

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **EPTIFIBATIDE INJECTION** safely and effectively. See full prescribing information for **EPTIFIBATIDE INJECTION**.

EPTIFIBATIDE injection, for intravenous infusion only; not for intravenous bolus use

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

Eptifibatide injection is a platelet aggregation inhibitor indicated for:

- Treatment of acute coronary syndrome (ACS) managed medically or with percutaneous coronary intervention (PCI) (1.1)
- Treatment of patients undergoing PCI (including intracoronary stenting) (1.2)

DOSAGE AND ADMINISTRATION

Eptifibatide injection in GALAXY container is for intravenous infusion only, not for intravenous bolus use.

ACS or PCI: 180 mcg/kg IV bolus as soon as possible after diagnosis followed by infusion at 2 mcg/kg/min. (2.1, 2.2)

PCI: Add a second 180 mcg/kg bolus at 10 minutes. (2.2)

In patients with creatinine clearance less than 50 mL/min, reduce the infusion to 1 mcg/kg/min. (2.1, 2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 75 mg of eptifibatide per 100 mL in a single-dose GALAXY container. (3)

CONTRAINDICATIONS

- Bleeding diathesis or bleeding within the previous 30 days (4)
- Severe uncontrolled hypertension (4)
- Major surgery within the preceding 6 weeks (4)
- Stroke within 30 days or any history of hemorrhagic stroke (4)
- Coadministration of another parenteral GP IIb/IIIa inhibitor (4)
- Dependency on renal dialysis (4)
- Known hypersensitivity to any component of the product (4)

WARNINGS AND PRECAUTIONS

- Eptifibatide can cause serious bleeding. If bleeding cannot be controlled, discontinue eptifibatide immediately. Minimize vascular and other traumas. If heparin is given concomitantly, monitor aPTT or ACT. (5.1)
- Thrombocytopenia: Discontinue eptifibatide and heparin. Monitor and treat condition appropriately. (5.2)

ADVERSE REACTIONS

Bleeding and hypotension are the most commonly reported adverse reactions. (6.1)

To report **SUSPECTED ADVERSE REACTIONS**, contact **Baxter Healthcare at 1-866-888-2472** or **FDA at 1-800-FDA-1088** or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Coadministration of antiplatelet agents, thrombolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. Avoid concomitant use with other glycoprotein (GP) IIb/IIIa inhibitors. (7.1)

USE IN SPECIFIC POPULATIONS

- *Geriatric Use*: Risk of bleeding increases with age. (8.5)

See 17 for **PATIENT COUNSELING INFORMATION**.

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FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Acute Coronary Syndrome (ACS)
- 1.2 Percutaneous Coronary Intervention (PCI)

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing in Acute Coronary Syndrome (ACS)
- 2.2 Dosage in Percutaneous Coronary Intervention (PCI)
- 2.3 Important Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Bleeding
- 5.2 Thrombocytopenia

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Non-ST-Segment Elevation Acute Coronary Syndrome
- 14.2 Percutaneous Coronary Intervention (PCI)

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome (ACS)

Eptifibatide injection is indicated to decrease the rate of a combined endpoint of death or new myocardial infarction (MI) in patients with ACS (unstable angina [UA]/non-ST-elevation myocardial infarction [NSTEMI]), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI).

1.2 Percutaneous Coronary Intervention (PCI)

Eptifibatide injection is indicated to decrease the rate of a combined endpoint of death, new MI, or need for urgent intervention in patients undergoing PCI, including those undergoing intracoronary stenting [*see Clinical Studies (14.1, 14.2)*].

2 DOSAGE AND ADMINISTRATION

Eptifibatide injection in GALAXY container is for intravenous infusion only, not for intravenous bolus use. Before infusion of eptifibatide injection, the following laboratory tests should be performed to identify pre-existing hemostatic abnormalities: hematocrit or hemoglobin, platelet count, serum creatinine, and PT/aPTT. In patients undergoing PCI, the activated clotting time (ACT) should also be measured.

The activated partial thromboplastin time (aPTT) should be maintained between 50 and 70 seconds unless PCI is to be performed. In patients treated with heparin, bleeding can be minimized by close monitoring of the aPTT and ACT.

2.1 Dosing in Acute Coronary Syndrome (ACS)

Indication	Normal Renal Function	Creatinine Clearance less than 50 mL/min
Patients with ACS	180 mcg/kg intravenous (IV) bolus as soon as possible after diagnosis, followed by continuous infusion of 2 mcg/kg/min.	180 mcg/kg IV bolus as soon as possible after diagnosis, followed by continuous infusion of 1 mcg/kg/min.
	<ul style="list-style-type: none">• Infusion should continue until hospital discharge or initiation of coronary artery bypass graft surgery (CABG), up to 72 hours.• If a patient is to undergo PCI, the infusion should be continued until hospital discharge or for up to 18 to 24 hours after the procedure, whichever comes first, allowing for up to 96 hours of therapy.• Aspirin, 160 to 325 mg, should be given daily.	

