Package leaflet: Information for the user

Eptifibatide 0.75 mg/ml solution for infusion

Eptifibatide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eptifibatide Infusion is and what it is used for
2. What you need to know before you are given Eptifibatide Infusion
3. How to use Eptifibatide Infusion
4. Possible side effects
5. How to store Eptifibatide Infusion
6. Contents of the pack and other information

1. What Eptifibatide Infusion is and what it is used for

The name of your medicine is **'**Eptifibatide 0.75 mg/ml, Solution for Infusion' but in the rest of the leaflet it will be called 'Eptifibatide Infusion'.

Eptifibatide Infusion contains the active ingredient eptifibatide. It is an inhibitor of platelet aggregation. This means that it helps to prevent blood clots from forming.

Eptifibatide Infusion is used in adults with manifestation of severe coronary insufficiency defined as spontaneous and recent chest pain with electrocardiographic abnormalities or biological changes. It is usually given with acetylsalicylic acid and unfractionated heparin.

2. What you need to know before you are given Eptifibatide Infusion

You must not be given Eptifibatide Infusion:
- If you are allergic to eptifibatide or any of the other ingredients of this medicine (listed in section 6).
- If you have recently had bleeding from your stomach, intestines, bladder or other organs, for example if you have seen abnormal blood in your stool or urine (except from menstrual bleeding) in the past 30 days.
- If you have had a stroke within the past 30 days or any bleeding in the brain (haemorrhagic stroke) (also, be sure your doctor knows if you ever had a stroke).
- If you have had a brain tumour or a condition that affects the blood vessels around the brain.
- If you had a major operation or severe injury during the past 6 weeks.
- If you have or have had bleeding problems.
- If you have or have had difficulty with your blood clotting or low blood platelet count.
- If you have or have had severe hypertension (high blood pressure).
- If you have or have had severe kidney or liver problems.

- If you have been treated with another medicinal product of the same type as Eptifibatide

Please tell your doctor if you have had any of these conditions. If you have any questions, ask your doctor or pharmacist.

Warnings and precautions
- Before and during your treatment with Eptifibatide Infusion, samples of your blood will be tested as a safety measure to limit the possibility of unexpected bleeding.
- During use of Eptifibatide Infusion, you will be checked carefully for any signs of unusual or unexpected bleeding.
- Eptifibatide Infusion is recommended for use only in adult, hospitalized patients in coronary care units.

Children and adolescents
- Eptifibatide Infusion is not intended for use in children or adolescents less than 18 years of age.

Other medicines and Eptifibatide Infusion
Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines.

In particular, tell your doctor of pharmacist if you are taking/using any of the following medicines:

- Blood thinners (oral anticoagulants such as warfarin or acenocoumarol) or
- Medicines that prevent blood clots, including low molecular weight heparin, dipyridamole, ticlopidine, acetylsalicylic acid (except those that you may be given as part of Eptifibatide treatment), thrombolytics, oral anticoagulants, dextran solutions, adenosine, sulfinpyrazone, prostacyclin, non-steroidal anti-inflammatory agents.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Eptifibatide Infusion is not usually recommended for use during pregnancy. Your doctor will weigh up the benefit to you against the risk to your baby of using eptifibatide while you are pregnant.

If you are breast-feeding a baby, breast-feeding should be interrupted during the treatment period.

Eptifibatide Infusion contains sodium
This medicinal product contains 1.6 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Eptifibatide Infusion

Eptifibatide is given into the vein by direct injection followed by an infusion (drip solution). The dose given is based on your weight. The recommended dose is 180 microgram/kg administered as a bolus (rapid intravenous injection), followed by an infusion (drip solution) of 2 microgram/kg/minute for up to 72 hours. If you have kidney disease, the infusion dose may be reduced to 1 microgram/kg/minute.

If percutaneous coronary intervention (PCI) is performed during Eptifibatide therapy, the intravenous solution may be continued for up to 96 hours.

You must also be given doses of acetylsalicylic acid and heparin (if not contraindicated in your case).

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any signs of bleeding, notify your doctor or nurse immediately. Very rarely, bleeding has become severe and even fatal. Safety measures to prevent this from happening include blood tests and careful checking by the healthcare professionals taking care of you.

If you develop severe allergic reaction or hives, notify your doctor or nurse immediately. Other events that may occur in patients, who require this type of treatment, include those that are related to the condition you are having treated, such as rapid or irregular heartbeat, low blood pressure, shock or cardiac arrest.

Very common side effects
(may affect more than 1 in 10 people)
- Minor or major bleeding, (for example, blood in urine, blood in stool, vomiting blood, or bleeding with surgical procedures)
- Anaemia (decreased number of red blood cells).

