For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

8027458-9093

EPTIBIND

(Eptifibatide Injection)

COMPOSITION

EPTIBIND 20

Each ml contains :

Eptifibatide	2 mg
Water for Injection I.P.	q.s.

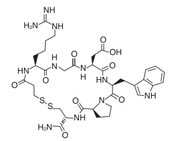
EPTIBIND 75

Each ml contains :

Eptifibatide	0.75 mg
Water for Injection I.P.	q.s.

DESCRIPTION

Eptifibatide is a cyclic heptapeptide containing six amino acids and one mercaptopropionyl (des-amino cysteinyl) residue. An interchain disulfide bridge is formed between the cysteine amide and the mercaptopropionyl moieties. Chemically it is N^6-(aminoiminomethyl)-N^2-(3-mercapto-1-oxopropyl-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide. Eptifibatide binds to the platelet receptor glycoprotein (GP) IIb/IIIa of human platelets and inhibits platelet aggregation. It has an empirical formula of $C_{35}H_{49}N_{11}O_9S_2$ and a molecular weight of 831.96. The structure of Eptifibatide is below :



CLINICAL PHARMACOLOGY

Mechanism of Action

Eptifibatide reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive ligands to GP IIb/IIIa. When administered intravenously, eptifibatide inhibits *ex-vivo* platelet aggregation using adenosine diphosphate (ADP) and other agonists in a dose- and concentration-dependent manner. Platelet aggregation inhibition is reversible following cessation of the eptifibatide infusion; this is thought to result from dissociation of eptifibatide from the platelet.

Pharmacodynamics

The Pharmacodynamics properties of Eptifibatide are reported as follows:

Infusion of eptifibatide into baboons caused a dose-dependent inhibition of *ex vivo* platelet aggregation, with complete inhibition of aggregation achieved at infusion rates greater than 5.0 μg/kg/min. In a baboon model that is refractory to aspirin and heparin, doses of eptifibatide that inhibit aggregation prevented acute thrombosis with only a modest prolongation (2- to 3-fold) of the bleeding time. Platelet aggregation in dogs was also inhibited by infusions of eptifibatide, with complete inhibition at 2.0 μg/kg/min. This infusion dose completely inhibited canine coronary thrombosis induced by coronary artery injury (Folts model).

Table 1 Platelet Inhibition and Bleeding Time

	IMPACT II 135/0.5*	PURSUIT 180/2.0†
Inhibition of platelet aggregation 15 min after bolus	69%	84%
Inhibition of platelet aggregation at steady state	40- 50%	> 90%
Bleeding-time prolongation at steady state	< 5x	< 5x
Inhibition of platelet aggregation 4h after infusion discontinuation	< 30%	< 50%
Bleeding-time prolongation 6h after infusion discontinuation	1 x	1.4 x

* 135-μg/kg bolus followed by a continuous infusion of 0.5 μg/kg/min.
† 180-μg/kg bolus followed by a continuous infusion of 2.0 μg/kg/min.

The eptifibatide dosing regimen used in the ESPRIT study included two 180-μg/kg bolus doses given 10 minutes apart combined with a continuous 2.0 μg/kg/min infusion. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT). There were no important differences between men and women or between age groups in the pharmacodynamic properties of eptifibatide. Differences among ethnic groups have not been assessed.

