

## **NAME OF THE MEDICINAL PRODUCT**

Eptifibatide Medi-Market 0.75 mg/ml,  
Solution for I.V infusion

Eptifibatide Medi-Market 2 mg/ml,  
Solution for I.V injection

## **QUALITATIVE AND QUANTITATIVE COMPOSITION**

### Eptifibatide Medi-Market 0.75 mg/ml, Solution for I.V infusion:

Each ml of solution for infusion contains 0.75 mg of eptifibatide.

One vial of 100 ml of solution for infusion contains 75 mg of eptifibatide.

### Excipient(s) with known effect:

Each 100 ml vial contains 143.8 mg of sodium

### Eptifibatide Medi-Market 2 mg/ml, Solution for I.V injection:

Each ml of solution for injection contains 2 mg of eptifibatide.

One vial of 10 ml of solution for injection contains 20 mg of eptifibatide.

### Excipient(s) with known effect:

Each 10 ml vial contains 14.4 mg of sodium

For the full list of excipients, see section 11.

## **1 THERAPEUTIC INDICATIONS**

Eptifibatide Medi-Market is indicated for the prevention of death and myocardial infarction in patients presenting with high-risk unstable angina or non-Q-wave myocardial infarction.

Eptifibatide Medi-Market is indicated in patients who are managed with standard medical therapies and/or with percutaneous coronary intervention.

Eptifibatide Medi-Market is also indicated as an adjunct to percutaneous transluminal coronary angioplasty (PTCA) balloon angioplasty, directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation angioplasty, or excimer laser angioplasty for the prevention of abrupt closure of the treated coronary vessel and related acute ischemic cardiac complications (death, myocardial infarction, need for urgent intervention).

Eptifibatide Medi-Market is intended for use with aspirin and heparin.

## **2 DOSAGE AND ADMINISTRATION**

Before infusion of eptifibatide Medi-Market, 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 Dosage 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 <ul style="list-style-type: none"><li>• Infusion should continue until hospital discharge or initiation of coronary artery bypass graft surgery (CABG), up to 72 hours.</li><li>• 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.</li><li>• Aspirin, 160 to 325 mg, should be given daily.</li></ul>	180 mcg/kg IV bolus as soon as possible after diagnosis, followed by continuous infusion of 1 mcg/kg/min

Eptifibatide Medi-Market 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"><li>• 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.</li><li>• In patients who undergo CABG surgery, eptifibatide Medi-Market infusion should be discontinued prior to surgery.</li><li>• Aspirin, 160 to 325 mg, should be given 1 to 24 hours prior to PCI and daily thereafter.</li></ul>	

- Eptifibatide Medi-Market 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 Medi-Market.

## 2.3 Important Administration Instructions

1. Inspect eptifibatide Medi-Market for particulate matter and discoloration prior to administration, whenever solution and container permit.
2. 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.
3. May administer eptifibatide Medi-Market 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.
4. Withdraw the bolus dose(s) of eptifibatide Medi-Market from the 10 mL vial into a syringe. Administer the bolus dose(s) by IV push.
5. Immediately following the bolus dose administration, initiate a continuous infusion of eptifibatide Medi-Market. When using an intravenous infusion pump, administer eptifibatide Medi-Market undiluted directly from the 100-mL vial. Spike the 100 mL vial with a vented infusion set. Center the spike within the circle on the stopper top.
6. Discard any unused portion left in the vial.

Administer eptifibatide Medi-Market by volume according to patient weight (see [Table 1](#)).

**Table 1. Eptifibatide Medi-Market 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 vial)	(from 0.75 mg/mL 100 mL vial)
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: 20 mg of eptifibatide Medi-Market in 10 mL (2 mg/mL), solution for injection.
- Injection: 75 mg of eptifibatide Medi-Market in 100 mL (0.75 mg/mL), solution for infusion.

### 4 CONTRAINDICATIONS

Treatment with eptifibatide Medi-Market 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 the active substance or to any of the excipients listed in section 11 (hypersensitivity reactions that occurred included anaphylaxis and urticaria).

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 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 criteria of the Thrombolysis in Myocardial Infarction Study group (TIMI) [see *Adverse Reactions (6.1)*]. Most major bleeding associated with eptifibatide injection 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 P2Y<sub>12</sub> 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 injection is associated with an increase in major and minor bleeding at the site of arterial sheath placement. After PCI, eptifibatide Medi-Market 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 Medi-Market 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 Medi-Market 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 Medi-Market 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 injection. In the event of acute profound thrombocytopenia or a confirmed platelet decrease to  $<100,000/\text{mm}^3$ , discontinue eptifibatide Medi-Market 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 injection initiated in patients with a baseline platelet count  $<100,000/\text{mm}^3$ . If a patient with low platelet counts is receiving eptifibatide Medi-Market, 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 Studies* (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 injection 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 Injection 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 Injection 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 injection 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 injection 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 Injection 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 injection 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 injection 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 injection 180/1.3, and 5 patients in the group treated with eptifibatide injection 180/2 experienced a hemorrhagic stroke. The overall incidence of stroke was 0.5% in patients receiving eptifibatide injection 180/1.3, 0.7% in patients receiving eptifibatide injection 180/2, and 0.8% in placebo patients.