Common side effects
(may affect up to 1in 10people)
- Inflammation of a vein
- Low blood pressure
- Shock or cardiac arrest
- Heart rate and rhythm disorders (rapid or slow or irregular heartbeat)

Uncommon side effects
(may affect up to1 in 100 people)
- Reduction in the number of platelets (blood cells necessary for blood clotting)
- Reduced blood flow to the brain

Very rare side effects
(may affect up to 1 in 10,000 people)
- Serious bleeding (for example, bleeding inside the abdomen, inside the brain, and into the lungs)
- Fatal bleeding
- Severe reduction in the number of platelets (blood cells necessary for blood clotting)
- Skin rash (such as hives)
- Sudden, severe allergic reaction: skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint (it may be fatal).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet**.**

You can also report side effects directly via the national reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be

completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option.
FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.imb.ie/
e-mail: imbpharmacovigilance@imb.ie

5. How to store Eptifibatide Infusion

Keep this medicine out of the sight and reach of children.

Single use only.

Once opened, use immediately. Any unused material after opening should be discarded.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

After Dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and 2-8°C.
From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are responsibility of the user.

Store in a refrigerator (2°C – 8°C). Store in the original package in order to protect from light. However, protection of Eptifibatide from light is not necessary during administration.

Do not use this medicine if you notice that the visual appearance has changed.

Eptifibatide infusion should not be used if it is noticed that particulate matter or discoloration is present.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eptifibatide Infusion contains

- The active substance is eptifibatide. 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.
- The other ingredients are citric acid monohydrate, sodium hydroxide (for pH-adjustment), water for injections.

What Eptifibatide Infusion looks like and contents of the pack

Eptifibatide infusion is a clear, colourless solution. It comes in a 100 ml Type I, clear glass, flint moulded vial plugged with 20 mm grey bromobutyl omniflex plus coated rubber stopper closure and sealed with a 20 mm pink flip-off aluminium seal.

Pack size:
100 ml vial, pack of one vial

Marketing Authorization Holder and Manufacturer
Generics [UK] Limited,
Station Close,
Potters Bar, EN6 lAG,
United Kingdom

Manufacturer
Agila Specialties Polska Sp.z.o.o.
10, Daniszewska Str
03-230 Warsaw
Poland

The leaflet was last revised in 02/2015.

The following information is intended for healthcare professionals only:

The complete SmPC (as TIL) of Eptifibatide 0.75 mg/ml solution for injection is provided as a separate document, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this medicinal product. Please refer to the TIL.

The following information is intended for healthcare professionals only.

TECHNICAL LEAFLET

Eptifibatide 0.75 mg/ml solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Eptifibatide 0.75 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 with known effect:
Each ml contains 1.6 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear colourless solution

pH: Between 5.0 and 5.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eptifibatide is intended for use with acetylsalicylic acid and unfractionated heparin.

Eptifibatide is indicated for the prevention of early myocardial infarction in adults presenting with unstable angina or non-Q-wave myocardial infarction, with the last episode of chest pain occurring within 24 hours and with electrocardiogram (ECG) changes and/or elevated cardiac enzymes.

Patients most likely to benefit from eptifibatide treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early PTCA (Percutaneous Transluminal Coronary Angioplasty) (see section 5.1).

4.2 Posology and method of administration

This product is for hospital use only. It should be administered by specialist physicians experienced in the management of acute coronary syndromes.

<u>Posology</u>

Adults (≥ 18 years of age) presenting with unstable angina (UA) or non-Q-wave myocardial infarction (NQMI)
The recommended dosage is an intravenous bolus of 180 microgram/kg administered as soon as possible following diagnosis, followed by a continuous infusion of 2.0 microgram/kg/min for up to 72 hours, until initiation of coronary artery bypass graft (CABG) surgery, or until discharge from the hospital (whichever occurs first). If Percutaneous Coronary Intervention (PCI) is performed during eptifibatide therapy, continue the infusion for 20-24 hours post-PCI for an overall maximum duration of therapy of 96 hours.

Emergency or semi-elective surgery
If the patient requires emergency or urgent cardiac surgery during the course of eptifibatide therapy, terminate the infusion immediately. If the patient requires semi-elective surgery, stop the eptifibatide infusion at an appropriate time to allow time for platelet function to return towards normal.

Hepatic impairment
Experience in patients with hepatic impairment is very limited. Administer with caution to patients with hepatic impairment in whom coagulation could be affected (see section 4.3, prothrombin time). It is contraindicated in patients with clinically significant hepatic impairment.

Renal impairment
In patients with moderate renal impairment (creatinine clearance ≥ 30 - < 50 ml/min**)**, an intravenous bolus of 180 microgram/kg should be administered followed by a continuous infusion dose of 1.0 microgram/kg/min for the duration of therapy. This recommendation is based on pharmacodynamic and pharmacokinetic data. The available clinical evidence cannot however confirm that this dose modification results in a preserved benefit (see section 5.1). Use in patients with more severe renal impairment is contraindicated (see section 4.3).

