Integril®

Eptifibatide Injection

Presentation
Integril® 2 Injection: Each ml of sterile solution contains Eptifibatide Acetate INN equivalent to Eptifibatide 2 mg.
Integril® 0.75 Injection: Each ml of sterile solution contains Eptifibatide Acetate INN equivalent to Eptifibatide 0.75 mg.

Description
Eptifibatide is a cyclic heptapeptide containing six amino acids and one mercaptopropionyl (des-amino cysteinyl) residue. Eptifibatide binds to the platelet receptor glycoprotein (GP) IIb/IIIa of human platelets and reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive ligands to GP IIb/IIIa.

Indications and uses
Eptifibatide is indicated-
- For the treatment of patients with acute coronary syndrome (unstable angina/non-ST- segment elevation myocardial infarction), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI).
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting.

Dosage and Administration
Acute Coronary Syndrome
In patients with normal renal function: The recommended adult dosage of Eptifibatide is an IV bolus of 180 μg/kg as soon as possible following diagnosis, followed by a continuous infusion of 2 μg/kg/min until hospital discharge or initiation of CABG surgery, up to 72 hours. If a patient is to undergo a PCI while receiving Eptifibatide, the infusion should be continued up to hospital discharge, or for up to 18 to 24 hours after the procedure, whichever comes first, allowing for up to 96 hours of therapy.
In patients with creatinine clearance <50 ml/min: The recommended adult dosage of Eptifibatide is an IV bolus of 180 μg/kg as soon as possible following diagnosis, immediately followed by a continuous infusion of 1 μg/kg/min.

Percutaneous Coronary Intervention (PCI)
In patients with normal renal function: The recommended adult dosage of Eptifibatide is IV bolus of 180 μg/kg administered immediately before the initiation of PCI followed by a continuous infusion of 2 μg/kg/min and a second 180 μg/kg bolus 10 minutes after the first bolus. Infusion should be continued until hospital discharge, or for up to 18 to 24 hours, whichever comes first. A minimum of 12 hours of infusion is recommended.
In patients with creatinine clearance <50 ml/min: The recommended adult dose of Eptifibatide is an IV bolus of 180 μg/kg administered immediately before the initiation of the procedure, immediately followed by a continuous infusion of 1 μg/kg/min and a second 180 μg/kg bolus administered 10 minutes after the first.
In patients who undergo CABG surgery, Eptifibatide infusion should be discontinued prior to surgery.

Eptifibatide Dosing Charts by Weight

Patient Weight (kg)	180 μg/kg Bolus Volume (2 mg/ml, 10 ml vial)	2 μg/kg/min Infusion Volume (0.75 mg/ml, 100 ml vial)	1 μg/kg/min Infusion Volume (0.75 mg/ml, 100 ml vial)
37-41	3.4 ml	6 ml/h	3 ml/h
42-46	4 ml	7 ml/h	3.5 ml/h
47-53	4.5 ml	8 ml/h	4 ml/h
54-59	5 ml	9 ml/h	4.5 ml/h
60-65	5.6 ml	10 ml/h	5 ml/h
66-71	6.2 ml	11 ml/h	5.5 ml/h
72-78	6.8 ml	12 ml/h	6 ml/h
79-84	7.3 ml	13 ml/h	6.5 ml/h
85-90	7.9 ml	14 ml/h	7 ml/h
91-96	8.5 ml	15 ml/h	7.5 ml/h
97-103	9 ml	16 ml/h	8 ml/h
104-109	9.5 ml	17 ml/h	8.5 ml/h
110-115	10.2 ml	18 ml/h	9 ml/h
116-121	10.7 ml	19 ml/h	9.5 ml/h
>121	11.3 ml	20 ml/h	10 ml/h

Aspirin and Heparin Dosing Recommendations
In the clinical trials that showed Eptifibatide to be effective, most patients received concomitant aspirin and heparin. The recommended aspirin and heparin doses to be used are as follows:

Acute Coronary Syndrome
Aspirin
160 to 325 mg orally initially and daily thereafter.

Heparin
Target aPTT 50 to 70 seconds during medical management
- If weight ≥ 70 kg, 5000 U bolus followed by infusion of 1000 U/hr.
- If weight < 70 kg, 60 U/kg bolus followed by infusion of 12 U/kg/hr.

Target ACT 200 to 300 seconds during PCI
- If heparin is initiated prior to PCI, additional boluses during PCI to maintain an ACT target of 200 to 300 seconds.
- Heparin infusion after the PCI is discouraged.

PCI
Aspirin
160 to 325 mg orally 1 to 24 hours prior to PCI and daily thereafter.

Heparin
Target ACT 200 to 300 seconds
- 60 U/kg bolus initially in patients not treated with heparin within 6 hours prior to PCI.
- Additional boluses during PCI to maintain ACT within target.
- Heparin infusion after the PCI is strongly discouraged.

Patients requiring thrombolytic therapy should have Eptifibatide infusions stopped.