In the IMPACT II study, intracranial hemorrhage was experienced by 1 patient treated with eptifibatide injection 135/0.5, 2 patients treated with eptifibatide injection 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 injection, 0.7% in patients receiving eptifibatide injection 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 injection group. In addition there was 1 case of cerebral infarction in the eptifibatide injection group.

### Immunogenicity/Thrombocytopenia

The potential for development of antibodies to eptifibatide has been studied in 433 subjects. Eptifibatide injection was nonantigenic in 412 patients receiving a single administration of eptifibatide injection (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 injection (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 injection can develop as a result of naturally occurring drug-dependent antibodies or those induced by prior exposure to eptifibatide injection. Similar antibodies were identified with other GP IIb/IIIa ligand-mimetic agents. Immune-mediated thrombocytopenia with eptifibatide injection may be associated with hypotension and/or other signs of hypersensitivity.

In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia ( $<100,000/\text{mm}^3$  or  $\geq 50\%$  reduction from baseline) 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 injection 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 injection (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 injection 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

The following adverse reactions have been reported in post-approval use of eptifibatid injection in combination with heparin and aspirin. 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: 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)*].

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il>

## 7 DRUG INTERACTIONS

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

Co-administration 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

Available data on eptifibatid use in pregnant women from published literature and the pharmacovigilance database are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Untreated myocardial infarction can be fatal to the pregnant woman and fetus [*see Clinical Considerations*]. In animal reproduction studies, there was no evidence of adverse developmental effects when eptifibatid was administered intravenously to pregnant rats and rabbits at approximately 4 times the recommended maximum daily human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Clinical Considerations

*Disease-associated maternal and/or embryo/fetal risk:* Myocardial infarction is a medical emergency in pregnancy which can be fatal to the pregnant woman and fetus if left untreated. Therapy for the pregnant woman should not be withheld because of potential concerns regarding the effects of eptifibatid Medi-Market on the fetus.

#### Data

*Animal Data:* Embryo-fetal development studies have been performed by continuous intravenous infusion of eptifibatid in pregnant rats during the period of organogenesis 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 during the period of organogenesis 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 eptifibatid.

## 8.2 Lactation

### Risk Summary

There are no available data on the presence of eptifibatide in human milk, the effects on the breastfed infant, or the effects on milk production. As eptifibatide is a peptide, it is likely to be destroyed in the infant's gastrointestinal tract and not absorbed orally by the breastfed infant.

## 8.4 Pediatric Use

Safety and effectiveness of eptifibatide injection 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 injection. The incidence of bleeding complications was higher in the elderly in both placebo and eptifibatide injection 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 injection 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 injection in patients dependent on dialysis has not been established.

## 10 OVERDOSAGE

There has been only limited experience with overdosage of eptifibatide injection. 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.

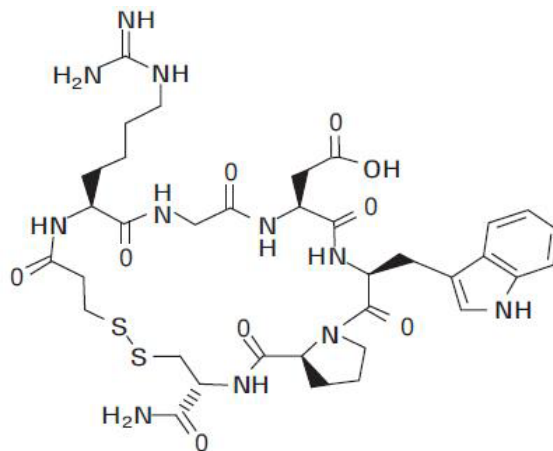
Eptifibatide was not lethal to rats, rabbits, or monkeys when administered by continuous intravenous infusion for 90 minutes at a total dose of 45 mg/kg (about 2 to 5 times the recommended maximum daily human dose on a body surface area basis). Symptoms of acute toxicity were loss of righting reflex, 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 N<sup>6</sup>-(aminoiminomethyl)-N<sup>2</sup>-(3-mercapto-1-oxopropyl)-L-lysylglycyl-L- $\alpha$ -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 Medi-Market is a clear, colorless, sterile, non-pyrogenic solution for intravenous (IV) use with an empirical formula of C<sub>35</sub>H<sub>49</sub>N<sub>11</sub>O<sub>9</sub>S<sub>2</sub> and a molecular weight of 831.96. Each 10 mL vial contains 2 mg/mL of eptifibatide and each 100 mL vial contains 0.75 mg/mL of eptifibatide. Each vial of either size also contains 5.25 mg/mL citric acid, sodium hydroxide and water for injections.