Paediatric population
The safety and efficacy of eptifibatide in children and adolescents below 18 years of age has not been established. No data are available.

Method of administration

Eptifibatide solution for infusion must be used in conjunction with Eptifibatide solution for injection.

Concurrent administration of unfractionated heparin is recommended unless this is contraindicated for reasons such as a history of thrombocytopenia associated with use of heparin (see "Heparin administration', section 4.4). Eptifibatide is also intended for concurrent use with acetylsalicylic acid, as it is part of standard management of patients with acute coronary syndromes, unless its use is contraindicated

4.3 Contraindications

Eptifibatide must not be used to treat patients with:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Evidence of gastrointestinal bleeding, gross genitourinary bleeding or other active abnormal bleeding within the previous 30 days of treatment.
- History of stroke within 30 days or any history of hemorrhagic stroke.
- Known history of intracranial disease (neoplasm, arteriovenous malformation, aneurysm).
- Major surgery or severe trauma within past 6 weeks.
- A history of bleeding diathesis.
- Thrombocytopenia (< 100,000 cells/mm^3).
- Prothrombin time > 1.2 times control, or International Normalized Ratio (INR) ≥ 2.0

- Severe hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg on antihypertensive therapy)
- Severe renal impairment (creatinine clearance < 30 ml/min) or dependency on renal dialysis;
- Clinically significant hepatic impairment
- Concomitant or planned administration of another parenteral glycoprotein (GP) IIb/IIIa inhibitor.

4.4 Special warnings and precautions for use

Bleeding

Eptifibatide is an antithrombotic agent that acts by inhibition of platelet aggregation; therefore the patients must be observed carefully for indications of bleeding during treatment (see section 4.8). Women, the elderly, patient with low body weight or with moderate renal impairment (creatinine clearance > 30 - < 50 ml/min) may have an increased risk of bleeding. Monitor these patients closely with regard to bleeding.

An increased risk of bleeding may also be observed in patients who receive early administration of eptifibatide (e.g. upon diagnosis) compared to receiving it immediately prior to PCI, as seen in the early ACS trial. Unlike the approved posology in the EU, all patients in this trial were administered a double bolus before the infusion (see section 5.1)

Bleeding is most common at the arterial access site in patients undergoing percutaneous arterial procedures. All potential bleeding sites (e.g. catheter insertion sites; arterial venous, or needle puncture sites; cutdown sites; gastrointestinal and genitourinary tracts) must be observed carefully. Other potential bleeding sites such as central and peripheral nervous system and retroperitoneal sites, must be carefully considered too.

Because eptifibatide inhibits platelet aggregation, caution must be employed when it is used with other medicinal products that affect haemostasis, including ticlopidine, clopidogrel, thrombolytics, oral anticoagulants, dextran solutions, adenosine, sulfinpyrazone, prostacyclin, non-steroidal anti-inflammatory agents, or dypyridamole (see section 4.5).

There is no experience with eptifibatide and low molecular weight heparins.

There is limited therapeutic experience with eptifibatide in patients for whom thrombolytic therapy is generally indicated (e.g., acute transmural myocardial infarction with new pathological Q-waves or elevated ST-segments or left bundle branch block in the ECG). Consequently the use of eptifibatide is not recommended in these circumstances (see section 4.5).

Eptifibatide should be stopped immediately if circumstances arise that necessitate thrombolytic therapy or if the patient must undergo an emergency CABG surgery or requires an intraortic balloon pump.

If serious bleeding occurs that is not controllable with pressure, the eptifibatide should be stopped immediately and any unfractionated heparin that is given concomitantly.

Arterial procedures

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

Thrombocytopenia and Immunogencity related to GP IIb/IIIa inhibitors

Eptifibatide inhibits platelet aggregation, but does not appear to affect the viability of platelets. As demonstrated in clinical trials, the incidence of thrombocytopenia was low, and similar in patients treated with eptifibatide or placebo. Thrombocytopaenia, including acute profound thrombocytopenia, has been observed with eptifibatide administration post-marketing (see section 4.8).

The mechanism, whether immune- and/or non-immune-mediated, by which eptifibatide may induce thrombocytopaenia is not fully understood. However, treatment with eptifibatide was associated with antibodies that recognise GPIIb/IIIa occupied by eptifibatide, suggesting an immune-mediated mechanism. Thrombocytopaenia occurring after first exposure to a GPIIb/IIIa inhibitor may be explained by the fact that antibodies are naturally present in some normal individuals.
Since either repeat exposure with any GP IIb/IIIa ligand-mimetic agent (like abciximab or eptifibatide) or first-time exposure to a GP IIb/IIIa inhibitor may be associated with immune-mediated thrombocytopenic responses, monitoring is required, i.e. platelet counts should be monitored prior to treatment, within 6 hours of administration, and at least once daily thereafter while on therapy and immediately at clinical signs of unexpected bleeding tendency.