Pharmacokinetics

The pharmacokinetics of eptifibatide are linear and dose proportional for bolus doses ranging from 90 to 250 microgram/kg and infusion rates from 0.5 to 3.0 microgram/kg/min. For a 2.0 microgram/kg/min infusion, mean steady-state plasma eptifibatide concentrations range from 1.5 to 2.2 microgram/ml in patients with coronary artery disease. These plasma concentrations are achieved rapidly when the infusion is preceded by a 180 microgram/kg bolus. The extent of eptifibatide binding to human plasma protein is about 25 %. In the same population, plasma elimination half-life is approximately 2.5 hours, plasma clearance 55 to 80 ml/kg/hr and volume of distribution of approximately 185 to 260 ml/kg. In healthy subjects, renal excretion accounted for approximately 50 % of total body clearance; approximately 50 % of the amount cleared is excreted unchanged. In patients with moderate to severe renal insufficiency (creatinine clearance < 50 ml/min), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled. However, in a population pharmacokinetic study there was no evidence of a pharmacokinetic interaction between eptifibatide and the following concomitant medicinal products: amlodipine, atenolol, atropine, captopril, cefazolin, diazepam, digoxin, diltiazem, diphenhydramine, enalapril, fentanyl, furosemide, heparin, lidocaine, lisinopril, metoprolol, midazolam, morphine, nitrates, nifedipine, and warfarin.

INDICATIONS

- 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.

CONTRAINDICATIONS

- Hypersensitivity to Eptifibatide or to any component of the formulation.
- Evidence of gastrointestinal bleeding, gross genitourinary bleeding or other active abnormal bleeding within the previous 30 days of treatment.
- History of stroke within 30 days or any history of hemorrhagic stroke.
- Known history of intracranial disease (neoplasm, arteriovenous malformation, aneurysm)
- Major surgery or severe trauma within past 6 weeks.
- A history of bleeding diathesis
- Thrombocytopaenia (<1,00,000 cells/mm^3)
- Severe hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg) not adequately controlled on antihypertensive therapy.
- Prothrombin time >1.2 times control, or international Normalized Ratio (INR) ≥ 2.0
- Severe renal impairment (creatinine clearance <30 mL/min) or dependency on renal dialysis.
- Clinically significant hepatic impairment
- Concomitant or planned administration of another parenteral GP IIb/IIIa inhibitor.

WARNINGS AND PRECAUTIONS

Bleeding

Administration of Eptifibatide is associated with an increase in major and minor bleeding, as classified by the criteria of the Thrombolysis in Myocardial Infarction Study group (TIMI). Women, the elderly and patients with low body weight or with moderate renal impairment (creatinine clearance ≥ 30 - < 50 ml/min) may have an increased risk of bleeding. Monitor these patients closely with regard to bleeding. Bleeding is most common at the arterial access site in patients undergoing percutaneous arterial procedures. All potential bleeding sites, e.g., Catheter insertion sites, arterial, venous, or needle puncture sites; cut down sites; gastrointestinal and genitourinary tracts must be observed carefully. Other potential bleeding sites such as central and peripheral nervous system and retroperitoneal sites, must be carefully considered too. Caution advised when Eptifibatide is used with other medicinal products that affect haemostasis, including Ticlopidine, Clopidogrel, Thrombolytics, Oral anticoagulants, Dextran solutions, Adenosine, Sulfinpyrazone, Prostacyclin, Non-steroidal anti-inflammatory agents, or Dipyridamole. There is no experience with Eptifibatide and low molecular weight heparins. There is limited therapeutic experience with Eptifibatide in patients for whom thrombolytic therapy is generally indicated (e.g., Acute transmural myocardial infarction with new pathological Q-waves or elevated ST-segments or left bundle branch block in the ECG). Consequently its use is not recommended in these conditions. Stop the infusion immediately if circumstances arise that necessitate thrombolytic therapy or if the patient must undergo an emergency CABG surgery or requires an intraortic balloon pump. If serious bleeding occurs that is not controllable with pressure, immediately stop the drug and any unfractionated heparin that is given concomitantly.

Arterial procedures

During treatment with Eptifibatide there is a significant increase in bleeding rates, especially in the femoral artery area, where the catheter sheath is introduced. Take care to ensure that only the anterior wall of the femoral artery is punctured. Arterial sheaths may be removed when coagulation has returned to normal (eg. when activated clotting time [ACT] is less than 180 seconds usually 2-6 hours after discontinuation of heparin). After removal of the introducer sheath, careful haemostasis must be ensured under close observation.

