PRODUCT MONOGRAPH

[Pr]EPTIFIBATIDE INJECTION

Eptifibatide Injection

Intravenous Solution

2 mg/mL bolus Injection

0.75 mg/mL Injection (as infused)

Platelet Aggregation Inhibitor

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PRODUCT MONOGRAPH

PrEPTIFIBATIDE INJECTION

Platelet Aggregation Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

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

Pharmacodynamics: Eptifibatide inhibits platelet aggregation induced by adenosine diphosphate (ADP) and other agonists in a dose- and concentration-dependent manner. The effect of eptifibatide is observed immediately after administration of a 180 mcg/kg intravenous bolus. When followed by a 2.0 mcg/kg/min continuous infusion, this regimen produces a >80% inhibition of 20 μM ADP-induced *ex vivo* platelet aggregation, (at physiologic calcium concentrations) in more than 80% of patients, after more than 8 hours of infusion. Platelet inhibition was reversed, with a >50% return of platelet function towards baseline 4 hours after discontinuation of an infusion of 2.0 mcg/kg/min.

The eptifibatide dosing regimen used in the ESPRIT study was similar to that used in the PURSUIT study (a 180 mcg/kg bolus followed by a 2.0 mcg/kg/min infusion), but added a second 180 mcg/kg bolus ten minutes after the first bolus to avoid a transient decrease in platelet aggregation inhibition before reaching steady-state with the continuous 2.0 mcg/kg/min infusion. This dosing regimen is recommended in order to maintain platelet aggregation inhibition above 80% in the early time points when percutaneous coronary intervention (PCI) is performed (see **Pharmacokinetics**).

Administration of eptifibatide by intravenous bolus and infusion to healthy male subjects causes up to a 5-fold increase in bleeding time, which is reversible upon discontinuation of the infusion with bleeding times returning toward baseline within 4 to 6 hours. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT) (see also **PRECAUTIONS**; **Drug Interactions**).

There were no important differences between age groups on the inhibition by eptifibatide of adenosine diphosphate-induced platelet aggregation. 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 mcg/kg and infusion rates from 0.5 to 3.0 mcg/kg/min. The administration of a single bolus followed by an infusion produces an early peak level, followed by a small decline until steady state plasma concentrations are achieved (within 4-6 hours). In situations in which continuous inhibition is critical during the first 1-2 hours, e.g., when PCI is performed, this decline can be prevented by administering a second 180 mcg/kg bolus ten minutes after the first. Plasma elimination half-life is approximately 2.5 hours. The extent of eptifibatide binding to human plasma protein is about 25%. In patients with unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI), plasma clearance is 55 mL/kg/h and the volume of distribution is approximately 185 mL/kg. In healthy subjects, renal clearance accounts for approximately 50% of total body clearance, with the majority of the drug excreted in the urine as eptifibatide, deamidated eptifibatide, and other more polar metabolites. No major metabolites have been detected in human plasma. Total drug clearance is decreased by approximately 50% and steady-state plasma eptifibatide concentrations are doubled in patients with moderate renal impairment (creatinine clearance of ≥30 - <50 mL/min, using the Cockcroft-Gault equation) (see **DOSAGE AND ADMINISTRATION** for the Cockcroft-Gault equation).

Clinical studies have included 2,418 patients with serum creatinine between 1.0 and 2.0 mg/dL (for the 180 mcg/kg bolus followed by a 2.0 mcg/kg/min infusion) and 7 patients with serum creatinine between 2.0 and 4.0 mg/dL (for the 135 mcg/kg bolus and the 0.5 mcg/kg/min infusion), without dose adjustment. An additional 8 patients with serum creatinine between 2.0 and 4.0 mg/dL were enrolled in the ESPRIT study and received an intravenous bolus of 180 mcg/kg, immediately followed by a continuous infusion of 1.0 mcg/kg/min and a second 180 mcg/kg bolus administered ten minutes after the first.

Special Populations: Patients in clinical studies were older than the subjects in clinical pharmacology studies, and they had lower total body clearance and higher eptifibatide plasma levels. However, clinical studies were conducted in patients with UA/NSTEMI ranging in age from 20 to 94 years, without dose adjustment for age. Limited data are available for patients over 75 years of age weighing less than 50 kg. Men and women showed no important differences in the pharmacokinetics of eptifibatide.

INDICATIONS AND CLINICAL USE

Eptifibatide injection is indicated for the treatment of patients presenting with symptoms of unstable angina (UA)/non-ST-segment elevation myocardial infarction (NSTEMI), including those patients who may subsequently undergo percutaneous coronary intervention (PCI) as well as those who will be managed medically.

Eptifibatide Injection is indicated for the treatment of patients undergoing PCI including those undergoing intracoronary stenting.

Eptifibatide Injection is intended for use with ASA and heparin.

CONTRAINDICATIONS

Treatment with eptifibatide is contraindicated in patients with:

- A history of bleeding diathesis, or evidence of active abnormal bleeding within the previous 30 days.
- Thrombocytopenia (< 100,000 cells/mm^3)
- Prothrombin time >1.2 times control, or International Normalized Ration (INR) ≥2.0.
- 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.
- Known history of intracranial disease (neoplasm, arteriovenous malformation, aneurysm).
- Current or planned administration of another parenteral GP IIb/IIIa inhibitor.
- Severe renal impairment (creatinine clearance <30 mL/min) or dependency on renal dialysis.
- Known hypersensitivity to any component of the product.
- Clinically significant liver disease.

WARNINGS

Bleeding: Bleeding is the most common complication encountered during Eptifibatide Injection therapy. Administration of Eptifibatide Injection is associated with an increase in major and minor bleeding, as classified by the Thrombolysis in Myocardial Infarction Study group (TIMI) criteria (see **ADVERSE REACTIONS**). Most major bleeding associated with Eptifibatide Injection has been at the arterial access site for cardiac catheterization or from the gastrointestinal or genitourinary tract.

All potential bleeding sites (e.g., catheter insertion sites, arterial, venous or needle puncture sites; cutdown sites; gastrointestinal, genitourinary and retroperitoneal sites) should be observed carefully.

In patients undergoing PCI, patients receiving Eptifibatide Injection experienced an increase in major bleeding compared to those receiving placebo without a significant increase in transfusion requirement. Special care should be employed to minimize the risk of bleeding among these patients (see **PRECAUTIONS**). IF BLEEDING CANNOT BE CONTROLLED WITH PRESSURE, INFUSION OF Eptifibatide Injection AND ANY CONCOMITANT HEPARIN SHOULD BE STOPPED IMMEDIATELY.

Clinical data suggest that the risk of major and minor bleeding due to Eptifibatide Injection therapy may be increased in patients weighing less than 70 kg.

Platelet Count <100,000/mm^3: Because it is an inhibitor of platelet aggregation, caution should be exercised when administering eptifibatide to patients with a platelet count <100,000/mm^3;

there has been no clinical experience with eptifibatide initiated in patients with a platelet count <100,000/mm^3.

PRECAUTIONS

Bleeding:

Coronary artery bypass grafting (CABG): Treatment with Eptifibatide Injection is not associated with an increase in bleeding in association with CABG. Eptifibatide Injection infusion should be discontinued prior to undergoing CABG.

Percutaneous coronary intervention - Care of the femoral artery access site: Treatment with Eptifibatide Injection is associated with an increase in major and minor bleeding particularly at the site of arterial access for femoral sheath placement. In patients undergoing PCI, Eptifibatide Injection infusion should be continued for up to 18-24 hours post-procedure or until hospital discharge, whichever comes first. Heparin use is discouraged after the PCI procedure. The femoral artery sheath may be removed during treatment with Eptifibatide Injection . It is recommended that heparin be discontinued 3-4 hours prior to sheath removal and a decline in aPTT to <45 seconds or activated clotting time (ACT) to <150 seconds be documented. Heparin and Eptifibatide Injection should be discontinued and sheath hemostasis should be achieved at least 2-4 hours before hospital discharge.

Maintaining Target aPTT and ACT: The aPTT should be maintained between 50 and 70 seconds unless PCI is to be performed. For angioplasty done during the PURSUIT study, a target ACT of 300 to 350 seconds was stipulated. Patients receiving an Eptifibatide Injection 180 mcg/kg bolus followed by a 2 mcg/kg/min infusion experienced an increased incidence of bleeding relative to placebo, primarily at the femoral access site. The ESPRIT study stipulated a target ACT of 200 to 300 seconds during intracoronary stenting. Patients receiving an Eptifibatide Injection 180 mcg/kg bolus
followed by a 2 mcg/kg/min infusion and a second 180 mcg/kg bolus ten minutes after the first (mean ACT 284 seconds) experienced an increased incidence of bleeding relative to placebo (mean ACT 276 seconds), primarily at the femoral artery access site. At these lower ACTs, bleeding was less than previously reported with eptifibatide in the PURSUIT and IMPACT II studies. Moreover, there was little increase in transfusion requirements.