If either a confirmed platelet decrease to < 100,000/mm^3 or acute profound thrombocytopaenia is observed, discontinuation of each treatment medication having known or suspected thrombocytopenic effects, including eptifibatide, heparin and clopidogrel, should be considered immediately. The decision to use platelet transfusions should be based upon clinical judgment on an individual basis.

In patients with previous immune-mediated thrombocytopaenia from other parenteral GP IIb/IIIa inhibitors, there are no data with the use of eptifibatide. Therefore, it is not recommended to administer eptifibatide in patients who have previously experienced immune mediated thrombocytopenia with GP IIb/IIIa inhibitors, including eptifibatide.

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

UA/NQMI
For a patient who weighs ≥ 70 kg, it is recommended that a bolus dose of 5,000 units is given, followed by a constant intravenous infusion of 1,000 units/hr. If the patient weighs < 70 kg, a bolus dose of 60 units/kg is recommended, followed by an infusion of 12 units/kg/hr. The activated partial thromboplastin time (aPTT) must be monitored in order to maintain a value between 50 and 70 seconds, above 70 seconds there may be an increased risk of bleeding.
If PCI is to be performed in the setting of UA/NQMI monitor the activated clotting time (ACT) to maintain a value between 300-350 seconds. Stop heparin administration if the ACT exceeds 300 seconds; do not administer until the ACT falls below 300 seconds.

Monitoring of laboratory values
Before infusion of eptifibatide, the following laboratory tests are recommended to identify pre-existing haemostatic abnormalities: prothrombin time (PT) and aPTT, serum creatinine, platelet count, haemoglobin and haematocrit levels. Haemoglobin, haematocrit, and platelet count are to be monitored as well within 6 hours after start of therapy and at least once daily thereafter while on therapy (or more often if there is evidence of a marked decrease). If the platelet count falls below 100,000/mm^3, further platelet counts are required to rule out pseudothrombocytopenia. Discontinue unfractionated heparin. In patients undergoing PCI, measure the ACT also.

This medicinal product contains 1.6 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin and dipyridamole
Eptifibatide did not appear to increase the risk of major and minor bleeding associated with concomitant use of warfarin and dipyridamole. Eptifibatide-treated patients who had a prothrombin time (PT) > 14.5 seconds and received warfarin concomitantly did not appear to be at an increased risk of bleeding.

Eptifibatide and thrombolytic agents
Data are limited on the use of eptifibatide in patients receiving thrombolytic agents. There was no consistent evidence that eptifibatide increased the risk of major or minor bleeding associated with tissue plasminogen activator in either a PCI or an acute myocardial infarction study; eptifibatide appeared to increase the risk of bleeding when administered with streptokinase in an acute myocardial infarction study. The combination of reduced dose tenecteplase and eptifibatide compared to placebo and eptifibatide significantly increased the risk of both major and minor bleeding when administered concomitantly in an acute ST-elevation myocardial infarction study.

In an acute myocardial infarction study involving 181 patients, eptifibatide (in regimens up to a bolus injection of 180 microgram/kg, followed by an infusion up to 2 microgram/kg/min for up to 72 hours) was administered concomitantly with streptokinase (1.5 million units over 60 minutes). At the highest infusion rates (1.3 microgram/kg/min and 2.0 microgram/kg/min) studied, eptifibatide was associated with an increased incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of eptifibatide in pregnant women.

Animal studies are insufficient with respect to effects on pregnancy, embryonal/ foetal development, parturition or postnatal development (see section 5.3). The potential risk for humans is unknown.

Eptifibatide should not be used during pregnancy unless clearly necessary.

Breastfeeding
It is unknown whether eptifibatide is excreted in human milk. Interruption of breast-feeding during the treatment period is recommended.

Fertility
There is no data available regarding the effect of eptifibatide on fertility.

4.7 Effects on ability to drive and use machines

Not relevant, as eptifibatide is intended for use only in hospitalized patients.

4.8 Undesirable effects

The majority of undesirable effects experienced by patients treated with eptifibatide were generally related to bleeding, or to cardiovascular events that occur frequently in this patient population.

Clinical Trials
The data sources used to determine adverse reaction frequency descriptors included two phase III clinical studies (PURSUIT and ESPRIT). These trials are briefly described below:

PURSUIT: This was a randomized, double-blind evaluation of the efficacy and safety of eptifibatide versus placebo for reducing mortality and myocardial (re)infarction in patients with unstable angina or non-Q-wave myocardial infarction.

ESPRIT: This was a double-blind, multicentre, randomized, parallel-group, placebo-controlled trial evaluating the safety and efficacy of eptifibatide therapy in patients scheduled to undergo non-emergent percutaneous coronary intervention (PCI) with stent implantation.