Thrombocytopaenia

Thrombocytopaenia, including acute profound thrombocytopaenia, has been reported with Eptifibatide administration. Platelet counts should be monitored prior to treatment, within 6 hours of administation, and at least once daily thereafter while on therapy and immediately at clinical signs of unexpected bleeding tendency. If the patient experiences a confirmed platelet decrease to <100,000/mm^3, discontinue Eptifibatide and unfractionated heparin and monitor and treat the patient appropriately. The decision to use platelet transfusions should be based upon clinical judgment on an individual basis. In patients with previous thrombocytopaenia from other parenteral GP IIb/IIIa inhibitors, there are no data with the use of Eptifibatide, and thus these patients require close monitoring.

Heparin administration

Heparin administration is recommended unless a contraindication (such as a history of thrombocytopaenia associated with use of heparin) is present.

UA/NQMI: For a patient who weighs ≥70 kg, it is recommended that a bolus dose of 5,000 units is given, followed by a constant intravenous infusion of 1,000 units/hr. If the patient weighs < 70 kg, a bolus dose of 60 units/kg is recommended, followed by an infusion of 12 units/kg/hr. The activated partial thromboplastin time (aPTT) must be monitored in order to maintain a value between 50 and 70 seconds, above 70 seconds there may be an increased risk of bleeding.

If PCI is to be performed in the setting of UA/NQMI, monitor the activated clotting time (ACT) to maintain a value between 300-350 seconds. Stop heparin administration if the ACT exceeds 300 seconds; do not administer until the ACT falls below 300 seconds.

Monitoring of Laboratory values

Before infusion of Eptifibatide treatment, the following laboratory tests are recommended before treatment to identify pre-existing hemostatic abnormalities: prothrombin time (PT) and aPTT, serum creatinine, platelet count, haemoglobin or haematocrit levels. Haemoglobin, haematocrit and platelet count are to be monitored as well within 6 hours after start of therapy and at least once daily thereafter while on therapy (or more often if there is evidence of a marked decrease). If the platelet count falls below 100, 00/mm^3, further platelet counts are required to rule out pseudothrombocytopaenia. Discontinue unfractionated heparin. In patients undergoing PCI, measure the ACT also. Patients must be monitored for bleeding and treated if necessary.

Immunogenicity

Immunogenic response or antibodies against Eptifibatide have been observed in isolated cases in native patients or in rare cases of patients re-exposed to Eptifibatide. If treatment with Eptifibatide is repeated, no diminished therapeutic response is expected.

Renal Insufficiency

In patients with an estimated creatinine clearance < 50 mL/min, the infusion dose should be reduced to 1 μg/kg/min. There has been no clinical experience in patients dependent on dialysis and in patients with a platelet count < 100,000/mm^3.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of eptifibatide. Eptifibatide was not genotoxic in the Ames test, the mouse lymphoma cell (L 5178Y, TK+/-) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Administered by continuous intravenous infusion at total daily doses up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis), eptifibatide had no effect on fertility and reproductive performance of male and female rats.

Interaction with other medicinal products and other forms of interaction

Warfarin and dipyridamole

Eptifibatide did not increase the risk of major and minor bleeding associated with concomitant use of warfarin and dipyridamole.

Eptifibatide and thrombolytic agents

Data are limited on the use of eptifibatide in patients receiving thrombolytic agents. There was no consistent evidence that eptifibatide increased the risk of major or minor bleeding associated with tissue plasminogen activator in either a PCI or an acute myocardial infarction study; Eptifibatide appeared to increase the risk of bleeding when administered with streptokinase in an acute myocardial infarction study. The combination of reduced dose tenecteplase and eptifibatide compared to placebo and eptifibatide significantly increased the risk of both major and minor bleeding when administered concomitantly in an acute ST-elevation myocardial infarction study. In an acute myocardial infarction study involving 181 patients it is reported that, eptifibatide (in regimens up to a bolus injection of 180 microgram/kg, followed by an infusion up to 2 microgram/kg/min for up to 72 hours) was administered concomitantly with streptokinase (1.5 million units over 60 minutes). At the highest infusion rates (1.3 microgram/kg/min and 2.0 microgram/kg/min) studied, eptifibatide was associated with an increased incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone.