Eptifibatide injection should be given concomitantly with heparin dosed to achieve the following parameters:

During Medical Management: Target aPTT 50 to 70 seconds

- If weight greater than or equal to 70 kg, 5000-unit bolus followed by infusion of 1000 units/h.
- If weight less than 70 kg, 60-units/kg bolus followed by infusion of 12 units/kg/h.

During PCI: Target ACT 200 to 300 seconds

- 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.

2.2 Dosage in Percutaneous Coronary Intervention (PCI)

Indication	Normal Renal Function	Creatinine Clearance less than 50 mL/min
Patients with PCI	180 mcg/kg (IV) bolus immediately before PCI followed by continuous infusion of 2 mcg/kg/min and a second bolus of 180 mcg/kg (given 10 minutes after the first bolus).	180 mcg/kg IV bolus immediately before PCI followed by continuous infusion of 1 mcg/kg/min and a second bolus of 180 mcg/kg (given 10 minutes after the first bolus).
	<ul style="list-style-type: none">• Infusion should be continued until hospital discharge, or for up to 18 to 24 hours, whichever comes first. A minimum of 12 hours of infusion is recommended.• In patients who undergo CABG surgery, eptifibatide injection infusion should be discontinued prior to surgery.• Aspirin, 160 to 325 mg, should be given 1 to 24 hours prior to PCI and daily thereafter.	

- Eptifibatide injection should be given concomitantly with heparin to achieve a target ACT of 200 to 300 seconds. Administer 60-units/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 discontinue eptifibatide injection.

2.3 Important Administration Instructions

1. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Use only if solution is clear and container and seals are intact. Check for minute leaks prior to use by squeezing bag firmly. If leaks are found, discard solution as sterility may be impaired. If the administration port protector is damaged, detached or not present, discard the container as the solution path sterility may be compromised.
2. Do not use GALAXY containers in series connections. Such use would result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete. If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.
3. This premixed solution is for intravenous infusion only, no further dilution is required. Not For Intravenous Bolus Use.
4. Do not introduce supplemental medication or additives into the GALAXY container.
5. May administer eptifibatide injection in the same intravenous line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil. Do not administer eptifibatide injection through the same intravenous line as furosemide.
6. May administer eptifibatide injection 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.
7. Withdraw the bolus dose(s) of eptifibatide injection from the 10-mL vial into a syringe. Administer the bolus dose(s) by IV push.
8. Immediately following the bolus dose administration, initiate a continuous infusion of eptifibatide injection. When using an intravenous infusion pump, administer eptifibatide injection undiluted directly from the 100-mL GALAXY container.
9. The premixed GALAXY container is for single-dose only, discard any unused portion.

Administer eptifibatide injection by volume according to patient weight (see Table 1).

Table 1: Eptifibatide Injection Dosing Charts by Weight

Patient Weight		180-mcg/kg Bolus Volume	2-mcg/kg/min Infusion Volume (CrCl greater than or equal to 50 mL/min)	1-mcg/kg/min Infusion Volume (CrCl less than 50 mL/min)
(kg)	(lb)	(from 2 mg/mL vial)	(from 0.75-mg/mL 100-mL GALAXY container)	(from 0.75-mg/mL 100-mL GALAXY container)
37-41	81-91	3.4 mL	6 mL/h	3 mL/h
42-46	92-102	4 mL	7 mL/h	3.5 mL/h
47-53	103-117	4.5 mL	8 mL/h	4 mL/h
54-59	118-130	5 mL	9 mL/h	4.5 mL/h
60-65	131-143	5.6 mL	10 mL/h	5 mL/h
66-71	144-157	6.2 mL	11 mL/h	5.5 mL/h
72-78	158-172	6.8 mL	12 mL/h	6 mL/h
79-84	173-185	7.3 mL	13 mL/h	6.5 mL/h
85-90	186-198	7.9 mL	14 mL/h	7 mL/h
91-96	199-212	8.5 mL	15 mL/h	7.5 mL/h
97-103	213-227	9 mL	16 mL/h	8 mL/h
104-109	228-240	9.5 mL	17 mL/h	8.5 mL/h
110-115	241-253	10.2 mL	18 mL/h	9 mL/h
116-121	254-267	10.7 mL	19 mL/h	9.5 mL/h
>121	>267	11.3 mL	20 mL/h	10 mL/h

3 DOSAGE FORMS AND STRENGTHS

- Injection: 75 mg of eptifibatide per 100 mL (0.75 mg/mL) in a single-dose GALAXY container, for intravenous infusion only, not for intravenous bolus use

4 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
- Severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled on antihypertensive therapy
- Major surgery within the preceding 6 weeks
- History of stroke within 30 days or any history of hemorrhagic stroke
- Current or planned administration of another parenteral GP IIb/IIIa inhibitor
- Dependency on renal dialysis
- Hypersensitivity to eptifibatide or any component of the product (hypersensitivity reactions that occurred included anaphylaxis and urticaria).