PRIDE was a randomized, placebo-controlled, multi-center trial conducted in 126 patients with coronary artery disease undergoing angioplasty, prior to the PURSUIT study. The pharmacodynamics of three dosing regimens of Eptifibatide Injection were assessed. All infusions were continued for 24 hours post-angioplasty. The incidence of bleeding events in patients receiving Eptifibatide Injection as a 180 mcg/kg bolus and 2 mcg/kg/min infusions and heparin targeted at an ACT of 200-250 was similar to that seen in patients receiving placebo and heparin targeted at an ACT of 300-350 seconds. The study was not powered to assess clinical efficacy.

The aPTT or ACT should be checked prior to arterial sheath removal. The sheath should not be

removed unless the aPTT is <45 seconds or the ACT is <150 seconds.

Table 1 displays the risk of major bleeding according to the maximum aPTT attained within 72 hours in the PURSUIT study.

Table 1

Major Bleeding by Maximal aPTT within 72 Hours in the PURSUIT Study

	Placebo n (%)	**Eptifibatide 180 mcg/kg bolus, 2.0 mcg/kg/min infusion n (%)**
Maximum aPTT (seconds)		
< 50	44/721 (6.1%)	44/743 (5.9%)
50-70 (recommended)	92/908 (10.1%)	99/883 (11.2%)
>70	281/2,786 (10.1%)	345/2,811 (12.3%)

Care of puncture sites: Arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, nasogastric tubes, and automatic blood pressure cuffs should be minimized. When obtaining intravenous access, non-compressible sites (e.g., subclavian or jugular veins) should be avoided. Document and monitor vascular puncture sites. Consider using saline or heparin locks for blood drawing. Remove dressings gently.

Laboratory Monitoring: Before infusion of Eptifibatide Injection, the following tests should be conducted: platelet count, hematocrit or hemoglobin, serum creatinine and PT/aPTT. In patients undergoing PCI, the ACT should also be measured in patients who have already received heparin. During and following Eptifibatide Injection treatment, platelet counts and extent of heparin anticoagulation, as assessed by ACT, should be monitored closely. Platelet counts should be monitored 2 to 4 hours following administration of the Eptifibatide Injection bolus, and at 24 hours post-infusion termination or prior to patient discharge, whichever occurs first.

Thrombocytopenia: If a patient experiences a platelet decrease (<100,000/mm^3), additional platelet counts should be determined (see **ADVERSE REACTIONS**, **Tables 9**, **10** and **11**). If thrombocytopenia is confirmed, Eptifibatide Injection and heparin should be discontinued immediately and the condition appropriately monitored and treated.

From post market experience, acute thrombocytopenia has been reported. Upon discontinuation of Eptifibatide Injection, acute thrombocytopenia has been reported to be reversible. The rapid reversibility of the pharmacologic action is due to the short plasma half-life of Eptifibatide Injection (approximately 2.5 hours) and the rapid disassociation of Eptifibatide Injection from the platelet

receptor GP IIb/IIIa.

Prolongation of bleeding time: Administration of Eptifibatide Injection by intravenous bolus and infusion causes up to a 5-fold increase in bleeding time. This increase is reversible upon discontinuation of the infusion with bleeding times returning towards baseline within 4 to 6 hours. When administered alone, Eptifibatide Injection has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

Renal Impairment: Renal and non-renal clearance of eptifibatide account for approximately 50% each. Total drug clearance is decreased by approximately 50% and steady-state plasma eptifibatide concentrations are doubled in patients with moderate renal impairment (creatinine clearance of ≥30 - <50 mL/min, using Cockcroft-Gault equation) (see **DOSAGE AND ADMINISTRATION** for the Cockcroft-Gault equation).Therefore, the infusion dose should be reduced to 1.0 mcg/kg/min in such patients.

No clinical data are available for patients dependent on renal dialysis. *In vitro* studies have indicated that eptifibatide may be cleared from plasma by dialysis.

Pregnancy: Reproduction and teratology studies have been performed by continuous intravenous infusion of eptifibatide in pregnant rats at total daily doses of up to 72 mg/kg/day (24 times the recommended maximum daily human dose of 3 mg/kg/day) and pregnant rabbits at total daily doses of up to 36 mg/kg/day (12 times the recommended maximum daily human dose). These studies revealed no evidence of impaired fertility or harm to the fetus due to eptifibatide. Eptifibatide has been shown to cross the placenta in pregnant rats. There are, however, no adequate and well-controlled studies in pregnant women with eptifibatide. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether eptifibatide is excreted in human milk. Therefore, nursing should be discontinued during the period of drug administration.

Pediatric Use: Safety and effectiveness of eptifibatide in children have not been established.

Use in Elderly: **Table 2** and **Table 3** show bleeding events and transfusions for patients ≥65 years old and ≥75 years old, respectively, in the PURSUIT study. The incidence of bleeding complications was higher in the elderly in both placebo and eptifibatide groups, and the incremental risk of eptifibatide-associated bleeding was greater in older patients. No dose adjustment was made in the elderly population, but patients over 75 years of age had to weigh at least 50 kg to be enrolled in the PURSUIT study; no such limitation was stipulated in the ESPRIT study (see **ADVERSE REACTIONS**).

Table 2

Bleeding Events and Transfusions within 30 Days of Randomization for Patients ≥65 Years Old

PURSUIT Study

	Placebo	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion
	n (%) of Patients	
Major Bleeding [a,c]	230/2,220 (10.4%)	269/2,209 (12.2%)
Minor Bleeding [a,c]	190/2,220 (8.6%)	358/2,209 (16.2%)
Bleeding Requiring Transfusions [b]	307/2,270 (13.5%)	375/2,237 (16.8%)

a: For major and minor bleeding, patients are counted only once according to the most severe classification.

b: Includes transfusions of any type: whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

c: Incidence in patients with sufficient clinical information to determine bleeding status.

Table 3
Bleeding Events and Transfusions within 30 Days of Randomization for Patients ≥75 Years Old
PURSUIT Study

	Placebo	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion
	n (%) of Patients	
Major Bleeding [a,c]	53/655 (8.1%)	78/663 (11.8%)
Minor Bleeding [a,c]	56/655 (8.5%)	130/663 (19.6%)
Bleeding Requiring Transfusions [b]	81/672 (12.1%)	121/673 (18.0%)

a: For major and minor bleeding, patients are counted only once according to the most severe classification.
b: Includes transfusions of any type: whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.
c: Incidence in patients with sufficient clinical information to determine bleeding status.

Drug Interactions: Eptifibatide Injection has been studied concomitantly with heparin and ASA (see **CLINICAL TRIALS**). The use of Eptifibatide Injection, in combination with heparin and ASA, has been associated with an increase in bleeding compared to heparin and ASA alone. Because eptifibatide inhibits platelet aggregation, caution should be employed when it is used with other medications that affect hemostasis, including **thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, dipyridamole, ticlopidine and clopidogrel.** To avoid potentially additive pharmacological effects, concomitant treatment with **other inhibitors of platelet receptor GP IIb/IIIa** should be avoided.

In the ESPRIT study, clopidogrel or, in a few cases, ticlopidine were used routinely starting the day of intracoronary stenting.

Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PCI when ACT exceeded 350 seconds (see **PRECAUTIONS**).

Thrombolytics: Limited data are available on the use of Eptifibatide Injection with thrombolytic agents. In a 180 patient study with the accelerated alteplase regimen, the coadministration of Eptifibatide Injection up to 180 mcg/kg and 0.75 mcg/kg/min did not increase the incidence of major bleeding or transfusions compared to patients receiving alteplase alone. In another 181 patient study with streptokinase (1.5 million units over 60 minutes), the coadministration of increasing Eptifibatide Injection doses was well tolerated up to an infusion rate of 1.3 and 2.0 mcg/kg/min, where there was an increased incidence of bleeding and transfusions.

Based on the limited data on the use of Eptifibatide Injection in patients receiving thrombolytic

agents, the bleeding risk due to combination with thrombolytic therapy cannot be estimated. Therefore, the concomitant treatment with thrombolytic agents should be used judiciously after the risk and benefit are carefully assessed for individual patients by the physician.

Lastly, experience in 40 patients who received a combination of full dose Eptifibatide Injection (180 mcg/kg and 2.0 mcg/kg/min) and full dose thrombolytic therapy revealed a 25% incidence of major bleeding events.

Pharmacokinetic and Pharmacodynamic Interaction with Enoxaparin: The use of enoxaparin dosed as a 1.0 mg/kg subcutaneous injection every 12 hours in place of unfractionated heparin did not alter the pharmacokinetics of eptifibatide or the level of platelet aggregation inhibition.

ADVERSE REACTIONS

A total of 16,782 patients were treated in the Phase III clinical trials (PURSUIT, IMPACT II and ESPRIT). These 16,782 patients had a mean age of 62 years (range 20 to 94). Eighty-nine percent of the patients were Caucasian, with the remainder being predominantly Black (5%) and Hispanic (5%). Sixty-eight percent (68%) were men. Because of the different regimens used in PURSUIT, IMPACT II and ESPRIT, data from the three studies were not pooled.

Bleeding: The results of bleeding events and transfusions in the PURSUIT study during infusion and within 30 days are displayed in **Table 4**, and **Table 5** respectively. The results of bleeding events and transfusions in the IMPACT II and ESPRIT studies are displayed in **Table 6** and **Table 7**, respectively.

