty (PTCA) or atherectomy.

In this setting, tirofiban has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure.

Tirofiban has been studied in a setting that included aspirin and heparin.

### Dosage And Administration

#### Recommended Dosage

In most patients, TIROCIP 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 for TIROCIP.

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Most Patients</th>
<th>Severe Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 Min Loading</td>
<td>Maintenance Infusion</td>
</tr>
<tr>
<td></td>
<td>Infusion Rate (mL/hr)</td>
<td>Rate (mL/hr)</td>
</tr>
<tr>
<td>30-37</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>38-45</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>46-54</td>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>
No dosage adjustment is recommended for elderly or female patients. In PRISM-PLUS, tirofiban was administered in combination with heparin for 48 to 108 hours. The infusion should be continued through angiography and for 12 to 24 hours after angioplasty or atherectomy.

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 vial with a syringe. Do not use vials in series connections such use can result in air embolism by drawing air from the first vial if it is empty of solution. Any unused solution should be discarded.

Directions for Use

TIROCIP Injection is supplied as 100 mL of 0.9% sodium chloride containing 50 mcg/mL tirofiban. To open the vial, 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; if any leaks are found, the sterility is suspect and the solution should be discarded. Do not use unless the solution is clear and the seal is intact. Suspend the vial from its eyelet support, remove the plastic protector from the outlet port, and attach a conventional administration set.

TIROCIP may be administered in the same intravenous line as atropine sulfate, dobutamine, dopamine, epinephrine HCl, famotidine injection, furosemide, lidocaine, midazolam HCl, morphine sulfate, nitroglycerin, potassium chloride, and propranolol HCl. TIROCIP should not be administered in the same intravenous line as diazepam.

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 mmHg)
- concomitant use of another parenteral GP IIb/IIIa inhibitor
- acute pericarditis

**Warnings And Precautions**

**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 in the PRISM study, there were no clinically significant effects of co-administration of the following 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.

**Bleeding**

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 Myocardial Infarction Study group (TIMI). Most major bleeding associated with tirofiban occurs at the arterial access site for cardiac catheterization. Fatal bleedings have been reported.

Tirofiban should be used with caution in patients with platelet count <150,000/mm$^3$, in patients with hemorrhagic retinopathy, and in chronic hemodialysis patients.

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.

**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 vascular 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 activated partial thromboplastin time (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 maintained on complete bed rest with the head of
the bed elevated 30° and the 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, epidural procedures, 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). In patients who have previously received GP IIb/IIIa receptor antagonists, consideration should be given to earlier monitoring of platelet count. If the patient experiences a platelet decrease to <90,000/mm³, additional platelet counts should be performed to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, tirofiban and heparin should be discontinued and the condition appropriately monitored and treated.

In addition, the APTT should be determined before treatment and the anticoagulant effects of heparin should be carefully monitored by repeated determinations of APTT and the dose should be adjusted accordingly. Potentially life-threatening bleeding may occur especially when heparin is administered with other products affecting hemostasis, such as GP IIb/IIIa receptor antagonists. 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.

Renal Impairment

In clinical studies, patients with severe renal insufficiency (creatinine clearance <30 mL/min) showed decreased plasma clearance of tirofiban. The dosage of TIROCIP should be reduced in these patients (see DOSAGE and ADMINISTRATION).

Hepatic Impairment

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

Pregnancy

Category B

Tirofiban has been shown to cross the placenta in pregnant rats and rabbits. 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. 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.

Lactation

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 TIROCIP, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

Of the total number of patients in controlled clinical studies of tirofiban, 42.8% were ≥65 years, while 11.7% were ≥75
years. 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 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. The
overall incidence of non-bleeding adverse events was higher in older patients (compared to younger patients) but this
was true both for tirofiban with heparin and heparin alone. No dose adjustment is recommended for the elderly
population.

Undesirable Effects

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

<table>
<thead>
<tr>
<th></th>
<th>PRISM-PLUS* (UAP/Non-Q-Wave MI Study)</th>
<th>RESTORE* (Angioplasty/Atherectomy Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tirofiban† + Heparin‡ (n=773)%</td>
<td>Tirofiban§ + Heparin¶ (n=1071)%</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1.4 (11)</td>
<td>0.8 (6)</td>
</tr>
<tr>
<td>(TIMI Criteria)#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>10.5 (81)</td>
<td>8.0 (64)</td>
</tr>
<tr>
<td>(TIMI Criteria)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusions</td>
<td>4.0 (31)</td>
<td>2.8 (22)</td>
</tr>
</tbody>
</table>

* 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 # Hemoglobin drop of >50 g/L with or without an identified site, intracranial hemorrhage, or cardiac tamponade.
Hemoglobin drop of >30 g/L with bleeding from a known site, spontaneous gross hematuria, hematemesis or hemothysis.

There were no reports of intracranial bleeding in the PRISM-PLUS study for tirofiban in combination with heparin or in the
heparin control group. The incidence of intracranial bleeding in the RESTORE study was 0.1% for tirofiban 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 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban + Heparin</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Prior to Procedures</td>
<td>2/773</td>
<td>0.3</td>
</tr>
<tr>
<td>Following Angiography</td>
<td>9/697</td>
<td>1.3</td>
</tr>
<tr>
<td>Following PTCA</td>
<td>6/239</td>
<td>2.5</td>
</tr>
</tbody>
</table>

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 are shown below.

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban + Heparin</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>5/29</td>
<td>17.2</td>
</tr>
<tr>
<td>RESTORE</td>
<td>3/12</td>
<td>25.0</td>
</tr>
</tbody>
</table>

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. The incremental risk of bleeding in patients treated with tirofiban 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:

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban + Heparin (n=1953) %</th>
<th>Heparin (n=1887) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema/swelling</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pain, pelvic</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Reaction, vasovagal</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Cardiovascular System
Bradycardia
Dissection, coronary artery
Musculoskeletal System
Pain, leg
Nervous System/Psychiatric
Dizziness
Skin and Skin Appendage
Sweating

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 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 with heparin and the heparin alone groups.

Allergic Reactions/ Readministration

Although no patients in the clinical trial database developed anaphylaxis and/or hives requiring discontinuation of the infusion of tirofiban, 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 concomitantly with heparin were related to bleeding. Decreases in hemoglobin (2.1%) and hematocrit (2.2%) were observed in the group receiving tirofiban 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 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 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/mm³).

### Overdosage

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 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. 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.

### Packaging Information

TIROCIP: Vial of 5 mg tirofiban per 100 mL (50 mcg per mL)

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Last reviewed: July 2013

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TIROCIP Injection

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