In PURSUIT, bleeding and non-bleeding events were collected from hospital discharge to the 30 day visit. In ESPIRIT, bleeding events were reported at 48 hours, and non-bleeding events were reported at 30 days. While thrombolysis in Myocardial Infarction TIMI bleeding criteria were used to categorize the incidence of major and minor bleeding in both the PURSUIT and the ESPRIT trials, PURSUIT data was collected within 30 days while ESPRIT data was limited to events within 48 hours or discharge, whichever came first.

The undesirable effects are listed by body system and frequency.
Frequencies are defined as below:
Very common (≥1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1,000 to < 1/100)
Rare (≥1/10,000 to < 1/1000)
Very rare (<1/10,000)

These are absolute reporting frequencies without taking into account placebo rates. For a particular adverse reaction, if data was available from both PURSUIT and ESPRIT, then the highest reported incidence was used to assign adverse reaction frequency.

Note that causality has not been determined for all adverse reactions.

Blood and lymphatic system disorders:	
Very Common	Bleeding (major and minor bleeding including femoral artery access, CABG- related, gastrointestinal, genitourinary, retroperitoneal, intracranial, haematemesis, haematuria, oral/ oropharyngeal, haemoglobin/ haematocrit decreased and other)
Uncommon	Thrombocytopenia
Nervous system disorders:	
Uncommon	Cerebral ischaemia.
Cardiac disorders:	
Common	Cardiac arrest, ventricular fibrillation, ventricular tachycardia, congestive heart failure, atrioventricular block, atrial fibrillation.
Vascular disorders	
Common	Shock, hypotension, phlebitis.

Cardiac arrest, congestive heart failure, atrial fibrillation, hypotension, and shock, which are commonly reported events from the PURSUIT trial, were events related to the underlying disease.

Administration of epfitibatide is associated with an increase in major and minor bleeding as classified by the criteria of the TIMI study group. At the recommended therapeutic dose, as administered in the PURSUIT trial involving nearly 11,000 patients, bleeding was the most common complication encountered during eptifibatide therapy. The most common bleeding complications were associated with cardiac invasive procedures (coronary artery bypass grafting (CABG) - related or at femoral artery access site).

Minor bleeding was defined in the PURSUIT trial as spontaneous gross haematuria, spontaneous haematemesis, observed blood loss with a haemoglobin decrease of more than 3g/dl, or a haemoglobin decrease of more than 4g/dl in the absence of an observed bleeding site. During treatment with eptifibatide in this study, minor bleeding was a very common complication (>1/10, or 13.1% for eptifibatide versus 7.6% for placebo). Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PCI, when ACT exceeded 350 seconds (see section 4.4, heparin use).

Major bleeding was defined in the PURSUIT trial as either an intracranial haemorrhage or a decrease in haemoglobin concentrations of more than 5 g/dl. Major bleeding was also very common and reported more frequently with eptifibatide than with placebo in the PURSUIT study (>1/10 or 10.8% versus 9.3%), but it was infrequent in the vast majority of patients who did not undergo CABG within 30 days of inclusion in the study. In patients undergoing CABG, the incidence of bleeding was not increased by eptifibatide compared to the patients treated with placebo. In the subgroup of patients undergoing PCI, major bleeding was observed commonly, in 9.7 % of eptifibatide treated patients vs. 4.6 % of placebo-treated patients.

The incidence of severe or life threatening bleeding events with eptifibatide was 1.9% compared to 1.1% with placebo. The need for blood transfusions was increased modestly by eptifibatide treatment (11.8% versus 9.3% for placebo).

Changes during eptifibatide treatment result from its known pharmacological action, i.e., inhibition of platelet aggregation. Thus, changes in laboratory parameters associated with bleeding (e.g. bleeding time) are common and expected. No apparent differences were observed between patients treated with eptifibatide or with placebo in values for liver function (SGOT/AST, SGPT/ALT, bilirubin, alkaline phosphatase) or renal function (serum creatinine, blood urea nitrogen).

Post-marketing experience

Blood and lymphatic system disorders	
Very rare	Fatal bleeding (the majority involved central and peripheral nervous system disorders: cerebral or intracranial haemorrhages); pulmonary haemorrhage, acute profound thrombocytopenia, haematoma.
Immune system disorders	
Very rare	Anaphylactic reactions.
Skin and subcutaneous tissue disorders	
Very rare	Rash, application site disorders such as urticaria.

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. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace

Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.imb.ie/
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

The experience in humans with overdose of eptifibatide is extremely limited. There was no indication of severe adverse reactions associated with administration of accidental large bolus doses, rapid infusion reported as overdose or large cumulative doses. In the PURSUIT trial, there were 9 patients who received bolus and/or infusion doses more than double the recommended dose, or who were identified by the investigator as having received an overdose. There was no excessive bleeding in any of these patients, although one patient undergoing CABG surgery was reported as having had a moderate bleed. Specifically, no patients experienced an intracranial bleed.