5 WARNINGS AND PRECAUTIONS

5.1 Bleeding

Bleeding is the most common complication encountered during eptifibatide therapy. 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) [see *Adverse Reactions (6.1)*]. Most major bleeding associated with eptifibatide has been at the arterial access site for cardiac catheterization or from the gastrointestinal or genitourinary tract. Minimize the use of arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, and nasogastric tubes. When obtaining intravenous access, avoid non-compressible sites (e.g., subclavian or jugular veins).

Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents

Risk factors for bleeding include older age, a history of bleeding disorders, and concomitant use of drugs that increase the risk of bleeding (thrombolytics, oral anticoagulants, nonsteroidal anti-inflammatory drugs, and P2Y₁₂ inhibitors). Concomitant treatment with other inhibitors of platelet receptor glycoprotein (GP) IIb/IIIa should be avoided. In patients treated with heparin, bleeding can be minimized by close monitoring of the aPTT and ACT [see *Dosage and Administration (2)*].

Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI)

In patients undergoing PCI, treatment with eptifibatide is associated with an increase in major and minor bleeding at the site of arterial sheath placement. After PCI, eptifibatide infusion should be continued until hospital discharge or up to 18 to 24 hours, whichever comes first. Heparin use is discouraged after the PCI procedure. Early sheath removal is encouraged while eptifibatide is being infused. Prior to removing the sheath, it is recommended that heparin be discontinued for 3 to 4 hours and an aPTT of <45 seconds or ACT <150 seconds be achieved. In any case, both heparin and eptifibatide should be discontinued and sheath hemostasis should be achieved at least 2 to 4 hours before hospital discharge. If bleeding at access site cannot be controlled with pressure, infusion of eptifibatide and heparin should be discontinued immediately.

5.2 Thrombocytopenia

There have been reports of acute, profound thrombocytopenia (immune-mediated and non-immune mediated) with eptifibatide. In the event of acute profound thrombocytopenia or a confirmed platelet decrease to <100,000/mm³, discontinue eptifibatide and heparin (unfractionated or low-molecular weight). Monitor serial platelet counts, assess the presence of drug-dependent antibodies, and treat as appropriate [see *Adverse Reactions (6.1)*].

There has been no clinical experience with eptifibatide initiated in patients with a baseline platelet count <100,000/mm³. If a patient with low platelet counts is receiving eptifibatide, their platelet count should be monitored closely.

6 ADVERSE REACTIONS

The following serious adverse reaction is also discussed elsewhere in the labeling:

- Bleeding [see *Contraindications (4)* and *Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A total of 16,782 patients were treated in the Phase III clinical trials (PURSUIT, ESPRIT, and IMPACT II) [see *Clinical Trials (14)*]. These 16,782 patients had a mean age of 62 years (range: 20-94 years). Eighty-nine percent of the patients were Caucasian, with the remainder being predominantly Black (5%) and Hispanic (5%). Sixty-eight percent were men. Because of the different regimens used in PURSUIT, IMPACT II, and ESPRIT, data from the 3 studies were not pooled.

Bleeding and hypotension were the most commonly reported adverse reactions (incidence $\geq 5\%$ and greater than placebo) in the eptifibatide controlled clinical trial database.

Bleeding

The incidence of bleeding and transfusions in the PURSUIT and ESPRIT studies are shown in Table 2. Bleeding was classified as major or minor by the criteria of the TIMI study group. Major bleeding consisted of intracranial hemorrhage and other bleeding that led to decreases in hemoglobin greater than 5 g/dL. Minor bleeding 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.

Table 2: Bleeding and Transfusions in the PURSUIT and ESPRIT Studies

	PURSUIT (ACS)	
	Placebo n (%)	Eptifibatide 180/2 n (%)
Patients	4696	4679
Major bleeding*	425 (9.3%)	498 (10.8%)
Minor bleeding*	347 (7.6%)	604 (13.1%)
Requiring transfusions†	490 (10.4%)	601 (12.8%)
	ESPRIT (PCI)	
	Placebo n (%)	Eptifibatide 180/2/180 n (%)
Patients	1024	1040
Major bleeding*	4 (0.4%)	13 (1.3%)
Minor bleeding*	18 (2%)	29 (3%)
Requiring transfusions†	11 (1.1%)	16 (1.5%)

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

* 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 reactions 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, 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% versus 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 observed only for the femoral artery access site (3.2% versus 2.8%).