ADVERSE REACTIONS

The majority of undesirable effects experienced by patients treated with eptifibatide were generally related to bleeding, or to cardiovascular events that occur frequently in this patient population. In a Phase-III clinical trial study of eptifibatide (PURSUIT, ESPRIT, and IMPACT II), the following adverse effects have been reported.

Bleeding

According to TIMI study, the bleeding is categorized in major and minor category. Major bleeding events consisted of intracranial hemorrhage and other bleeding that led to decreases in hemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, other observed blood loss with a hemoglobin decrease of more than 3 g/dL, and other hemoglobin decreases that were greater than 4 g/dL but less than 5 g/dL. In patients who received transfusions, the corresponding loss in hemoglobin was estimated through an adaptation of the method of Landefeld et al.

Bleeding Events and Transfusions in the PURSUIT, ESPRIT, and IMPACT II Studies

	Placebo n (%)	Eptifibatide (180/1.3) * n (%)	Eptifibatide (180/2) n (%)
PURSUIT			
Patients	4696	1472	4679
Major bleeding†	425 (9.3%)	152 (10.5%)	498 (10.8%)
Minor bleeding†	347 (7.6%)	152 (10.5%)	604 (13.1%)
Requiring transfusions‡	490 (10.4%)	188 (12.8%)	601 (12.8%)
ESPRIT			
	Placebo n (%)	Eptifibatide 180/2.0/180 n (%)	
Patients	1024	1040	
Major bleeding†	4 (0.4%)	13 (1.3%)	
Minor bleeding†	18 (2.0%)	29 (3.0%)	
Requiring transfusions‡	11 (1.1%)	16 (1.5%)	
IMPACT II			
	Placebo n (%)	Eptifibatide 135/0.5 n (%)	Eptifibatide 135/0.75 n (%)
Patients	1285	1300	1286
Major bleeding†	55 (4.5%)	55 (4.4%)	58 (4.7%)
Minor bleeding†	115 (9.3%)	146 (11.7%)	177 (14.2%)
Requiring transfusions‡	66 (5.1%)	71 (5.5%)	74 (5.8%)

Note: Denominator is based on patients for whom data are available.

* Administered only until the first interim analysis.
† For major and minor bleeding, patients are counted only once according to the most severe classification.
‡ Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

The majority of major bleeding events in the ESPRIT study occurred at the vascular access site (1 and 8 patients, or 0.1% and 0.8% in the placebo and eptifibatide groups, respectively). Bleeding at "other" locations occurred in 0.2% and 0.4% of patients, respectively.

In the PURSUIT study it was reported that, the greatest increase in major bleeding in eptifibatide-treated patients compared to placebo-treated patients was also associated with bleeding at the femoral artery access site (2.8% vs 1.3%). Oropharyngeal (primarily gingival), genitourinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly in eptifibatide-treated patients compared to placebo-treated patients.

Among patients experiencing a major bleed in the IMPACT II study, an increase in bleeding on eptifibatide versus placebo was reported only at the femoral artery access site (3.2% vs 2.8%).In the next table the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT study. The most common bleeding complications were related to cardiac revascularization (CABG-related or femoral artery access site bleeding).

	Placebo n (%)	Eptifibatide (180/1.3) * n (%)	Eptifibatide (180/2) n (%)
Patients	4577	1451	4604
Overall incidence of major bleeding	425 (9.3%)	152 (10.5%)	498 (10.8%)
Breakdown by procedure:			
CABG	375 (8.2%)	123 (8.5%)	377 (8.2%)
Angioplasty without CABG	27 (0.6%)	16 (1.1%)	64 (1.4%)
Angiography without angioplasty or CABG	11 (0.2%)	7 (0.5%)	29 (0.6%)
Medical therapy only	12 (0.3%)	6 (0.4%)	28 (0.6%)

Denominators are based on the total number of patients whose TIMI classification was resolved.