## 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 injection inhibited *ex vivo* platelet aggregation induced by adenosine diphosphate (ADP) and other agonists in a dose- and concentration-dependent manner. The effect of eptifibatide injection was observed immediately after administration of a 180 mcg/kg intravenous bolus. [Table 4](#) shows the effects of dosing regimens of eptifibatide injection 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**

	<b>PURSUIT 180/2*</b>
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 injection 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 injection 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 injection 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 ( $\geq 10$  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 Eptifibatide Injection 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 ( $\geq 10$  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 eptifibatide injection 180 mcg/kg bolus followed by a 2 mcg/kg/min infusion (180/2), or to eptifibatide injection 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 eptifibatide 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.

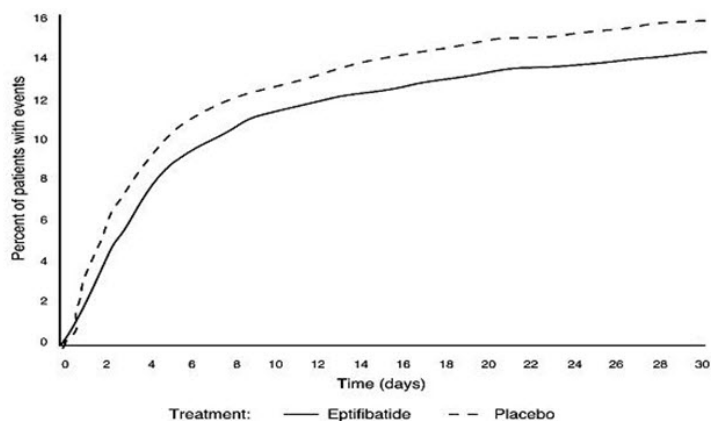
The primary endpoint of the study was the occurrence of death from any cause or new MI (evaluated by a blinded Clinical Endpoints Committee) within 30 days of randomization.

Compared to placebo, eptifibatide injection 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 eptifibatide injection 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**

<b>Death or MI</b>	<b>Placebo (n=4739) n (%)</b>	<b>Eptifibatide Injection (180 mcg/kg bolus then 2 mcg/kg/min infusion) (n=4722) n (%)</b>	<b>p-value</b>
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 injection 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 Injection (180 mcg/kg bolus 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 injection 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 injection (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 injection 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 injection 180/2.

## 14.2 Percutaneous Coronary Intervention (PCI)

### *IMPACT II (Eptifibatide Injection 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/mm<sup>3</sup>, 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 injection (135/0.5);
- 2) 135 mcg/kg bolus followed by a continuous infusion of 0.75 mcg/kg/min of eptifibatide injection (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 injection 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 injection group. As in the PURSUIT study, the effects of eptifibatide injection were seen early and persisted throughout the 30-day period.

**Table 7. Clinical Events in the IMPACT II Study**

	Placebo n (%)	Eptifibatide Injection (135 mcg/kg bolus then 0.5 mcg/kg/min infusion) n (%)	Eptifibatide Injection (135 mcg/kg bolus then 0.75 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
<b>Death, MI, or Urgent Intervention</b>			
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 days (primary endpoint)	149 (11.6%)	118 (9.1%)	128 (10%)
p-value versus placebo		0.035	0.179
<b>Death or MI</b>			
30 days	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 Injection 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/mm<sup>3</sup>, 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 injection 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 injection 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 injection. A treatment benefit in patients who received eptifibatide injection 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 Injection* (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 injection 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 injection at 48 hours (2.1% for placebo, 1% for eptifibatide injection; p=0.029). Consistent with previous studies of GP IIb/IIIa inhibitors, most of the benefit achieved acutely with eptifibatide injection was in the reduction of MI. Eptifibatide injection 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 injection 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 injection) enrolled in the ESPRIT trial (98.1% of the initial enrollment). Twelve-month clinical event data were available for 1964 patients (988 on eptifibatide injection), representing 95.2% of the initial enrollment. As shown in [Table 9](#), the treatment effect of eptifibatide injection 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**

	<b>Placebo (n=1024)</b>	<b>Eptifibatide Injection (n=1040)</b>	<b>Hazard Ratio (95% CI)</b>
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 Medi-Market injection is supplied as a sterile solution in 10 mL glass vials containing 20 mg of eptifibatide and 100 mL glass vials containing 75 mg of eptifibatide.

Pack size: 1 vial.

### 16.2 Storage

Vials should be stored refrigerated at 2° to 8°C.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 16.3.

### 16.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

#### After dilution:

For the diluted product, chemical and physical compatibility with 0.9% sodium chloride solution for infusion and 0.9% sodium chloride solution for infusion with 5% dextrose with and without potassium chloride has been demonstrated for up to 120 hours below 25° C.

From a microbiological point of view, unless the method of opening/ reconstitution/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

For single use only.

## 18 MANUFACTURER

Hainan Poly Pharm. Co., Ltd., Guilinyang Economic Development Area, Meilan District, Haikou, Hainan 571127, People's Republic of China.

## **19 LICENSE HOLDER**

A.L. MEDI-MARKET LTD., 3, HAKATIF ST., EMEK HEFER INDUSTRIAL PARK, 3877701

## **20 LICENSE NUMBERS**

Eptifibatide Medi-Market 0.75 mg/ml: 174-87-36668-99

Eptifibatide Medi-Market 2 mg/ml: 174-88-36669-99

Revised in January 2025