Table 3 displays 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). A corresponding table for ESPRIT is not presented, as every patient underwent PCI in the ESPRIT study and only 11 patients underwent CABG.

Table 3: Major Bleeding by Procedures in the PURSUIT Study

	Placebo n (%)	Eptifibatide 180/2 n (%)
Patients	4577	4604
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%)

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

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 resulting in discontinuation of the study drug was more frequent among patients receiving eptifibatide than placebo (4.6% versus 0.9% in ESPRIT, 8% versus 1% in PURSUIT, 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, 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 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, 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.

Immunogenicity/Thrombocytopenia

The potential for development of antibodies to eptifibatide has been studied in 433 subjects. Eptifibatide was nonantigenic in 412 patients receiving a single administration of eptifibatide (135-mcg/kg bolus followed by a continuous infusion of either 0.5 mcg/kg/min or 0.75 mcg/kg/min), and in 21 subjects to whom eptifibatide (135-mcg/kg bolus followed by a continuous infusion of 0.75 mcg/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.

In patients with suspected eptifibatide-related immune-mediated thrombocytopenia, IgG antibodies that react with the GP IIb/IIIa complex were identified in the presence of eptifibatide and in eptifibatide-naïve patients. These findings suggest acute thrombocytopenia after the administration of eptifibatide can develop as a result of naturally occurring drug-dependent antibodies or those induced by prior exposure to eptifibatide. Similar antibodies were identified with other GP IIb/IIIa ligand-mimetic agents. Immune-mediated thrombocytopenia with eptifibatide may be associated with hypotension and/or other signs of hypersensitivity.

In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100,000/mm³ 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.

Other Adverse Reactions

In the PURSUIT and ESPRIT studies, the incidence of serious nonbleeding adverse reactions 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 reaction that occurred at a rate of at least 1% and was more common with eptifibatide than placebo (7% versus 6%) was hypotension. Most of the serious nonbleeding adverse reactions consisted of cardiovascular reactions typical of a UA population. In the IMPACT II study, serious nonbleeding adverse reactions 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 reactions other than bleeding was uncommon in the PURSUIT, IMPACT II, and ESPRIT studies, with no single reaction occurring in >0.5% of the study population (except for "other" in the ESPRIT study).

6.2 Postmarketing Experience

Because the reactions below are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been reported in postmarketing experience, primarily with eptifibatide in combination with heparin and aspirin: cerebral, GI, and pulmonary hemorrhage. Fatal bleeding reactions have been reported. Acute profound thrombocytopenia, as well as immune-mediated thrombocytopenia, has been reported [see *Adverse Reactions (6.1)*].

7 DRUG INTERACTIONS

7.1 Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents

Coadministration of antiplatelet agents, thrombolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. Concomitant treatment with other inhibitors of platelet receptor GP IIb/IIIa should be avoided.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 (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. 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, eptifibatide should be used during pregnancy only if clearly needed.

8.2 Lactation

Risk Summary

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.

8.4 Pediatric Use

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

8.5 Geriatric Use

The PURSUIT and IMPACT II clinical studies enrolled patients up to the age of 94 years (45% were age 65 and over; 12% were age 75 and older). There was no apparent difference in efficacy between older and younger patients treated with eptifibatide. 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 the older patients. No dose adjustment was made for elderly patients, 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 (6.1)*].

8.6 Renal Impairment

Approximately 50% of eptifibatide is cleared by the kidney in patients with normal renal function. Total drug clearance is decreased by approximately 50% and steady-state plasma eptifibatide concentrations are doubled in patients with an estimated CrCl <50 mL/min (using the Cockcroft-Gault equation). Therefore, the infusion dose should be reduced to 1 mcg/kg/min in such patients [see *Dosage and Administration (2)*]. The safety and efficacy of eptifibatide in patients dependent on dialysis has not been established.

10 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.

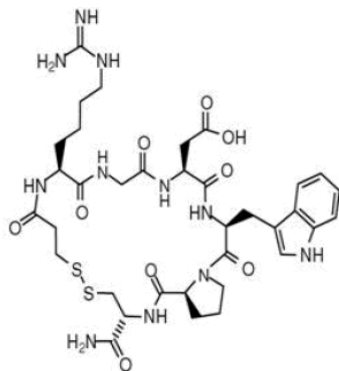
Eptifibatide was not lethal to rats, rabbits, or monkeys when administered by continuous intravenous infusion for 90 minutes at a total dose of 45 mg/kg (about 2 to 5 times the recommended maximum daily human dose on a body surface area basis). Symptoms of acute toxicity were loss of righting reflex, 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.