* Administered only until the first interim analysis.

In the PURSUIT and ESPRIT studies, the risk of major bleeding with eptifibatide increased as patient weight decreased. This relationship was most apparent for patients weighing less than 70 kg. Bleeding adverse events resulting in discontinuation of the study drug were more frequent among patients receiving eptifibatide than placebo (4.6% vs 0.9% in ESPRIT, 8% vs 1% in PURSUIT, 3.5% vs 1.9% in IMPACT II).

Intracranial Hemorrhage and Stroke

Intracranial hemorrhage was rare in the PURSUIT, IMPACT II, and ESPRIT clinical studies. In the PURSUIT study, 3 patients in the placebo group, 1 patient in the group treated with eptifibatide 180/1.3 and 5 patients in the group treated with eptifibatide 180/2.0 experienced a hemorrhagic stroke. The overall incidence of stroke was 0.5% in patients receiving eptifibatide 180/1.3, 0.7% in patients receiving eptifibatide 180/2.0, and 0.8% in placebo patients.

In the IMPACT II study, intracranial hemorrhage was experienced by 1 patient treated with eptifibatide 135/0.5, 2 patients treated with eptifibatide 135/0.75 and 2 patients in the placebo group. The overall incidence of stroke was 0.5% in patients receiving 135/0.5 eptifibatide, 0.7% in patients receiving eptifibatide 135/0.75 and 0.7% in the placebo group. In the ESPRIT study, there were 3 hemorrhagic strokes, 1 in the placebo group, and 2 in the eptifibatide group. In addition there was 1 case of cerebral infarction in the eptifibatide group.

Thrombocytopenia

In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100,000/mm^3 or ≥50% reduction from baseline) and the incidence of platelet transfusions were similar between patients treated with eptifibatide and placebo. In the ESPRIT study, the incidence was 0.6% in the placebo group and 1.2% in the eptifibatide group.

Allergic Reactions

In the PURSUIT study, anaphylaxis was reported in 7 patients receiving placebo (0.15%) and 7 patients receiving eptifibatide 180/2.0 (0.16%). In the IMPACT II study, anaphylaxis was reported in 1 patient (0.08%) on placebo and in no patients on eptifibatide. In the IMPACT II study, 2 patients (1 patient [0.04%] receiving eptifibatide and 1 patient [0.08%] receiving placebo) discontinued study drug because of allergic reactions. In the ESPRIT study, there were no cases of anaphylaxis reported. There were 3 patients who suffered an allergic reaction, 1 on placebo and 2 on eptifibatide. In addition, 1 patient in the placebo group was diagnosed with urticaria. The potential for development of antibodies to eptifibatide has been studied and reported in 433 subjects. Eptifibatide was nonantigenic in 412 patients receiving a single administration of eptifibatide (135-μg/kg bolus followed by a continuous infusion of either 0.5 μg/kg/min or 0.75 μg/kg/min), and in 21 subjects to whom eptifibatide (135-μg/kg bolus followed by a continuous infusion of 0.75 μg/kg/min) was administered twice, 28 days apart. In both cases, plasma for antibody detection was collected approximately 30 days after each dose. The development of antibodies to eptifibatide at higher doses has not been evaluated.