Instructions for Administration
1. Eptifibatide solutions should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
2. Eptifibatide may be administered in the same IV line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil. Eptifibatide should not be administered through the same IV line as furosemide.
3. Eptifibatide may be administered in the same IV line with 0.9% NaCl or 5% dextrose. With either vehicle, the infusion may also contain up to 60 mEq/L of KCl.
4. The bolus dose(s) of Eptifibatide should be withdrawn from the 10 ml vial into a syringe. The bolus dose(s) should be administered by IV push.
5. Immediately following the bolus dose administration, a continuous infusion of Eptifibatide should be initiated. When using an intravenous infusion pump, Eptifibatide should be administered undiluted directly from the 100 ml vial. The 100 ml vial should be spiked with a vented infusion set. Care should be taken to center the spike within the circle on the stopper top.

Side-effects
Bleeding is the most common adverse effect. Adverse reactions include intracranial hemorrhage and stroke, thrombocytopenia, allergic reactions and hypotension.

Contraindications
- A history of bleeding diathesis, or evidence of active abnormal bleeding within the previous 30 days.
- Severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled on antihypertensive therapy.
- Major surgery within the preceding 6 weeks.
- History of stroke within 30 days or any history of hemorrhagic stroke.
- Current or planned administration of another parenteral GP IIb/IIIa inhibitor.
- Dependency on renal dialysis.
- Known hypersensitivity to any component of the product.

Precautions and Warnings
- In patients undergoing PCI, Eptifibatide Injection is associated with an increase in major and minor bleeding at the site of arterial sheath placement. Special care should be employed to minimize the risk of bleeding among these patients.
- If bleeding cannot be controlled with pressure, infusion of Eptifibatide and concomitant heparin should be stopped immediately.
- Because Eptifibatide inhibits platelet aggregation, caution should be employed when it is used with drugs that affect hemostasis, including thrombolytics, oral anticoagulants, NSAIDs, and dipyridamole.
- Use with other GP IIb-IIIa inhibitors should be avoided.
- Eptifibatide is cleared in part by the kidney and its plasma concentrations are doubled in patients with renal disease (creatinine clearance <50 ml/min). Therefore, the infusion dose of Eptifibatide needs to be reduced to 1 mcg/kg/min in these patients. Eptifibatide is contraindicated in patients who are dependent upon renal dialysis.
- Caution should be exercised when administering eptifibatide to patients with a platelet count <100,000/mm^3.
- Bleeding is the most common complication encountered during Eptifibatide therapy. The majority of excess major bleeding events were localized at the femoral artery access site. Oropharyngeal, genitourinary, gastrointestinal, and retroperitoneal bleeding were seen more commonly with eptifibatide compared with placebo.
- Arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, and nasogastric tubes should be minimized. When obtaining intravenous access, noncompressible sites (e.g., subclavian or jugular veins) should be avoided.
- Before infusion of Eptifibatide, the following laboratory tests should be performed to identify preexisting hemostatic abnormalities: hematocrit or hemoglobin, platelet count, serum creatinine, and PT/aPTT. In patients undergoing PCI, the activated clotting time (ACT) should also be measured.

Use in Pregnancy & Lactation
Pregnancy: Category B. Animal studies revealed no evidence of harm to the fetus due to Eptifibatide. There are, however, no adequate and well-controlled studies in pregnant women with Eptifibatide.
Lactating Mothers: It is not known whether Eptifibatide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Eptifibatide is administered to a nursing mother.

Use in Children
Safety and effectiveness of Eptifibatide in pediatric patients have not been studied.

Drug Interactions
- In various clinical studies, eptifibatide was used concomitantly with unfractionated heparin and aspirin. In another study, clopidogrel or ticlopidine were used routinely starting the day of PCI. Because eptifibatide inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, NSAIDS and dipyridamole. To avoid potentially additive pharmacologic effects, concomitant treatment with other inhibitors of platelet receptor GP IIb/IIIa should be avoided.
- Enoxaparin did not alter the pharmacokinetics of Eptifibatide.

Overdosage
- There has been only limited experience with overdosage of Eptifibatide. Symptoms of acute toxicity were loss of righting reflex, dyspnea, ptosis, and decreased muscle tone in rabbits, and petechial hemorrhages in the femoral and abdominal areas of monkeys.
- From in vitro studies, eptifibatide is not extensively bound to plasma proteins and thus may be cleared from plasma by dialysis.

Storage
- Vials should be stored refrigerated at 2°- 8 °C (36°- 46 °F).
- Vials may be transferred to room temperature storage for up to 2 months.
- Unused portion left in the vial should be discarded.
- Vials should be protected from light until administration.

Commercial pack
Integril® 2 Injection: Each vial contains 10 ml of sterile solution.
Integril® 0.75 Injection: Each vial contains 100 ml of sterile solution.

Manufactured by
Incepta Pharmaceuticals Ltd
Savar, Dhaka, Bangladesh
® Registered Trademark

V.N.02

IG2