11 DESCRIPTION

Eptifibatide is a cyclic heptapeptide containing 6 amino acids and 1 mercaptopropionyl (des-amino cysteinyl) residue. An interchain disulfide bridge is formed between the cysteine amide and the mercaptopropionyl moieties. Chemically it is N⁶-(aminoiminomethyl)-N²-(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.

The eptifibatide peptide is produced by solution-phase peptide synthesis, and is purified by preparative reverse-phase liquid chromatography and lyophilized. The structural formula is:



Eptifibatide Injection is a clear, colorless, sterile, non-pyrogenic solution for intravenous infusion with an empirical formula of C₃₅H₄₉N₁₁O₉S₂ and a molecular weight of 831.96. Eptifibatide injection is a refrigerated, premixed, sterile, non-pyrogenic single-dose solution packaged in the GALAXY container (PL 2501 plastic). The 100 mL container consists of 0.75 mg/mL of eptifibatide. The container also contains 5.25 mg/mL citric acid and sodium hydroxide to adjust the pH to 5.35.

The GALAXY container is fabricated from a specially designed multilayered plastic (PL 2501). Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

12 CLINICAL PHARMACOLOGY

12.1 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 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.

12.2 Pharmacodynamics

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 mcg/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 mcg/kg/min. This infusion dose completely inhibited canine coronary thrombosis induced by coronary artery injury (Folts model).

Human pharmacodynamic data were obtained in healthy subjects and in patients presenting with UA or NSTEMI and/or undergoing percutaneous coronary intervention. Studies in healthy subjects enrolled only males; patient studies enrolled approximately one-third women. In these studies, eptifibatide inhibited *ex vivo* platelet aggregation induced by adenosine diphosphate (ADP) and other agonists in a dose- and concentration-dependent manner. The effect of eptifibatide was observed immediately after administration of a 180-mcg/kg intravenous bolus. Table 4 shows the effects of dosing regimens of eptifibatide used in the IMPACT II and PURSUIT studies on *ex vivo* platelet aggregation induced by 20 μM ADP in PPACK-anticoagulated platelet-rich plasma and on bleeding time. The effects of the dosing regimen used in ESPRIT on platelet aggregation have not been studied.

Table 4: Platelet Inhibition and Bleeding Time

	PURSUIT 180/2*
Inhibition of platelet aggregation 15 min after bolus	84%
Inhibition of platelet aggregation at steady state	>90%
Bleeding-time prolongation at steady state	<5x
Inhibition of platelet aggregation 4h after infusion discontinuation	<50%
Bleeding-time prolongation 6h after infusion discontinuation	1.4x

* 180-mcg/kg bolus followed by a continuous infusion of 2 mcg/kg/min.

The eptifibatide dosing regimen used in the ESPRIT study included two 180-mcg/kg bolus doses given 10 minutes apart combined with a continuous 2-mcg/kg/min infusion.

When administered alone, eptifibatide has no measurable effect on PT or 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.

12.3 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 mcg/kg/min. Plasma elimination half-life is approximately 2.5 hours. Administration of a single 180-mcg/kg bolus combined with an infusion produces an early peak level, followed by a small decline prior to attaining steady state (within 4-6 hours). This decline can be prevented by administering a second 180-mcg/kg bolus 10 minutes after the first. The extent of eptifibatide binding to human plasma protein is about 25%. Clearance in patients with coronary artery disease is about 55 mL/kg/h. 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, deaminated eptifibatide, and other, more polar metabolites. No major metabolites have been detected in human plasma.

Special Populations

Geriatric

Patients in clinical studies were older (range: 20-94 years) than those in the clinical pharmacology studies. Elderly patients with coronary artery disease demonstrated higher plasma levels and lower total body clearance of eptifibatide when given the same dose as younger patients. Limited data are available on lighter weight (<50 kg) patients over 75 years of age.

Renal Impairment

In patients with moderate to severe renal insufficiency (CrCl <50 mL/min using the Cockcroft-Gault equation), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels approximately doubled [see *Use in Specific Populations (8.6) and Dosage and Administration (2)*].

Hepatic Impairment

No studies have been conducted in patients with hepatic impairment.

Gender

Males and females have not demonstrated any clinically significant differences in the pharmacokinetics of eptifibatide.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

Eptifibatide was studied in 3 placebo-controlled, randomized studies. PURSUIT evaluated patients with acute coronary syndromes: UA or NSTEMI. Two other studies, ESPRIT and IMPACT II, evaluated patients about to undergo a PCI. Patients underwent primarily balloon angioplasty in IMPACT II and intracoronary stent placement, with or without angioplasty, in ESPRIT.

14.1 Non-ST-Segment Elevation Acute Coronary Syndrome

Non-ST-segment elevation acute coronary syndrome is defined as prolonged (≥ 10 minutes) symptoms of cardiac ischemia within the previous 24 hours associated with either ST-segment changes (elevations between 0.6 mm and 1 mm or depression >0.5 mm), T-wave inversion (>1 mm), or positive CK-MB. This definition includes "unstable angina" and "NSTEMI" but excludes MI that is associated with Q waves or greater degrees of ST-segment elevation.

PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Eptifibatid Therapy)

PURSUIT was a 726-center, 27-country, double-blind, randomized, placebo-controlled study in 10,948 patients presenting with UA or NSTEMI. Patients could be 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. Important exclusion criteria included a history of bleeding diathesis, evidence of abnormal bleeding within the previous 30 days, uncontrolled hypertension, major surgery within the previous 6 weeks, stroke within the previous 30 days, any history of hemorrhagic stroke, serum creatinine >2 mg/dL, dependency on renal dialysis, or platelet count $<100,000/\text{mm}^3$.

Patients were randomized to placebo, to eptifibatid 180-mcg/kg bolus followed by a 2-mcg/kg/min infusion (180/2), or to eptifibatid 180-mcg/kg bolus followed by a 1.3-mcg/kg/min infusion (180/1.3). The infusion was continued for 72 hours, until hospital discharge, or until the time of CABG, whichever occurred first, except that if PCI was performed, the eptifibatid infusion was continued for 24 hours after the procedure, allowing for a duration of infusion up to 96 hours.

The lower-infusion-rate arm was stopped after the first interim analysis when the 2 active-treatment arms appeared to have the same incidence of bleeding.

Patient age ranged from 20 to 94 (mean 63) years, and 65% were male. The patients were 89% Caucasian, 6% Hispanic, and 5% Black, recruited in the United States and Canada (40%), Western Europe (39%), Eastern Europe (16%), and Latin America (5%).

This was a "real world" study; each patient was managed according to the usual standards of the investigational site; frequencies of angiography, PCI, and CABG therefore differed widely from site to site and from country to country. Of the patients in PURSUIT, 13% were managed with PCI during drug infusion, of whom 50% received intracoronary stents; 87% were managed medically (without PCI during drug infusion).

The majority of patients received aspirin (75-325 mg once daily). Heparin was administered intravenously or subcutaneously, at the physician's discretion, most commonly as an intravenous bolus of 5000 units followed by a continuous infusion of 1000 units/h. For patients weighing less than 70 kg, the recommended heparin bolus dose was 60 units/kg followed by a continuous infusion of 12 units/kg/h. A target aPTT of 50 to 70 seconds was recommended. A total of 1250 patients underwent PCI within 72 hours after randomization, in which case they received intravenous heparin to maintain an ACT of 300 to 350 seconds.

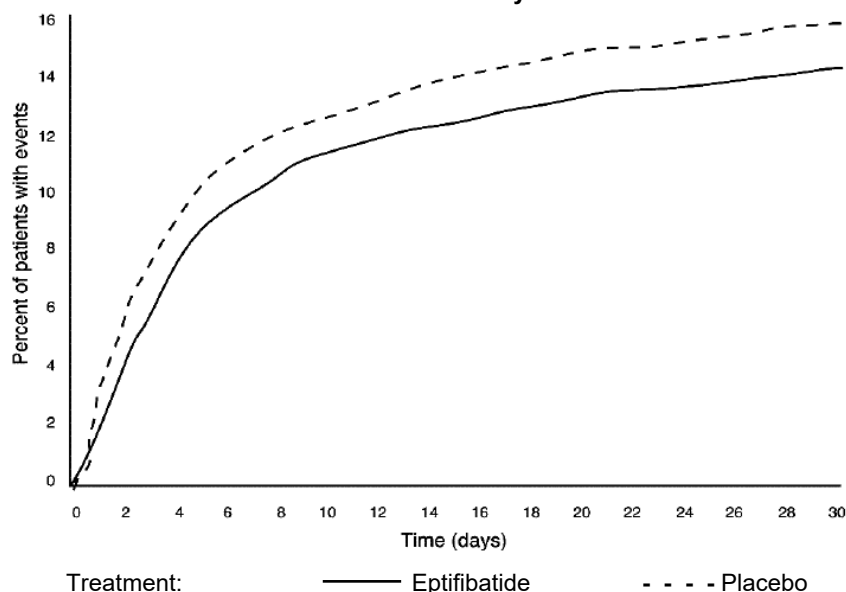
The primary endpoint of the study was the occurrence of death from any cause or new MI (evaluated by a blinded Clinical Endpoints Committee) within 30 days of randomization.

Compared to placebo, eptifibatid administered as a 180-mcg/kg bolus followed by a 2-mcg/kg/min infusion significantly ($p=0.042$) reduced the incidence of endpoint events (see Table 6). The reduction in the incidence of endpoint events in patients receiving eptifibatid was evident early during treatment, and this reduction was maintained through at least 30 days (see Figure 1). Table 5 also shows the incidence of the components of the primary endpoint, death (whether or not preceded by an MI) and new MI in surviving patients at 30 days.