Bleeding was classified as major or minor by the criteria of the TIMI study group. Major bleeding events were defined as either an intracranial hemorrhage or other bleeding that led to a decrease in hemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, observed blood loss with a hemoglobin decrease of more than 3 g/dL or more than 4 g/dL in the absence of an observed bleeding site. In patients who received transfusions, the corresponding loss in hemoglobin was estimated through an adaptation of the method of Landefeld *et al*.

Table 4

Bleeding Events and Transfusions during Infusion

PURSUIT Study

	Placebo	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion
	n (%) of Patients	
Major Bleeding [a,c]	59/4,577 (1.3%)	96/4,604 (2.1%)
Minor Bleeding [a,c]	89/4,577 (1.9%)	186/4,604 (4.0%)
Bleeding Requiring Transfusions [b]	19/4,696 (0.4%)	34/4,679 (0.7%)

a: For major and minor bleeding, patients are counted only once according to the most severe classification.

b: Includes transfusions of any type: whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

c: Incidence in patients with sufficient clinical information to determine bleeding status.

Table 5

Bleeding Events and Transfusions within 30 Days

PURSUIT Study

	Placebo	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion
	n (%) of Patients	
Major Bleeding [a,c]	425/4,577 (9.3%)	498/4,604 (10.8%)
Minor Bleeding [a,c]	347/4,577 (7.6%)	604/4,604 (13.1%)
Bleeding Requiring Transfusions [b]	490/4,696 (10.4%)	601/4,679 (12.8%)

a: For major and minor bleeding, patients are counted only once according to the most severe classification.

b: Includes transfusions of any type: whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

c: Incidence in patients with sufficient clinical information to determine bleeding status.

Table 6

Bleeding Events and Transfusions within 30 days

IMPACT II Study

	Placebo **(n %)**	**Eptifibatide** 135 mcg/kg bolus, 0.5 mcg/kg/min infusion **n (%)**	**Eptifibatide** 135 mcg/kg bolus, 0.75 mcg/kg/min infusion **n (%)**
Patients	1,285	1,300	1,286
Major Bleeding [a]	55 (4.5%)	55 (4.4%)	58 (4.7%)
Minor Bleeding [a]	115 (9.3%)	146 (11.7%)	177 (14.2%)
Bleeding Requiring Transfusions [b]	66 (5.1%)	71 (5.5%)	74 (5.8%)

Note: denominator is based on patients for whom data are available

a: For major and minor bleeding, patients are counted only once according to the most severe classification.

b: Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

Table 7

Bleeding Events and Transfusions within 48 hours*

ESPRIT Study

	Placebo **(n %)**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion **n (%)**
Patients	1,024	1,040
Major Bleeding [a]	4 (0.4%)	13 (1.3%)
Minor Bleeding [a]	18 (2.0%)	29 (3.0%)
Bleeding Requiring Transfusions [b]	11 (1.1%)	16 (1.5%)
Unresolved[c]	102	68

* Or discharge, whichever occurred first.

a:For major and minor bleeding, patients are counted only once according to the most severe classification.

b: Includes transfusions of any type: whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

c: Number of patients in who TIMI grade could not be ascertained; these patients are excluded from the denominator in the computation of percents.

In the PURSUIT study, treatment with Eptifibatide Injection resulted in an incremental risk of major bleeding (increase of 1.5%) and a higher incidence of transfusion (increase of 2.4%) than occurred with placebo. There was also an increase in minor bleeding events in patients treated with Eptifibatide Injection (increase of 5.5%) compared to placebo.

In the PURSUIT study, the greatest increase in major bleeding in eptifibatide-treated patients compared to placebo-treated patients was associated with bleeding at the femoral artery access site (2.8% versus 1.3%). Oropharyngeal (primarily gingival), genito-urinary, 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 observed only for the femoral artery access site (3.2% versus 2.8%).

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, while the number was even lower at the remaining sites (such as genito-urinary, gastrointestinal, and retroperitoneal bleeding).

Table 8 displays the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT study. The most common bleeding complications were associated with cardiac revascularization procedures (CABG-related or femoral artery access site bleeding).

A corresponding table for ESPRIT is not presented as every patient underwent stenting in the ESPRIT study and only 11 patients underwent CABG.

Table 8

Major Bleeding by Procedures in the PURSUIT Study*

	Placebo **(n %)**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion **n (%)**
Patients	4,577	4,604
Overall Incidence of Major Bleeding	425 (9.3%)	498 (10.8%)
Breakdown by Procedure:		
CABG	375 (8.2%)	377 (8.2%)
Angioplasty without CABG	27 (0.6%)	64 (1.4%)
Angiography without angioplasty or CABG	11 (0.2%)	29 (0.6%)
Medical Therapy Only	12 (0.3%)	28 (0.6%)

* Data through hospital discharge, including patients undergoing CABG.

Patients undergoing CABG accounted for most instances of major bleeding in both treatment groups. Patients undergoing coronary angioplasty accounted for most of the increased incidence of major bleeding among patients treated with Eptifibatide Injection compared to placebo.

In the PURSUIT and ESPRIT studies, the risk of major bleeding with Eptifibatide Injection increased inversely with patient weight. This relationship was most apparent for patients weighing less than 70 kg.

Bleeding adverse events resulting in discontinuation of study drug were more frequent among patients receiving Eptifibatide Injection than placebo (4.6% versus 0.9% in ESPRIT, 8% versus 1% in PURSUIT, and 3.5% versus 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, only 3 patients in the placebo group and 5 patients in the group treated with Eptifibatide Injection 180 mcg/kg bolus followed by a continuous infusion of 2.0 mcg/kg/min experienced hemorrhagic stroke. The overall incidence of stroke was 0.7% in patients receiving Eptifibatide Injection 180 mcg/kg bolus followed by a continuous infusion of 2.0 mcg/kg/min and 0.8% in placebo patients.

Investigator's assessment of all strokes within 6 months of randomization was 1.3% in patients receiving eptifibatide 180 mcg/kg bolus followed by a continuous infusion of 2.0 mcg/kg/min, and 1.5% in placebo patients, in the PURSUIT study.

In the IMPACT II study, intracranial hemorrhage was experienced by 1 patient treated with eptifibatide 135 mcg/kg bolus followed by a continuous infusion of 0.5 mcg/kg/min, 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 mcg/kg bolus followed by a continuous infusion of 0.5 mcg/kg/min eptifibatide, 0.7% in patients receiving eptifibatide 135 mcg/kg bolus followed by a continuous infusion of 0.75 mcg/kg/min 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 (180 mcg/kg bolus, followed by a continuous infusion of 2.0 mcg/kg/min, and a 180 mcg/kg bolus 10 minutes after the first) group. In addition, there was 1 case of cerebral infarction in the eptifibatide group. Both patients who experienced a hemorrhagic stroke while receiving eptifibatide had received >10,000 units of heparin.

Thrombocytopenia: In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100,000/mm^3 or >50% reduction from baseline) (see **Table 9** and **Table 10**) and the incidence of platelet transfusions were similar between patients treated with Eptifibatide Injection and placebo. In the ESPRIT study, the incidence was 0.6% in the placebo group and 1.2% in the eptifibatide group (see **Table 11**).

Table 9
Incidence of Marked Abnormalities in Platelets Post-Baseline for Patients Treated with Placebo or Eptifibatide Injection*

PURSUIT

Abnormalities	**Placebo**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion
Platelet Count		
<100,000/mm^3	225/4,587 (5%)	226/4,599 (5%)
≥50% Decrease from Baseline**	231/4,516 (5%)	250/4,544 (5%)
<50,000/mm^3	19/4,587 (<1%)	26/4,599 (1%)
<20,000/mm^3	2/4,587 (<1%)	9/4,599 (<1%)

* Data through hospital discharge, including patients undergoing CABG.
** Requires a baseline value and at least one post-baseline value. All other computations require only a post-baseline value.

Table 10
Incidence of Marked Abnormalities in Platelets Post-Baseline for Patients Treated with Placebo or Eptifibatide *

IMPACT II

Abnormalities	**Placebo**	**Eptifibatide** 135 mcg/kg bolus, 0.5 mcg/kg/min infusion	**Eptifibatide** 135 mcg/kg bolus, 0.75 mcg/kg/min infusion
Platelet Count			
<100,000/mm^3	31/1,285 (2.4%)	34/1,300 (2.6%)	36/1,286 (2.8%)
≥50% Decrease from Baseline**	39/1,285 (3.0%)	29/1,300 (2.2%)	33/1,286 (2.6%)
<50,000/mm^3	8/1,285 (0.6%)	2/1,300 (0.2%)	5/1,286 (0.4%)

Note: Percentages based on total population.

Table 11
Incidence of Marked Abnormalities in Platelets Post-Baseline for Patients Treated with Placebo or Eptifibatide Injection *

ESPRIT

Abnormalities	**Placebo** **n (%)**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion, 180 mcg/kg bolus 10 minutes after first **(n %)**
Platelet Count		
<100,000/mm^3	4/1,024 (0.4%)	9/1,040 (0.9%)
<100,000/mm3 or ≥50% Decrease from Baseline	6/1,024 (0.6%)	12/1,040 (1.2%)
≥50% Decrease from Baseline**	2/1,024 (0.2%)	9/1,040 (0.9%)
≥20,000 to <50,000/mm^3	0/1,024 (0%)	0/1,040 (0%)
<20,000/mm^3	0/1,024 (0%)	2/1,040 (0.2%)

* Data within 48 hours of treatment with Eptifibatide or Placebo.
** Requires a baseline value and at least one post-baseline value. All other computations require only a post-baseline value.