Potentially, an overdose of eptifibatide could result in bleeding. Because of its short half-life and rapid clearance, the activity of eptifibatide may be halted readily by discontinuing the infusion. Thus, although eptifibatide can be dialysed, the need for dialysis is unlikely.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent (platelet aggregation inhibitors excluding heparin). ATC code: B01AC16

Mechanism of action

Eptifibatide, a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide and one mercaptopropionyl (desamino cysteinyl) residue, is an inhibitor of platelet aggregation and belongs to the class of RGD (arginine-glycine-aspartate)-mimetics.

Eptifibatide reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the glycoprotein (GP)IIb/IIIa receptors.

Pharmacodynamic effects

Eptifibatide inhibits platelet aggregation in a dose- and concentration-dependent manner as demonstrated by *ex vivo* platelet aggregation using adenosine diphosphate (ADP) and other agonists to induce platelet aggregation. The effect of eptifibatide is observed immediately after administration of a 180 microgram/kg intravenous bolus. When followed by a 2.0 microgram/kg/min continuous infusion, this regimen produces a > 80 % inhibition of ADP-induced *ex vivo* platelet aggregation, at physiologic calcium concentrations, in more than 80 % of patients.

Platelet inhibition was readily reversed, with a return of platelet function towards baseline (> 50 % platelet aggregation) 4 hours after stopping a continuous infusion of 2.0 microgram/kg/min. Measurements of ADP-induced *ex vivo* platelet aggregation at physiologic calcium concentrations (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone anticoagulant) in patients presenting with unstable angina and Non Q-Wave Myocardial Infarction showed a concentration-dependent inhibition with an IC_{50} (50 % inhibitory concentration) of approximately 550 ng/ml and an IC_{80}(80 % inhibitory concentration) of approximately 1,100 ng/ml.

There is limited data with regards to platelet inhibition in patients with renal impairment. In patients with moderate renal impairment, (creatinine clearance 30 – 50mL/min) 100% inhibition was achieved at 24 hours following administration of 2 microgram/kg/min. In patients with severe renal impairment (creatinine clearance <30mL/min) administered 1microgram/kg/min, 80% inhibition was achieved in more than 80% of patients at 24 hours.

Clinical efficacy and safety

PURSUIT trial
The pivotal clinical trial for Unstable Angina (UA)/Non-Q Wave Myocardial Infarction (NQMI) was PURSUIT. This study was a 726-center, 27-country, double-blind, randomised, placebo-controlled study in 10,948 patients presenting with UA or NQMI. 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: ST depression > 0.5 mm of less than 30 minutes or persistent ST elevation > 0.5 mm not requiring reperfusion therapy or thrombolytic agents, T-wave inversion (> 1 mm),
- or increased CK-MB.

Patients were randomised to either placebo, eptifibatide 180 microgram/kg bolus followed by a 2.0 microgram/kg/min infusion (180/2.0), or eptifibatide 180 microgram/kg bolus followed by a 1.3 microgram/kg/min infusion (180/1.3).

The infusion was continued until hospital discharge, until the time of coronary artery bypass grafting (CABG) or for up to 72 hours, whichever occurred first. 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 180/1.3 arm was stopped after an interim analysis, as prespecified in the protocol, when the two active-treatment arms appeared to have a similar incidence of bleeding.

Patients were 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 eptifibatide infusion, of whom approximately 50% received intracoronary stents; 87% were managed medically (without PCI during eptifibatide infusion).

The vast majority of patients received acetylsalicylic acid (75-325 mg once daily).
Unfractionated heparin was administered intravenously or subcutaneously at the physician's discretion, most commonly as an intravenous bolus of 5,000 U followed by a continuous infusion of 1,000 U/h. A target aPTT of 50-70 seconds was recommended. A total of 1,250 patients underwent PCI within 72 hours after randomisation, in which case they received intravenous unfractionated heparin to maintain an activated clotting time (ACT) of 300-350 seconds.

The primary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (MI) (evaluated by a blinded Clinical Events Committee) within 30 days of randomisation. The component MI could be defined as asymptomatic with enzymatic elevation of CK-MB or new Q wave.

Compared to placebo, eptifibatide administered as 180/2.0 significantly reduced the incidence of the primary endpoint events (table 1): this represents around 15 events avoided for 1,000 patients treated:

Table 1:
Incidence of Death/CEC-Assessed MI («Treated as Randomised» Population)

Time	**Placebo**	**Eptifibatide**	**p-Value**

30 days	743/4,697 (15.8 %)	667/4,680 (14.3%)	0.034[a]
a: Pearson's chi-square test of difference between placebo and eptifibatide.			

Results on the primary endpoint were principally attributed to the occurrence of myocardial infarction.