Table 5: Clinical Events in the PURSUIT Study

	Placebo (n=4739) n (%)	Eptifibatid (180 mcg/kg bolus then 2 mcg/kg/min infusion) (n=4722) n (%)	p-value
3 days	359 (7.6%)	279 (5.9%)	0.001
7 days	552 (11.6%)	477 (10.1%)	0.016
30 days			
Death or MI (primary endpoint)	745 (15.7%)	672 (14.2%)	0.042
Death	177 (3.7%)	165 (3.5%)	
Nonfatal MI	568 (12%)	507 (10.7%)	

Figure 1: Kaplan-Meier Plot of Time to Death or Myocardial Infarction Within 30 Days of Randomization in the PURSUIT Study



Treatment with eptifibatide prior to determination of patient management strategy reduced clinical events regardless of whether patients ultimately underwent diagnostic catheterization, revascularization (i.e., PCI or CABG surgery) or continued to receive medical management alone. Table 6 shows the incidence of death or MI within 72 hours.

Table 6: Clinical Events (Death or MI) in the PURSUIT Study Within 72 Hours of Randomization

	Placebo	Eptifibatide (180 mcg/kg bolus then then 2 mcg/kg/min infusion)
Overall patient population	n=4739	n=4722
– At 72 hours	7.6%	5.9%
Patients undergoing early PCI	n=631	n=619
– Pre-procedure (nonfatal MI only)	5.5%	1.8%
– At 72 hours	14.4%	9%
Patients not undergoing early PCI	n=4108	n=4103
– At 72 hours	6.5%	5.4%

All of the effect of eptifibatide was established within 72 hours (during the period of drug infusion), regardless of management strategy. Moreover, for patients undergoing early PCI, a reduction in events was evident prior to the procedure.

An analysis of the results by sex suggests that women who would not routinely be expected to undergo PCI receive less benefit from eptifibatide (95% confidence limits for relative risk of 0.94 - 1.28) than do men (0.72 - 0.9). This difference may be a true treatment difference, the effect of other differences in these subgroups, or a statistical anomaly. No differential outcomes were seen between male and female patients undergoing PCI (see results for ESPRIT).

Follow-up data were available through 165 days for 10,611 patients enrolled in the PURSUIT trial (96.9% of the initial enrollment). This follow-up included 4566 patients who received eptifibatide at the 180/2 dose. As reported by the investigators, the occurrence of death from any cause or new MI for patients followed for at least 165 days was reduced from 13.6% with placebo to 12.1% with eptifibatide 180/2.

14.2 Percutaneous Coronary Intervention (PCI)

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

IMPACT II was a multicenter, double-blind, randomized, placebo-controlled study conducted in the United States in 4010 patients undergoing PCI. 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/mm³, 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 PCI for ongoing ACS. Patients were randomly assigned to 1 of 3 treatment regimens, each incorporating a bolus dose initiated immediately prior to PCI followed by a continuous infusion lasting 20 to 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 units/kg, with additional bolus infusions of up to 2000 additional units of heparin every 15 minutes to maintain an ACT of 300 to 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 1 dose of study drug.

As shown in Table 7, 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 7: Clinical Events in the IMPACT II Study

	Placebo n (%)	Eptifibatide (135 mcg/kg bolus then 0.5 mcg/kg/min infusion) n (%)	Eptifibatide (135 mcg/kg bolus then 0.5 mcg/kg/min infusion) n (%)
Patients	1285	1300	1286
Abrupt Closure	65 (5.1%)	36 (2.8%)	43 (3.3%)
p-value versus placebo		0.003	0.03
Death, MI, or Urgent Intervention			
24 hours	123 (9.6%)	86 (6.6%)	89 (6.9%)
p-value versus placebo		0.006	0.014
48 hours	131 (10.2%)	99 (7.6%)	102 (7.9%)
p-value versus placebo		0.021	0.045
30 hours	149 (11.6%)	118 (9.1%)	128 (10%)
p-value versus placebo		0.035	0.179
Death or MI			
30 hours	110 (8.6%)	89 (6.8%)	95 (7.4%)
p-value versus placebo		0.102	0.272
6 months	151 (11.9%)*	136 (10.6%)*	130 (10.3%)*
p-value versus placebo		0.297	0.182

* Kaplan-Meier estimate of event rate.

ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Eptifibatide Therapy)

The ESPRIT study was a multicenter, double-blind, randomized, placebo-controlled study conducted in the United States and Canada that enrolled 2064 patients undergoing elective or urgent PCI with intended intracoronary stent placement. Exclusion criteria included MI within the previous 24 hours, ongoing chest pain, administration of any oral antiplatelet or oral anticoagulant other than aspirin within 30 days of PCI (although loading doses of thienopyridine on the day of PCI were encouraged), planned PCI of a saphenous vein graft or subsequent "staged" PCI, prior stent placement in the target lesion, PCI 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/mm³, 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 received a wide variety of stents. 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 mcg/kg/min, and a second bolus of 180 mcg/kg administered 10 minutes later (180/2/180). Eptifibatide infusion was continued for 18 to 24 hours after PCI or until hospital discharge, whichever came first. Each patient received at least 1 dose of aspirin (162-325 mg) and 60 units/kg of heparin as a bolus (not to exceed 6000 units) if not already receiving a heparin infusion. Additional boluses of heparin (10-40 units/kg) could be administered in order to reach a target ACT between 200 and 300 seconds.

The primary endpoint of the ESPRIT study was the composite of death, MI, urgent target vessel revascularization (UTVR), and “bailout” to open-label eptifibatide due to a thrombotic complication of PCI (TBO) (e.g., visible thrombus, “no reflow,” or abrupt closure) at 48 hours. MI, UTVR, and TBO were evaluated by a blinded Clinical Events Committee.

As shown in Table 8, the incidence 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 8: Clinical Events in the ESPRIT Study

	Placebo (n=1024)	Eptifibatide* (n=1040)	Relative Risk (95% CI)	p-value
Death, MI, UTVR, or Thrombotic “Bailout”				
48 hours (primary endpoint)	108 (10.5%)	69 (6.6%)	0.629 (0.471, 0.84)	0.0015
30 days	120 (11.7%)	78 (7.5%)	0.64 (0.488, 0.84)	0.0011
Death, MI, or UTVR				
48 hours	95 (9.3%)	62 (6%)	0.643 (0.472, 0.875)	0.0045
30 days (key secondary endpoint)	107 (10.4%)	71 (6.8%)	0.653 (0.49, 0.871)	0.0034
Death or MI				
48 hours	94 (9.2%)	57 (5.5%)	0.597 (0.435, 0.82)	0.0013
30 days	104 (10.2%)	66 (6.3%)	0.625 (0.465, 0.84)	0.0016

* Eptifibatide was administered as 180 mcg/kg boluses at times 0 and 10 minutes and an infusion at 2 mcg/kg/min.

The need for thrombotic “bailout” was significantly reduced with eptifibatide at 48 hours (2.1% for placebo, 1% 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% for placebo to 5.4% (p=0.0015) and maintained that effect with significance at 30 days.

There was no treatment difference with respect to sex in ESPRIT. Eptifibatide reduced the incidence of the primary endpoint in both men (95% confidence limits for relative risk: 0.54, 1.07) and women (0.24, 0.72) at 48 hours.

Follow-up (12-month) mortality data were available for 2024 patients (1017 on eptifibatide) enrolled in the ESPRIT trial (98.1% of the initial enrollment). Twelve-month clinical event data were available for 1964 patients (988 on eptifibatide), representing 95.2% of the initial enrollment. As shown in Table 9, the treatment effect of eptifibatide seen at 48 hours and 30 days appeared preserved at 6 months and 1 year. Most of the benefit was in reduction of MI.

Table 9: Clinical Events at 6 Months and 1 Year in the ESPRIT Study

	Placebo (n=1024)	Eptifibatide (n=1040)	Hazard Ratio (95% CI)
Death, MI, or Target Vessel Revascularization			
6 months	187 (18.5%)	146 (14.3%)	0.744 (0.599, 0.924)
1 year	222 (22.1%)	178 (17.5%)	0.762 (0.626, 0.929)
Death, MI			
6 months	117 (11.5%)	77 (7.4%)	0.631 (0.473, 0.841)
1 year	126 (12.4%)	83 (8%)	0.63 (0.478, 0.832)

Percentages are Kaplan-Meier event rates.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Eptifibatide injection is supplied as a refrigerated, premixed, sterile, non-pyrogenic solution in single-dose GALAXY containers packed in individual cartons. The single-dose GALAXY plastic containers are available as follows:

Code	NDC No.	Container	Strength	Number of Cartons
2G3476	0338-9558-10	GALAXY single-dose	75 mg per 100 mL (0.75 mg per mL)	12 Cartons

16.2 Storage

GALAXY containers should be stored refrigerated at 2-8°C (36-46°F). GALAXY containers may be transferred to room temperature storage¹ for a period not to exceed 2 months. Upon transfer, Eptifibatide injection cartons must be marked by the dispensing pharmacist with a "DISCARD BY" date (2 months from the transfer date or the labeled expiration date, whichever comes first).

Protect from light. Retain in carton until time of use. Discard unused portion.

¹ Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Instruct patients to inform the doctor or healthcare provider about any medical conditions, medications, and allergies.

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