Allergic Reactions: The incidence of anaphylaxis in large randomized studies ranged from 0% to 0.16% for Eptifibatide Injection and from 0% to 0.15% for placebo. The number of patients who discontinued drug due to allergic reactions in these studies ranged from 0.04% to 0.2% for Eptifibatide Injection and from 0% to 0.1% for placebo. The potential for the development of antibodies to Eptifibatide Injection has been studied in 433 subjects, 21 of whom received a second Eptifibatide Injection administration after 28 days. No antibodies against Eptifibatide Injection were detected in blood samples collected at baseline and 30 days after drug administration.

Other Adverse Reactions: **Table 12** displays serious adverse events other than bleeding from the PURSUIT study which occurred in greater than or equal to 1% of treated patients in the Eptifibatide Injection or placebo group within 30 days of treatment initiation.

In the ESPRIT study, the incidence of serious non-bleeding adverse events was similar in

patients receiving placebo or eptifibatide (6% and 7%, respectively). In the IMPACT II study, serious non-bleeding events that occurred in greater than 1% of patients were uncommon and similar in incidence between placebo- and eptifibatide-treated patients.

Table 12

Serious Non-Bleeding Adverse Events among Treated Patients

PURSUIT Study

	Placebo (n=4,696)		**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion **(n=4,679)**	
Any Serious Non-Bleeding Adverse Event	**877**	**(19%)**	**890**	**(19%)**
Cardiovascular System				
Atrial Fibrillation	301	(6%)	294	(6%)
Hypotension	290	(6%)	324	(7%)
Congestive Heart Failure	257	(5%)	240	(5%)
Cardiac Arrest	127	(3%)	109	(2%)
Shock	117	(2%)	120	(3%)
Phlebitis	69	(1%)	64	(1%)
Atrioventricular Block	61	(1%)	70	(1%)
Ventricular Fibrillation	65	(1%)	59	(1%)
Ventricular Tachycardia	54	(1%)	51	(1%)
Hemic/Lymphatic System				
Thrombocytopenia	3	(<1%)	11	(<1%)
Nervous System				
Cerebral Ischemia	24	(1%)	18	(<1%)

There were no significant increases in serious non-bleeding events with Eptifibatide Injection relative to placebo. Serious non-bleeding adverse events were generally of a cardiovascular etiology and are expected in a patient population presenting with UA/NSTEMI.

In the PURSUIT, IMPACT II and ESPRIT trials, discontinuation of study drug due to adverse events other than bleeding was uncommon, with no single event occurring at >0.5% of the study population, except for "cardiovascular" in the IMPACT II study and "other" in the ESPRIT

study. In the PURSUIT study, the non-bleeding adverse events (>0.1%) leading to discontinuation occurred in the eptifibatide and placebo groups in the following body systems: 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 IMPACT II study, non-bleeding 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%).

In the ESPRIT study, the following non-bleeding adverse events leading to discontinuation occurred in the eptifibatide and placebo groups with an incidence of >0.1%: "other adverse events" (1.2% and 1.1%).

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Potentially, an overdose of Eptifibatide Injection could result in bleeding. Because of its short half-life and rapid clearance, the activity of Eptifibatide Injection may be halted readily by discontinuing the infusion. Eptifibatide Injection can also be dialyzed. In certain cases, treatment of overdose may require transfusion.

There was no indication of severe adverse events associated with administration of accidental large bolus doses, rapid infusion reported as overdose, or large cumulative doses.

There has been only limited experience with overdosage of eptifibatide. There were 9 patients in the PURSUIT study, 8 patients in the IMPACT II study and no patient in the ESPRIT study who received bolus doses and/or infusion doses more than double those called for in the protocols. In the PURSUIT study, there was no excessive bleeding in any of these patients, although one patient undergoing CABG was reported as having had a moderate bleed. None of these patients experienced an intracranial bleed or other major bleeding.

DOSAGE AND ADMINISTRATION

Eptifibatide Injection solution for injection must always be given as an intravenous bolus followed by the Eptifibatide Injection solution for infusion.

Unstable angina/non-ST-segment elevation myocardial infarction

The recommended adult dosage of Eptifibatide Injection in patients with UA/NSTEMI is an intravenous bolus of 180 mcg/kg (as soon as possible following diagnosis), followed immediately by a continuous infusion of 2.0 mcg/kg/min until hospital discharge or initiation of CABG surgery, up to 72 hours. If a patient undergoes PCI, Eptifibatide Injection infusion should be continued until hospital discharge or for up to 18-24 hours after the procedure, whichever comes first, allowing for 96 hours of therapy.

Patients weighing more than 121 kg should receive a maximum bolus of 22.6 mg (11.3 mL of the 2 mg/mL injection) followed by a maximum infusion rate of 15 mg (20 mL of the 0.75 mg/mL injection) per hour.

The recommended adult dosage of eptifibatide in patients with moderate renal impairment (creatinine clearance of ≥30 - <50 mL/min, using the Cockcroft-Gault* equation) is an intravenous bolus of 180 mcg/kg as soon as possible following diagnosis, immediately followed by a continuous infusion of 1.0 mcg/kg/min. Patients weighing more than 121 kg should receive a maximum bolus of 22.6 mg (11.3 mL of the 2 mg/mL injection) followed by a maximum infusion rate of 7.5 mg (10 mL of the 0.75 mg/mL injection) per hour.

Percutaneous coronary intervention (PCI)

The recommended adult dosage of Eptifibatide Injection is an intravenous bolus of 180 mcg/kg administered immediately before the initiation of PCI followed by a continuous infusion of 2.0 mcg/kg/min and a second 180 mcg/kg bolus 10 minutes after the first bolus. Infusion should be continued until hospital discharge or for up to 18-24 hours, whichever comes first. A minimum of 12 hours of infusion is recommended. Patients weighing more than 121 kg should receive a maximum of 22.6 mg (11.3 mL of the 2 mg/mL injection) per bolus followed by a maximum infusion rate of 15 mg (20 mL of the 0.75 mg/mL injection) per hour.

The recommended adult dose of eptifibatide in patients with moderate renal impairment (creatinine clearance of ≥30 -<50 mL/min, using the Cockcroft-Gault* equation), is an intravenous bolus of 180 mcg/kg administered immediately before the initiation of the procedure, followed by a second 180 mcg/kg bolus administered 10 minutes after the first bolus injection. Simultaneously with the first bolus dose, a continuous infusion of 1.0 mcg/kg/min should be started. Continue the infusion until hospital discharge or up to a maximum of 18-24 hours post PCI. A minimum of 12 hours of infusion is recommended. For severe renal impairment see CONTRAINDICATIONS.

Patients weighing more than 121 kg should receive a maximum bolus of 22.6 mg (11.3 mL of the 2 mg/mL injection) followed by a maximum infusion rate of 7.5 mg (10 mL of the 0.75 mg/mL injection) per hour.

In patients who undergo coronary artery bypass graft surgery, eptifibatide infusion should be discontinued prior to surgery.

*Using the Cockcroft-Gault equation, with actual body weight, creatinine clearance in mL/min is calculated as:

Males: $\frac{(140 - \text{age in years}) \times (\text{body weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$

Females: $\frac{(140 - \text{age in years}) \times (\text{body weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine in mg/dL})}$

Heparin and ASA Dosing Recommendations: In the PURSUIT, IMPACT II and ESPRIT trials, most patients received concomitant ASA and heparin (see **CLINICAL TRIALS**).

Unstable angina/non-ST-segment elevation myocardial infarction
ASA: 160 - 325 mg, given orally, initially and daily thereafter.

Heparin: Target aPTT 50 - 70 seconds during medical management
- if weight ≥70 kg, 5,000 U bolus followed by infusion of 1,000 U/h.
- if weight <70 kg, 60 U/kg bolus followed by infusion of 12 U/kg/h.

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

Percutaneous coronary intervention
ASA: 160 - 325 mg po 1 - 24 hours prior to PCI and daily thereafter.

Heparin: Target ACT 200 - 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 (see **PRECAUTIONS**; **Thrombolytics)**.

Instructions for Administration Like other parenteral drug products, Eptifibatide Injection solutions should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

1. Eptifibatide Injection may be administered in the same intravenous line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil. Eptifibatide Injection should not be administered through the same intravenous line as furosemide.
2. Eptifibatide Injection 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. Eptifibatide is for direct infusion and is piggy backed onto an existing intravenous line and should be administered undiluted directly from the vial.

3. The bolus dose(s) of Eptifibatide Injection should be withdrawn from the 10-mL vial into a syringe. The bolus dose(s) should be administered by IV push.