The reduction in the incidence of endpoint events in patients receiving eptifibatide appeared early during treatment (within the first 72-96 hours) and this reduction was maintained through 6 months, without any significant effect on mortality.

Patients most likely to benefit from eptifibatide treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina.
According to epidemiological findings, a higher incidence of cardiovascular events has been associated with certain indicators, for instance:

- −Age
- −Elevated heart rate or blood pressure
- −Persistent or recurrent ischemic cardiac pain
- −Marked ECG changes (in particular ST-segment abnormalities)
- −Raised cardiac enzymes or markers (e.g. CK-MB, troponins) and
- −Heart failure

PURSUIT was conducted at a time when the standard of care of managing acute coronary syndromes was different from that of present times in terms of thienopyridine use and the routine use of intracoronary stents.

ESPRIT trial
ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with eptifibatide Therapy) was a double-blind, randomised, placebo-controlled trial (n= 2,064) for nonurgent PCI with intracoronary stenting.

All patients received routine standard of care and were randomised to either placebo or eptifibatide (2 bolus doses of 180 microgram/kg and a continuous infusion until discharge from hospital or a maximum of 18-24 hours).

The first bolus and the infusion were started simultaneously, immediately before the PCI procedure and were followed by a second bolus 10 minutes after the first. The rate of infusion was 2.0 microgram/kg/min for patients with serum creatinine $\leq$ 175 micromols/l or 1.0 microgram/kg/min for serum creatinine > 175 up to 350 micromols/l.

In the eptifibatide arm of the trial, virtually all patients received acetylsalicylic acid (99.7 %), and 98.1% received a thienopyridine, (clopidogrel in 95.4 % and ticlopidine in 2.7 %). On the day of PCI, prior to catheterization, 53.2 % received a thienopyridine (clopidogrel 52.7%; ticlopidine 0.5 %) – mostly as a loading dose (300 mg or more). The placebo arm was comparable (acetylsalicylic acid 99.7%, clopidogrel 95.9%, ticlopidin 2.6%).

The ESPRIT trial used a simplified regimen of heparin during PCI that consisted of an initial bolus of 60 units/kg, with a target ACT of 200-300 seconds. The primary endpoint of the trial was death (D), MI, urgent target vessel revascularisation (UTVR), and acute antithrombotic rescue with GP IIb/IIIa inhibitor therapy (RT) within 48 hours of randomisation.

MI was identified per the CK-MB core laboratory criteria. For this diagnosis, within 24 hours after the index PCI procedure, there had to be at least two CK-MB values $\geq$ 3 x the upper limit of normal; thus, validation by the CEC was not required. MI could also be reported following CEC adjudication of an investigator report.

The primary endpoint analysis [quadruple composite of death, MI, urgent target vessel revascularisation (UTVR) and thrombolytic bail-out (TBO) at 48 hours] showed a 37 % relative and 3.9 % absolute reduction in the eptifibatide group (6.6 % events versus 10.5 %, p = 0.0015). Results on the primary endpoint were mainly attributed to the reduction of enzymatic MI occurrence, identified as the occurrence of early elevation of cardiac enzymes after PCI (80 out of 92 MIs in the placebo group vs. 47 out of 56 MIs in the eptifibatide group). The clinical relevance of such enzymatic MIs is still controversial.

Similar results were also obtained for the 2 secondary endpoints assessed at 30 days: a triple composite of death, MI and UTVR, and the more robust combination of death and MI.

The reduction in the incidence of endpoint events in patients receiving eptifibatide appeared early during treatment. There was no increased benefit thereafter, up to 1 year.

Prolongation of bleeding time
Administration of eptifibatide by intravenous bolus and infusion causes up to a 5-fold increase in bleeding time. This increase is readily reversible upon discontinuation of the infusion with bleeding times returning towards baseline in approximately 6 (2-8) hours. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

EARLY-ACS trial
EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome) was a study of early routine eptifibatide versus placebo (with delayed provisional use of eptifibatide in the catheterization laboratory) used in combination with antithrombotic therapies (ASA, UFH, bivalirudin, fondaparinux or low molecular weight heparin), in subjects with high-risk NSTE ACS. Patients were to undergo an invasive strategy for further management after receiving study drug for 12 to 96 hours. Patients could be medically managed, proceed to coronary artery bypass graft (CABG), or undergo percutaneous coronary intervention (PCI). Unlike the approved posology in the EU, the study used a double bolus of study drug (separated by 10 minutes) before the infusion.