Other Adverse Reactions

In the PURSUIT and ESPRIT studies, the incidence of serious non-bleeding adverse events was similar in patients receiving placebo or eptifibatide (19% and 19%, respectively, in PURSUIT; 6% and 7%, respectively, in ESPRIT). In PURSUIT, the only serious nonbleeding adverse event that occurred at a rate of at least 1% and was more common with eptifibatide than placebo (7% vs 6%) was hypotension. Most of the serious nonbleeding events consisted of cardiovascular events typical of an unstable angina population. In the IMPACT II study, serious nonbleeding events that occurred in greater than 1% of patients were uncommon and similar in incidence between placebo- and eptifibatide-treated patients. Discontinuation of study drug due to adverse events other than bleeding was uncommon in the PURSUIT, IMPACT II, and ESPRIT studies, with no single event occurring in >0.5% of the study population (except for "other" in the ESPRIT study). In the PURSUIT study, nonbleeding adverse events leading to discontinuation occurred in the eptifibatide and placebo groups in the following body systems with an incidence of ≥0.1%: cardiovascular system (0.3% and 0.3%), digestive system (0.1% and 0.1%), hemic/lymphatic system (0.1% and 0.1%), nervous system (0.3% and 0.4%), urogenital system (0.1% and 0.1%), and whole body system (0.2% and 0.2%). In the ESPRIT study, the following nonbleeding adverse events leading to discontinuation occurred in the eptifibatide and placebo groups with an incidence of ≥0.1%: "other" (1.2% and 1.1%). In the IMPACT II study, nonbleeding adverse events leading to discontinuation occurred in the 135/0.5 eptifibatide and placebo groups in the following body systems with an incidence of ≥0.1%: whole body (0.3% and 0.1%), cardiovascular system (1.4% and 1.4%), digestive system (0.2% and 0%), hemic/lymphatic system (0.2% and 0%), nervous system (0.3% and 0.2%), and respiratory system (0.1% and 0.1%).

Post-Marketing Experience

The following adverse events have been reported in post-marketing experience, primarily with eptifibatide in combination with heparin and aspirin: cerebral, GI, and pulmonary hemorrhage. Fatal bleeding events have been reported. Acute profound thrombocytopenia has been reported.

OVERDOSAGE

There has been only limited experience with overdosage of eptifibatide. There were 8 patients in the IMPACT II study, 9 patients in the PURSUIT study, and no patients in the ESPRIT study who received bolus doses and/or infusion doses more than double those called for in the protocols. None of these patients experienced an intracranial bleed or other major bleeding.Eptifibatide was not lethal to rats, rabbits, or monkeys when administered by continuous intravenous infusion for 90 minutes at a total dose of 45 mg/kg (about 2 to 5 times the recommended maximum daily human dose on a body surface area basis). 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.

DOSAGES AND ADMINISTRATION

The safety and efficacy of eptifibatide has been established in clinical studies that employed concomitant use of heparin and aspirin. Different dose regimens of eptifibatide were used in the major clinical studies.

Acute Coronary Syndrome

The recommended adult dosage of eptifibatide in patients with acute coronary syndrome and normal renal function is an intravenous 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 percutaneous coronary intervention (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.

Patients with Creatinine Clearance Less Than 50 mL/min

The recommended adult dosage of eptifibatide in patients with acute coronary syndrome with an estimated creatinine clearance (using the Cockcroft-Gault equation) <50 mL/min is an intravenous 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)

The recommended adult dosage of eptifibatide in patients with normal renal function is an intravenous 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.

Patients with Creatinine Clearance Less Than 50 mL/min

The recommended adult dose of eptifibatide in patients with an estimated creatinine clearance (using the Cockcroft-Gault equation) <50 mL/min is an intravenous 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 coronary artery bypass graft surgery, eptifibatide infusion should be discontinued prior to surgery.

Use the Cockcroft-Gault equation with actual body weight to calculate creatinine clearance:

Males: (140-age) × (actual body wt in kg) / 72 × (serum creatinine)

Females: (140-age) × (actual body wt in kg) × (0.85) / 72 × (serum creatinine)

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. Like other parenteral drug products, Eptifibatide solutions should be inspected visually for particulate matter and discard any unused solution after opening.
2. Eptifibatide may be administered in the same intravenous line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil. Eptifibatide should not be administered through the same intravenous line as furosemide.
3. Eptifibatide may be administered in the same IV line with 0.9% NaCl or 0.9% NaCl/5% dextrose. With either vehicle, the infusion may also contain up to 60 mEq/L of potassium chloride. No incompatibilities have been observed with intravenous administration sets. No compatibility studies have been performed with PVC bags.
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.