4. Immediately following the bolus dose administration, a continuous infusion of Eptifibatide Injection should be initiated. Using an intravenous infusion pump, Eptifibatide Injection 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 Injection is to be administered by volume according to patient weight. Patients should receive Eptifibatide Injection according to the following table:

Eptifibatide Injection Dosing Chart by Weight

Patient Weight		**Bolus Volume** (from 2 mg/mL vial)	**Infusion Volume** (from 0.75 mg/mL 100 mLvial)	
(kg)	**(lb)**	**180 mcg/kg**	**2.0 mcg/kg/min Cl_{creat}≥50 mL/min**	**1.0 mcg/kg/min Cl_{creat}<50 mL/min**
37-41	81-91	3.4 mL	6.0 mL/h	3.0 mL/h
42-46	92-102	4.0 mL	7.0 mL/h	3.5 mL/h
47-53	103-117	4.5 mL	8.0 mL/h	4.0 mL/h
54-59	118-130	5.0 mL	9.0 mL/h	4.5 mL/h
60-65	131-143	5.6 mL	10.0 mL/h	5.0 mL/h
66-71	144-157	6.2 mL	11.0 mL/h	5.5 mL/h
72-78	158-172	6.8 mL	12.0 mL/h	6.0 mL/h
79-84	173-185	7.3 mL	13.0 mL/h	6.5 mL/h
85-90	186-198	7.9 mL	14.0 mL/h	7.0 mL/h
91-96	199-212	8.5 mL	15.0 mL/h	7.5 mL/h
97-103	213-227	9.0 mL	16.0 mL/h	8.0 mL/h
104-109	228-240	9.5 mL	17.0 mL/h	8.5 mL/h
110-115	241-253	10.2 mL	18.0 mL/h	9.0 mL/h
116-121	254-267	10.7 mL	19.0 mL/h	9.5 mL/h
>121	>267	11.3 mL	20.0 mL/h	10.0 mL/h

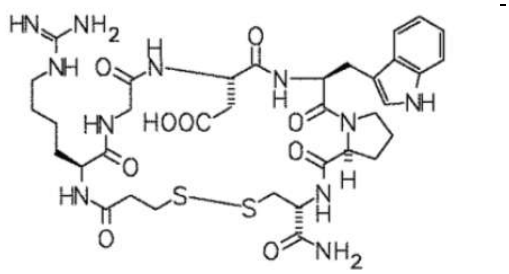
PHARMACEUTICAL INFORMATION

Drug Substance: Eptifibatide is a cyclic heptapeptide containing six amino acids and one mercaptopropionyl (des-aminocystinyl) residue. Eptifibatide is produced by solid-phase peptide synthesis, and is purified by preparative reverse-phase high pressure liquid chromatography and lyophilized.

Proper Name: Eptifibatide

Chemical Name: N^6-(aminoiminomethyl)-N^2-(3-mercapto-1-oxopropyl-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic(1-6)-disulfide.

Structural Formula:



Molecular Formula: $C_{35}H_{49}N_{11}O_9S_2$

Molecular Weight: 832.0

Description: Eptifibatide is a white or almost white powder.

pH: Between 5.0 to 5.5 with citrate buffer

Melting point: Not applicable.

Composition: Eptifibatide Injection is a clear, colorless, sterile, non-pyrogenic solution for intravenous (IV) use. Each 10-mL vial contains 2 mg/mL of eptifibatide in a 25 mM citric acid buffer, pH 5.0 to 5.5 or 0.75 mg/mL of eptifibatide in a 25 mM citric acid buffer, pH 5.0 to 5.5. Inactive ingredients: citric acid monohydrate, sodium hydroxide (used for adjusting pH), and water for injection.

Compatibility: Eptifibatide Injection may be administered in the same IV line with the following IV solutions: 0.9% NaCl, 0.9% NaCl and 5% dextrose and with IV solutions containing up to 60 mEq potassium chloride per liter. No incompatibilities have been observed with intravenous administration sets. No compatibility studies have been performed with PVC bags. Physical and chemical compatibility testing indicate that Eptifibatide Injection may be administered through an intravenous line with alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil.

Eptifibatide Injection should not be administered through an intravenous line with furosemide.

Stability and Storage Recommendations: Vials should be stored refrigerated at 2-8°C. Vials may be transferred to controlled room temperature storage (25°C with excursions permitted between 15-30ºC) protected from light, for a period not to exceed 2 months. Upon transfer, vials must be marked with a "DISCARD BY" date (2 months from the transfer date), which may not exceed the labeled expiration date.

AVAILABILITY OF DOSAGE FORMS

Eptifibatide Injection is supplied as a sterile solution:

- 10-mL vial, containing 20 mg of eptifibatide (2 mg/mL) for bolus injection
- 100-mL vial, containing 75 mg of eptifibatide (0.75 mg/mL) for intravenous infusion

Vials are for single use.

PHARMACOLOGY

Animal Pharmacology

The antithrombotic efficacy of Eptifibatide Injection was evaluated in a well-defined canine model of coronary artery thrombosis known as the Folts Model. Eptifibatide was found to inhibit *in vitro* canine platelet aggregation with an IC_{50} of 1.9 μM. Eptifibatide, at doses of 1, 2, or 4 mcg/kg/min, inhibited the cyclic flow reductions (and thus thrombus formation) within 20 minutes of starting the infusion.

In another canine study, eptifibatide inhibited *ex vivo* platelet aggregation at doses of 2-10 mcg/kg/min and increased bleeding at doses of 5-10 mcg/kg/min. Eptifibatide accelerated the rate of rt-PA-induced thrombolysis and reduced reocclusion.

The hematological effects of a continuous infusion of eptifibatide at 3.5, 5 and 10 mcg/kg/min were determined in the baboon. After approximately 25 min, the infusion of eptifibatide caused a dose-dependent inhibition of platelet aggregation with complete inhibition being achieved at infusion rates greater or equal to 5 mcg/kg/min. In addition, eptifibatide at a continuous dose of 5mcg/kg/min and 10 mcg/kg/min caused a dose-dependent prolongation of bleeding time.

In a second baboon study, eptifibatide alone increased bleeding time from 4.4 min to 7.3, 11.7, and >30 min at 0, 5, 10, and 20 mcg/kg/min, respectively. Heparin alone and ASA alone did not affect bleeding time. The combination of eptifibatide (5 mcg/kg/min) with ASA and heparin produced a prolongation of bleeding time to 21.7 and 26.9 min, respectively.

Pharmacokinetics: In rats, plasma concentrations of ^{14}C-eptifibatide-derived radioactivity declined rapidly with a terminal phase half-life ($t_{1/2}$) of about 5 hours following a single 2 mg/kg IV dose of the radiolabeled drug. Unchanged eptifibatide declined with an apparent $t_{1/2}$ of about 8min. Following single 2 and 20 mg/kg IV doses, the plasma concentrations of eptifibatide were dose-proportional and the $t_{1/2}$ (11 to 12 min) was dose-independent, indicating linear kinetics within the 2 to 20 mg/kg dose range.

In Cynomolgus monkeys, plasma concentrations of ^{14}C-eptifibatide-derived radioactivity declined with a $t_{1/2}$ of about 12 hours following a single 2 mg/kg IV dose of ^{14}C-eptifibatide. Unchanged eptifibatide, which accounted for approximately 93% of total plasma ^{14}C at 5 min post-dose, was eliminated rapidly with a $t_{1/2}$ of 17 min. At 2 hours post-dose, approximately 2% of plasma ^{14}C was due to unchanged drug.

Excretion of ^{14}C-eptifibatide-derived radioactivity was rapid in both rats and monkeys, and occurred primarily in the urine. In rats, approximately 14% of the radioactive dose was estimated to undergo enterohepatic circulation before being eliminated. Approximately 11 to 12% of the ^{14}C-eptifibatide dose was eliminated as $^{14}CO_2$, and this appeared to be independent of the position of the ^{14}C label in the molecule. However, the loss of ^{14}C seemed to occur primarily from the portion of the ^{14}C-eptifibatide dose undergoing enterohepatic circulation. Approximately 71% of the ^{14}C dose was recovered in urine and feces of Cynomolgus monkeys, suggesting that in this species, as in rats, a significant amount of the dose administered may have been eliminated as $^{14}CO_2$.

Following 3-day continuous IV infusion of eptifibatide in rats and Cynomolgus monkeys at the doses (1.44 to 72 mg/kg/day for rats and 1.44 to 18 mg/kg/day for monkeys) used in the 28-day continuous IV infusion toxicology studies, steady-state plasma concentrations were reached by 0.5 hour in rats and 8 hours in monkeys, and were dose-related. At termination of the IV infusion, the plasma drug concentrations declined rapidly with an apparent half-life of about 0.5 hour in rats and 1.2 to 1.5 hour in monkeys.

Eptifibatide was found to bind poorly to plasma proteins of rats (11 to 13%), rabbits (13 to 15%), Cynomolgus monkeys (17 to 19%). In all species, the binding was independent of concentration within the concentration range of 0.05 to 15 mcg/mL.

In male rats, ^{14}C-eptifibatide-derived radioactivity distributed rapidly into tissues, with the highest concentrations generally observed at the first evaluated time points (0.1 and 0.25 h) following IV administration. At 0.1 hour, the highest concentrations occurred in the urinary bladder and kidneys, and at the 0.25 hour, the highest concentrations occurred in the kidneys, content of small intestine, urinary bladder and liver. The radioactivity declined rapidly from all tissues. Whole-body autoradiography (WBA) confirmed the distribution pattern of ^{14}C observed by quantitative tissue dissection. In 19-day pregnant female rats, the distribution of ^{14}C following IV administration of ^{14}C-eptifibatide was generally similar to that described for male rats. Maximum concentrations of ^{14}C occurred at 0.1 hour post-dose in most maternal tissues. ^{14}C-eptifibatide penetrated the placental barrier slowly. The maximum concentrations of ^{14}C in fetal tissues (0.2 mcg eq/g) were very low relative to the maximum concentrations observed in maternal tissues (14-24 mcg eq/g).

^{14}C-eptifibatide was extensively metabolized to deamidated eptifibatide and to several polar metabolites by both rats and monkeys. The drug-derived radioactivity excreted into the bile by rats, and identified as deamidated eptifibatide, was reabsorbed from the intestinal tract and further metabolized to more polar metabolites. The plasma and urine metabolite profiles in rats and monkeys indicate that the metabolic disposition of eptifibatide is similar for the two species.

CLINICAL TRIALS

Eptifibatide Injection was evaluated in three placebo-controlled, randomized studies, one (PURSUIT) in patients with acute coronary syndrome (UA or NSTEMI) and two (IMPACT II and ESPRIT) in patients about to undergo PCI. Patients underwent primarily balloon angioplasty in IMPACT II and intracoronary stent placement, with or without angioplasty, in ESPRIT.

Unstable Angina/Non-ST-segment Elevation Myocardial Infarction

PURSUIT was a double-blind, randomized, placebo-controlled clinical study in 10,948 patients presenting with UA/NSTEMI, enrolled at 726 investigational centers in 27 countries. The single region with the largest contribution to enrolment was North America (United States and Canada, n=4,358). Patients were enrolled only if they had experienced cardiac ischemia at rest (≥10 minutes) within the previous 24 hours and had either ST-segment changes (elevations between 0.6 mm and 1 mm or depression >0.5 mm), T-wave inversion (>1 mm), or increased CK-MB.

Patients were randomized to either placebo or eptifibatide 180 mcg/kg bolus followed by a 2.0 mcg/kg/min continuous infusion, or eptifibatide 180 mcg/kg bolus followed by a 1.3 mcg/kg/min continuous infusion. The infusion was continued for 72 hours, until hospital discharge, or until initiation of coronary artery bypass graft (CABG), whichever occurred first. If coronary angioplasty was performed, the eptifibatide infusion was continued for 24 hours after the procedure, allowing for a duration of infusion up to 96 hours. As prescribed by the protocol, the lower infusion-rate arm was discontinued after the first interim analysis when the two active treatment arms showed similar safety profiles (incidence of bleeding).

Patients' age ranged between 20 and 94 (mean 63) years, and 65% were male. The patients were 89% Caucasian, 5% Black, 5% Hispanic, and 1% others. Forty percent of patients were enrolled in North America, 39% in Western Europe, 16% in Eastern Europe, and 4% in Latin America.

PURSUIT was a "real world" study with each patient managed according to the usual standards of the investigational site. Therefore, frequencies of angiography, frequencies/timing of coronary angioplasty and CABG, use of concomitant medication (heparin and ASA) differed widely among countries and sites. In the study, 13% of patients were managed with coronary angioplasty during drug infusion and 87% were managed medically (no coronary angioplasty during infusion). The North American population represents the single, most homogenous subgroup in terms of medical management. In this population, 24% were managed with coronary angioplasty and 76% were managed medically.

The majority of patients received ASA (75-325 mg once daily). Heparin was administered intravenously or subcutaneously, at the physician's discretion, usually as an intravenous bolus of 5,000 U followed by a continuous infusion of 1,000 U/h. For patients weighing less than 70 kg, the recommended heparin bolus dose was 60 U/kg followed by a continuous infusion of 12 U/kg/h. A target aPTT of 50-70 seconds was recommended. A total of 1,250 patients underwent coronary angioplasty within 72 hours after randomization, in which case they received

intravenous heparin to maintain an activated clotting time (ACT) of between 300-350 seconds.

The primary endpoint of the study was the occurrence of death from any cause or non-fatal myocardial infarction (MI) (evaluated by a blinded Clinical Events Committee) within 30 days of randomization. A secondary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (as reported by the investigators) within 6 months of randomization.

Eptifibatide administered as a 180 mcg/kg bolus followed by a 2.0 mcg/kg/min infusion significantly (p=0.042) reduced the incidence of death or myocardial infarction at 30 days compared to placebo (**Table 13**). The reduction in the incidence of death and myocardial infarction in patients receiving eptifibatide was evident early (at 72 hours; 7.6% and 5.9% for placebo and eptifibatide, respectively) during treatment and this reduction was maintained through six months (**Figure 1**).

Table 13
Clinical Events at 30 Days

PURSUIT Study

	Worldwide		**North America**	
Event	**Placebo (n=4,739)**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion **(n=4,722)**	**Placebo (n=1,919)**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion **(n=1,908)**
Primary Endpoint	745 (15.7%)	672 (14.2%)	288 (15.0%)	224 (11.7%)
p-value*	0.042		0.003	
Death	177 (3.7%)	165 (3.5%)	68 (3.5%)	54 (2.8%)
Non-Fatal MI	568 (12.0%)	507 (10.7%)	220 (11.5%)	170 (8.9%)

* From Pearson's chi-square test of differences between placebo and eptifibatide

Compared to placebo, treatment with eptifibatide reduced the incidence of the combined endpoint, as well as its components, death and myocardial infarction.

As shown in the Kaplan-Meier curve in **Figure 1**, investigators reported a reduction in death or MI from 13.6% with placebo to 12.1% with eptifibatide (p=0.021 log rank) within 6 months of randomization.

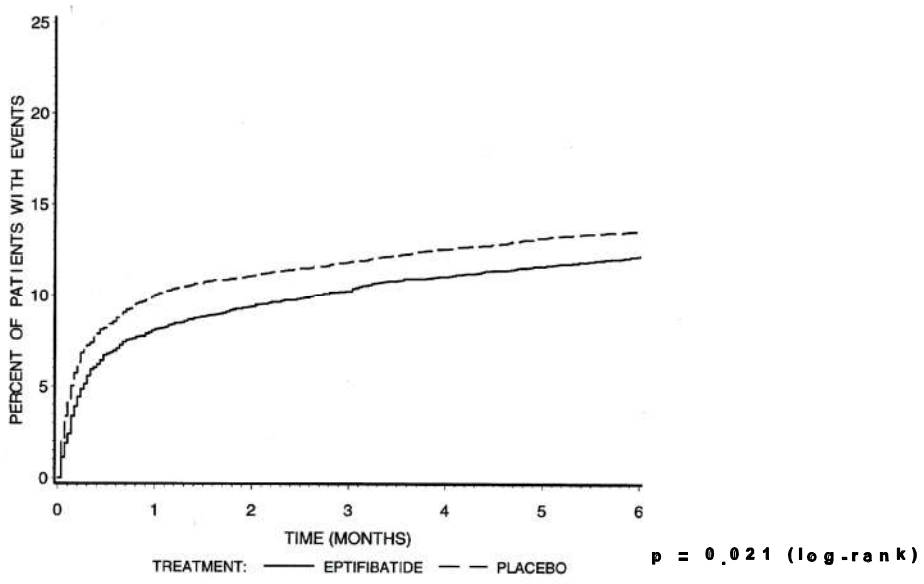


Figure 1: Kaplan-Meier Curve for Time to Death or Myocardial Infarction within 6 Months of Randomization

The analysis of the PURSUIT results revealed a complex interaction between treatment and region. **Figure 2** shows the odds ratio for death or nonfatal MI in various subgroups and as defined by geographic region. The results were also very heterogeneous among various geographic regions, with the greatest benefit observed in North American patients (see Factors Affecting the Outcomes in the North American Patient Population).

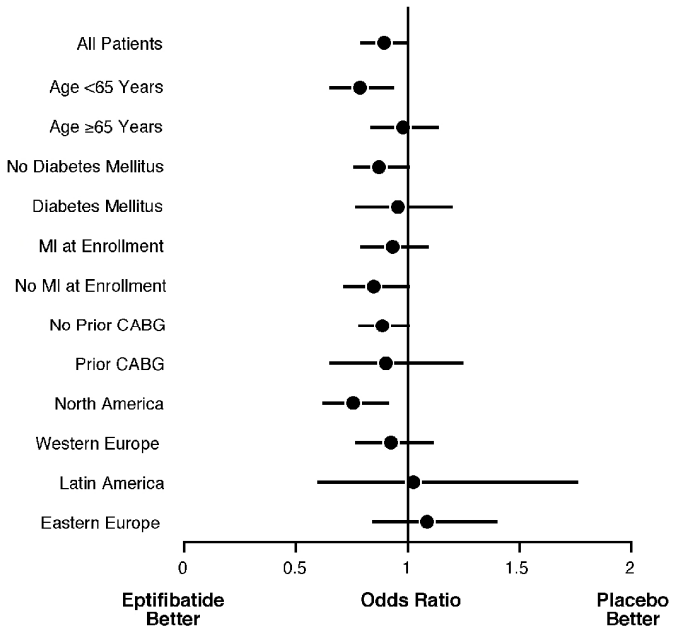


Figure 2: Odds Ratios for Death or Nonfatal Myocardial Infarction at 30 Days in Selected Subgroups of Patients. The horizontal lines indicate 95% confidence intervals. MI denotes myocardial infarction, and CABG coronary-artery bypass graft surgery.