Eptifibatide Dosing Charts by Weight

Patient	Weight	180-μg/kg Bolus Volume	2-μg/kg/min Infusion Volume		1-μg/kg/min Infusion Volume	
(kg)	(lb)	(from 2 mg/mL vial)	(from 2 mg/mL 100-mL vial)	(from 0.75 mg/mL 100-mL vial)	(from 2 mg/mL 100-mL vial)	(from 0.75 mg/mL 100-mL vial)
37-41	81-91	3.4 mL	2.0 mL/h	6.0 mL/h	1.0 mL/h	3.0 mL/h
42-46	92-102	4.0 mL	2.5 mL/h	7.0 mL/h	1.3 mL/h	3.5 mL/h
47-53	103-117	4.5 mL	3.0 mL/h	8.0 mL/h	1.5 mL/h	4.0 mL/h
54-59	118-130	5.0 mL	3.5 mL/h	9.0 mL/h	1.8 mL/h	4.5 mL/h
60-65	131-143	5.6 mL	3.8 mL/h	10.0 mL/h	1.9 mL/h	5.0 mL/h
66-71	144-157	6.2 mL	4.0 mL/h	11.0 mL/h	2.0 mL/h	5.5 mL/h
72-78	158-172	6.8 mL	4.5 mL/h	12.0 mL/h	2.3 mL/h	6.0 mL/h
79-84	173-185	7.3 mL	5.0 mL/h	13.0 mL/h	2.5 mL/h	6.5 mL/h
85-90	186-198	7.9 mL	5.3 mL/h	14.0 mL/h	2.7 mL/h	7.0 mL/h
91-96	199-212	8.5 mL	5.6 mL/h	15.0 mL/h	2.8 mL/h	7.5 mL/h
97-103	213-227	9.0 mL	6.0 mL/h	16.0 mL/h	3.0 mL/h	8.0 mL/h
104-109	228-240	9.5 mL	6.4 mL/h	17.0 mL/h	3.2 mL/h	8.5 mL/h
110-115	241-253	10.2 mL	6.8 mL/h	18.0 mL/h	3.4 mL/h	9.0 mL/h
116-121	254-267	10.7 mL	7.0 mL/h	19.0 mL/h	3.5 mL/h	9.5 mL/h
>121	>267	11.3 mL	7.5 mL/h	20.0 mL/h	3.7 mL/h	10.0 mL/h

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

Pregnancy

Pregnancy Category B

Teratology studies have been reported for continuous intravenous infusion of eptifibatide in pregnant rats at total daily doses of up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis) and in pregnant rabbits at total daily doses of up to 36 mg/kg/day (also about 4 times the recommended maximum daily human dose on a body surface area basis). These studies revealed no evidence of harm to the fetus due to eptifibatide. However, there are no adequate and well-controlled studies in pregnant women with eptifibatide. Because animal reproduction studies are not always predictive of human response, eptifibatide should be used during pregnancy only if clearly needed.

Pediatric Use

Safety and effectiveness of eptifibatide in pediatric patients have not been studied.

Nursing 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.

Geriatric Use

There was no apparent difference in efficacy between older and younger patients treated with eptifibatide.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store between 2^{0}C to 8^{0}C. Protect from light until administration. Keep out of reach of children

PRESENTATION

EPTIBIND 20 and EPTIBIND 75 are avialable as Single use vial, for intravenous use only.

EPTIBIND 20 is available as 10 ml vial

EPTIBIND 75 is available as 100 ml vial

torrent

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :
Gland Pharma Limited
D.P. Pally, Dundigal Post, Hyderabad - 500 043, India.

LEA/019323-00