Table 14 summarizes the incidence of the primary endpoint in the worldwide and North American study population in patients who did and did not undergo coronary angioplasty within 72 hours of randomization.

Table 14
Endpoint at 30 Days for Patients With and Without Coronary Angioplasty
in the First 72 Hours After Randomization

PURSUIT Study

	Worldwide		**North America**	
Incidence of Death and/or MI	**Placebo**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion	**Placebo**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion
Coronary Angioplasty Within First 72 h	106/631 (16.8%)	73/619 (11.8%)*	77/464 (16.6%)	54/472 (11.4%)*
No Coronary Angioplasty Within First 72 h	634/4,108 (15.6%)	599/4,103 (14.6%)	211/1,455 (14.5%)	170/1,436 (11.8%)*

* p-value <0.05 versus placebo

The incidence of death or myocardial infarction was lower in the patients treated with eptifibatide compared to placebo, regardless of whether they were managed medically or underwent coronary angioplasty. In North America, patients treated with eptifibatide and managed medically showed a statistically significant reduction in the incidence of death or MI at 30 days. Worldwide, the degree of benefit in patients managed medically was less than that seen in North America. In addition, among those patients who underwent coronary angioplasty within the first 72 hours after randomization, a reduction in the incidence of myocardial infarction was seen prior to the procedure in the patients receiving eptifibatide in the worldwide population (5.5% for placebo versus 1.8% for eptifibatide) and the North American sub-population (4.5% for placebo versus 1.7% for eptifibatide).

Treatment with eptifibatide reduced clinical events in patients undergoing coronary angioplasty during drug administration and in those receiving medical management alone. **Table 15** shows the incidence of death or MI within 72 hours of randomization.

Table 15
Clinical Events (Death or MI) in the PURUIT Study
Within 72 Hours of Randomization

	Placebo	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion
Overall Patient Population -At 72 Hours	n=4,739 7.6%	n=4,722 5.9%
Patients undergoing early coronary angioplasty -Pre-procedure (nonfatal MI only) -At 72 hours	n=631 5.5% 14.4%	n=619 1.8% 9.0%
Patients not undergoing early coronary angioplasty - At 72 hours	n=4,108 6.5%	n=4,103 5.4%

All of the effect of eptifibatide was established within 72 hours (during the period of drug infusion). Moreover, for patients undergoing early coronary angioplasty, a reduction in events was evident prior to the procedure. The benefit in coronary angioplasty patients was derived primarily from North American patients as 75% of the procedures were performed in North America.

Factors Affecting Outcomes in the North American Patient Population: There are a number of differences between North American patients and those from the rest of the world that may potentially affect the response to treatment. The major differences arise from different medical practices during the course of the trial, as well as from different entry characteristics.

Differences that reflect practice patterns (such as early catheterization, early coronary angioplasty, and concomitant heparin/aspirin use) and those that reflect a different health status at baseline interact in a very complex manner to produce different patient prognoses.

Table 16 summarizes those variables that may reflect important differences in practice patterns or patient populations. In brief, the North American patients had a higher incidence of concomitant anti-thrombotic therapy (both heparin and ASA), more prior and concomitant cardiovascular (diagnostic and surgical) procedures, greater history of cardiovascular disease, less severe symptoms of cardiovascular disease at presentation, lower blood pressure on admission, and weighed more.

Table 16

Variables in Practice Patterns and Patient Populations
(North America vs. Outside North America)

PURSUIT Study

Type of Factor	Surrogates Which Reflect This Type of Factor	% of Patients in NA with Surrogate	% of Patients Outside of NA with Surrogate
Patient Treatment in Hospital	Catheterization within 72 hours	66.1%	15.8%
	Angioplasty within 72 hours	24.5%	5.6%
	Heparin during hospitalization	97.2%	85.0%
Demographic Characteristics	Weight <74 kg	31.5%	42.6%
	Weight >95 kg	22.1%	7.0%
	Blacks	12.5%	0.2%
Cardiovascular disease History	Hypertension	61.1%	51.5%
	Family History of CAD	43.7%	30.0%
	Chest Pain- CHAC Class III or IV	36.0%	47.9%
	No ST Changes at Qualification	13.5%	4.2%
Prior CV Procedures	Prior Angioplasty	20.7%	7.6%
	Prior CABG	19.9%	6.7%
Concomitant Medications Prior to Randomization	ASA	74.5%	56.5%
	Lipid Lowering Agent	21.0%	11.6%
	Oral Nitrates	67.4%	51.2%
	Heparin	81.4%	72.0%
Baseline CV Characteristics	DBP ≥90mm Hg	10.6%	23.1%
	SBP ≥140mm Hg	31.2%	40.7%

Percutaneous Coronary Intervention

IMPACT II (Eptifibatide Injection to Minimize Platelet Aggregation and Prevent Coronary Thrombosis)

IMPACT II, the first large study conducted with eptifibatide, was a multi-center, double-blind, randomized, placebo-controlled study conducted in the United States in 4,010 patients undergoing coronary angioplasty. Major exclusion criteria included a history of bleeding diathesis, major surgery within 6 weeks of treatment, gastrointestinal bleeding within 30 days, any stroke or structural CNS abnormality, uncontrolled hypertension, PT >1.2 times control, hematocrit <30%, platelet count <100,000/mm^3, and pregnancy.

Patient age ranged from 24 to 89 (mean 60) years, and 75% were male. The patients were 92% Caucasian, 5% Black, and 3% Hispanic.

Forty-one percent of the patients underwent coronary angioplasty for ongoing acute coronary

syndrome. Patients were randomly assigned to one of three treatment regimens, each incorporating a bolus dose initiated immediately prior to coronary angioplasty followed by a continuous infusion lasting 20-24 hours: 1) 135 mcg/kg bolus followed by a continuous infusion of 0.5 mcg/kg/min of eptifibatide (135/0.5); 2) 135 mcg/kg bolus followed by a continuous infusion of 0.75 mcg/kg/min of eptifibatide (135/0.75); or 3) a matching placebo bolus followed by a matching placebo continuous infusion. Each patient received aspirin and an intravenous heparin bolus of 100 U/kg, with additional bolus infusions of up to 2,000 additional units of heparin every 15 minutes to maintain an ACT of 300-350 seconds.

The primary endpoint was the composite of death, MI, or urgent revascularization, analyzed at 30 days after randomization in all patients who received at least one dose of study drug.

As shown in **Table 17**, each eptifibatide regimen reduced the rate of death, MI, or urgent intervention, although at 30 days, this finding was statistically significant only in the lower-dose eptifibatide group. As in the PURSUIT study, the effects of eptifibatide were seen early and persisted throughout the 30-day period.

Table 17

Clinical Events in the IMPACT II Study

	Placebo n (%)	**Eptifibatide** 135 mcg/kg bolus, 0.5 mcg/kg/min Infusion **n (%)**	**Eptifibatide** 135 mcg/kg bolus, 0.75 mcg/kg/min Infusion **n (%)**
Patients	1,285	1,300	1,286
Abrupt Closure	65 (5.1%)	36 (2.8%)	43 (3.3%)
p-value vs. placebo		0.003	0.03
Death, MI, or Urgent Intervention			
24 hours	123 (9.6%)	86 (6.6%)	89 (6.9%)
p-value vs. placebo		0.006	0.014
48 hours	131 (10.2%)	99 (7.6%)	102 (7.9%)
p-value vs. placebo		0.021	0.045
30 days (primary endpoint)	149 (11.6%)	118 (9.1%)	128 (10.0%)
p-value vs. placebo		0.035	0.179
Death or MI			
30 days	110 (8.6%)	89 (6.8%)	95 (7.4%)
p-value vs. placebo		0.102	0.272
6 months	151 (11.9%)*	136 (10.6%)*	130 (10.3%)*
p-value vs. placebo		0.297	0.182

* Kaplan-Meier estimate of event rate

ESPRIT (Enhanced Suppression of the Platelet IIB/IIIA Receptor with Eptifibatide Therapy)

Eptifibatide Injection was evaluated in ESPRIT, a multi-center, double-blind, randomized, placebo-controlled study conducted in the United States and Canada that enrolled 2,064 patients undergoing elective or urgent intracoronary stenting. Exclusion criteria included MI within the previous 24 hours, ongoing chest pain, administration of any oral anti-platelet or oral anticoagulant other than aspirin within 30 days of intracoronary stenting (although loading doses of thienopyridine on the day of intracoronary stenting were encouraged), planned intracoronary stenting of a saphenous vein graft or subsequent "staged" intracoronary stenting, prior stent placement in the target lesion, intracoronary stenting within the previous 90 days, a history of bleeding diathesis, major surgery within 6 weeks of treatment, gastrointestinal bleeding within 30 days, any stroke or structural CNS abnormality, uncontrolled hypertension, PT >1.2 times control, hematocrit <30%, platelet count <100,000/mm^3, and pregnancy.

Patient age ranged from 24 to 93 (mean 62) years and 73% of patients were male. The study enrolled 90% Caucasian, 5% African American, 2% Hispanic and 1% Asian patients. Patients were randomized either to placebo or eptifibatide administered as an intravenous bolus of 180 mcg/kg followed immediately by a continuous infusion of 2.0 mcg/kg/min, and a second bolus of 180 mcg/kg administered 10 minutes later. Eptifibatide infusion was continued for up to 18-24 hours after intracoronary stenting or until hospital discharge, whichever came first. Each patient received at least one dose of aspirin (162-325 mg) and 60 U/kg of heparin as a bolus (not to exceed 6,000 units) if not already receiving a heparin infusion. Additional boluses of heparin (10-40 U/kg) could be administered in order to reach a target ACT between 200 and 300 seconds.

Based upon this study design, ESPRIT was intended to evaluate the incremental benefits and risks of adding GP IIb/IIIa inhibitor therapy to currently employed management strategies at the time of intracoronary stenting, which include deployment of single or multiple stents of varying lengths and sizes in difficult-to-treat coronary vessels, almost universal use of thienopyridine therapy (primarily front-loaded clopidogrel) on the day of the procedure, and administration of low-dose heparin (i.e., ACT of 200-300 seconds) at time of intracoronary stenting.

The primary endpoint of the ESPRIT study was the composite of death, myocardial infarction, urgent target vessel revascularization and "bail-out" to open label eptifibatide due to a thrombotic complication of intracoronary stenting (thrombotic "bail-out") (e.g., visible thrombus, "no reflow", or abrupt closure) at 48 hours. Myocardial infarction, urgent target vessel revascularization and thrombotic "bail-out" were evaluated by a blinded Clinical Events Committee.

As shown in **Table 18**, the incidence of each of the primary endpoint and selected secondary endpoints was significantly reduced in patients who received eptifibatide. A treatment benefit in

patients who received eptifibatide was seen by 48 hours and at the end of the 30-day observation period.

Table 18

Clinical Events in the ESPRIT Study

	Placebo **n (%)** **1,024**	**Eptifibatide** 180 mcg/kg bolus, 2.0 mcg/kg/min infusion, 180 mcg/kg bolus 10 minutes after the first **n (%)** **1,040**
Death, MI, Urgent Target Vessel Revascularization or Thrombotic "Bail-Out"		
48 Hours (primary endpoint)	108 (10.5%)	69 (6.6%)
p-value vs. placebo		0.0015
30 Days	120 (11.7%)	78 (7.5%)
p-value vs. placebo		0.0011
Death, MI, or Urgent Target Vessel Revascularization		
48 Hours	95 (9.3%)	62 (6.0%)
p-value vs. placebo		0.0045
30 Days (secondary endpoint)	107 (10.4%)	71 (6.8%)
p-value vs. placebo		0.0034
Death or MI		
48 Hours	94 (9.2%)	57 (5.5%)
p-value vs. placebo		0.0013
30 Days	104 (10.2%)	66 (6.3%)
p-value vs. placebo		0.0016

The need for thrombotic "bail-out" was significantly reduced with eptifibatide at 48 hours (2.1% for placebo, 1.0% for eptifibatide; p=0.029).

Consistent with previous studies of GP IIb/IIIa inhibitors, most of the benefit achieved acutely with eptifibatide was in the reduction of MI. Eptifibatide reduced the occurrence of MI at 48 hours from 9.0% for placebo to 5.4% (p=0.0015) and maintained that effect with significance at 30 days.

In the ESPRIT study, diabetics did not have more major or minor bleeding, tranfusion requirement or access site complications. The efficacy of eptifibatide was similar in diabetic and non-diabetic patients.

Although ESPRIT was not initially designed to study clinical outcomes for more than 30 days, the protocol was amended at the end of the original study to follow-up consenting patients (n = 2064) for a period of 1 year. This long-term observation revealed a sustained reduction in the composite endpoint of death or MI at 6 months from 11.5% in the placebo group to 7.4% in the Eptifibatide Injection treated group (odds ratio 0.631 [95% CI 0.473, 0.841], p = 0.0015) and at 1 year from 12.4% in the placebo group to 8.0% in the Eptifibatide Injection treated group (odds ratio 0.630 [95% CI 0.478, 0.832], p = 0.001). A reduction in the composite endpoint of death, MI or target vessel revascularization was also maintained at 6 months from 18.5% in the placebo group to 14.3% in the Eptifibatide Injection treated group (odds ratio 0.744 [95% CI 0.599, 0.924], p = 0.0072) and at 1 year from 22.1% in the placebo group to 17.5% in the Eptifibatide Injection treated group (odds ratio 0.762 [95% CI 0.626, 0.929], p = 0.0068). At 1 year, a consistent treatment effect was seen between patients with and without diabetes. The rate of death or myocardial infarction was 7.8% and 13.4% in the Eptifibatide Injection and placebo groups respectively (n=466).

TOXICOLOGY

Acute Toxicity: The safety evaluation studies conducted with eptifibatide do not indicate any evidence of unexpected significant toxic effects. Single dose toxicity studies were conducted in rats, rabbits and monkeys; doses up to 500 mcg/kg/minute administered by continuous intravenous infusion for 90 minutes did not cause mortality and were well-tolerated by all species.

In rabbits, a dose-dependent decrease in platelet counts of the 50 and 500 mcg/kg/minute (for 90 minutes)-dosed females was attributed to administration of eptifibatide. Findings in the monkeys were limited to petechial hemorrhages in the femoral and/or abdominal regions, which lasted for one to three days.

Long-Term Toxicity: Repeated dose studies were conducted in rats and monkeys by continuous intravenous infusion for 14 days and 28 days. The 28-day studies were followed by 14-day recovery periods. There were no findings in rats from either study attributable to the administration of eptifibatide. The no-effect level in rats was greater than 72.0 mg/kg/day (24 times the maximum recommended daily human dose of 3 mg/kg/day).

In monkeys, administration of up to 7.2 mg/kg/day of eptifibatide for 28 days by continuous intravenous infusion did not produce any sign of toxicity. One 18 mg/kg/day-dosed monkey had evidence of hemorrhage in the skeletal muscles, which may have contributed to the decreased blood cell count, hemoglobin, hematocrit, mean cell volume and mean cell hemoglobin and the increased reticulocyte count. The effects observed in the monkeys are the expected pharmacologic responses to high doses of eptifibatide.

The no-toxic effect level in the 14-day monkey study was 7.2 mg/kg/day (2.4 times the

maximum recommended daily human dose). The hemorrhages observed in one 7.2 mg/kg/dosed monkey were considered to be equivocal. Three out of five monkeys administered 72.0 mg/kg/day died or were sacrificed during the study due to contusions, excessive bleeding and/or petechial hemorrhages, which resulted in anemia. Total protein albumin and globulin values were reduced in all 72.0 mg/kg dosed monkeys. At necropsy, focal hemorrhages in various organs were observed.

Long-term studies in animals have not been performed to determine the carcinogenic potential of eptifibatide. No carcinogenicity studies were conducted because clinical use of eptifibatide is limited to short-term intravenous dosing.

Mutagenicity: The mutagenic potential of eptifibatide was tested in four assays. Eptifibatide was not genotoxic in the Ames assay at doses up to 667 mcg/mL, in the mouse lymphoma cell forward mutation assay at doses up to 1,000 mcg/mL, in the human lymphocyte chromosome aberrations test or in the mouse micronucleus test.

Reproduction and Fertility: In a fertility study in rats, dosing with eptifibatide had no effect on the course of pregnancy. No evidence of fertility or parental toxicity nor effects upon parental reproductive performance were observed at daily doses up to 72.0 mg/kg (24 times the maximum recommended daily human dose).

Teratology: Embryo-fetal toxicity studies in rats and rabbits showed that treatment with eptifibatide had no effect on the course of pregnancy, or embryo or fetal viability. There was no toxicologically significant maternal toxicity, embryo lethality, fetotoxicity or teratogenicity at daily doses of eptifibatide up to 72.0 mg/kg in rats or up to 36.0 mg/kg in rabbits (24 and 12 times the maximum recommended daily human dose, respectively). In a peri- and postnatal study in rats, there was no evidence of maternal toxicity at daily doses up to 72.0 mg/kg of eptifibatide. Post-weaning, physical, reflex, behavioral and reproductive development of the rats showed no eptifibatide-related effects.

Local Tolerance: The potential intravenous irritation of eptifibatide was studied in rabbits; no difference in the degree of erythema between eptifibatide and the vehicle-treated ears was observed at 24 or 72 hours, after a single 15-minute infusion of 10 mcg/kg/min.

Other Studies: Studies in mice and guinea pigs demonstrated that eptifibatide does not induce delayed-type hypersensitivity in mice and is not antigenic in guinea pigs.

Two *in vitro* studies demonstrated that eptifibatide did not produce hemolysis or plasma protein flocculation.
A 14-day toxicity study of degraded eptifibatide in monkeys did not produce any signs of toxicity at daily doses up to 7.2 mg/kg. These results were similar to those of the previous 14- and 28-day toxicity studies conducted in monkeys.

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