Early routine eptifibatide in this high-risk NSTE-ACS optimally-treated population who were managed with an invasive strategy did not result in a statistically significant reduction in the composite primary endpoint of rate of death, MI, RI-UR, and TBO within 96 hours compared with a regimen of delayed provisional eptifibatide (9.3% in early eptifibatide patients vs. 10.0% in patients assigned to delayed provisional eptifibatide; odds ratio=0.920; 95% CI=0.802-1.055; p=0.234). GUSTO severe/life threatening bleeding was uncommon and comparable in both treatment groups (0.8%). GUSTO moderate or severe/life threatening bleeding occurred significantly more often with early routine eptifibatide (7.4% vs. 5.0% in delayed provisional eptifibatide group; p <0.001). Similar differences were noted for TIMI major haemorrhage (118 [2.5%] in early routine use vs. 83 [1.8%] in delayed provisional use; p=0.016).

No statistically significant benefit of early routine eptifibatide strategy was demonstrated in the subgroup of patients who were managed medically or during the medical management periods prior to PCI or CABG.

In a post hoc analysis of the EARLY ACS trial the risk benefit of dose reduction in patients with moderate renal impairment is inconclusive. The primary endpoint event rate was 11.9 % in patients who received a reduced dose (1microgram/kg/min) vs 11.2% in patients who received the standard dose (2microgram/kg/min) when eptifibatide was administered in the early routine fashion (p=0.81). With delayed provisional eptifibatide administration, the event rates were 10% vs 11.5% in patients who received reduced dose and standard dose respectively (p=0.61). TIMI major bleeding occurred in 2.7 % of patients who received a reduced dose (1microgram/kg/min) vs 4.2% of patients who received the standard dose (2microgram/kg/min) when eptifibatide was administered in the early routine fashion (p=0.36). With delayed provisional eptifibatide administration, the TIMI major events were 1.4% vs 2.0% in patients

who received reduced dose and standard dose respectively (p=0.54). There were no notable differences observed with GUSTO severe bleeding rates.

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetics of eptifibatide are linear and dose proportional for bolus doses ranging from 90 to 250 microgram/kg and infusion rates from 0.5 to 3.0 microgram/kg/min. For a 2.0 microgram/kg/min infusion, mean steady-state plasma eptifibatide concentrations range from 1.5 to 2.2 microgram/ml in patients with coronary artery disease. These plasma concentrations are achieved rapidly when the infusion is preceded by a 180 microgram/kg bolus.

Distribution
The extent of eptifibatide binding to human plasma protein is about 25 %.

Biotransformation
In the same population, plasma elimination half-life is approximately 2.5 hours, plasma clearance 55 to 80 ml/kg/hr and volume of distribution of approximately 185 to 260 ml/kg.

Elimination
In healthy subjects, renal excretion accounted for approximately 50 % of total body clearance; approximately 50 % of the amount cleared is excreted unchanged. In patients with moderate to severe renal impairment (creatinine clearance < 50 ml/min), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled.

Interactions
No formal pharmacokinetic interaction studies have been conducted. However, in a population pharmacokinetic study there was no evidence of a pharmacokinetic interaction between eptifibatide and the following concomitant medicinal products: amlodipine, atenolol, atropine, captopril, cefazolin, diazepam, digoxin, diltiazem, diphenhydramine, enalapril, fentanyl, furosemide, heparin, lidocaine, lisinopril, metoprolol, midazolam, morphine, nitrates, nifedipine, and warfarin.

5.3 Preclinical safety data

Toxicology studies conducted with eptifibatide include single and repeated dose studies in the rat, rabbit and monkey, reproduction studies in the rat and rabbit, *in vitro* and *in vivo* genetic toxicity studies, and irritation, hypersensitivity and antigenicity studies. No unexpected toxic effects for an agent with this pharmacologic profile were observed and findings were predictive of clinical experience, with bleeding effects being the principal adverse event. No genotoxic effects were observed with eptifibatide.

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 (about 4 times the recommended maximum daily human dose on a body surface area basis). These studies revealed no evidence of impaired fertility or harm to the foetus due to eptifibatide. Reproduction studies in animal species where eptifibatide shows a similar pharmacologic activity as in humans are not available. Consequently these studies are not suitable to evaluate the toxicity of eptifibatide on reproductive function (see section 4.6).

The carcinogenic potential of eptifibatide has not been evaluated in long-term studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Eptifibatide is not compatible with furosemide.

In the absence of compatibility studies, Eptifibatide must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 18 months

After Dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and 2-8°C.
From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are responsibility of the user.

Once opened: use immediately

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light. However, protection of eptifibatide solution from light is not necessary during administration.
For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

Type I, clear glass, 100ml flint moulded vial plugged with 20 mm grey bromobutyl omniflex plus coated rubber stopper closure and sealed with a 20 mm pink flip-off aluminium seal.

Packs containing 1 vial.

6.6 Special precautions for disposal and other handling

Physical and chemical compatibility testing indicate that eptifibatide may be administered through an intravenous line with atropine sulfate, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, tissue plasminogen activator, or verapamil. Eptifibatide is compatible with 0.9 % sodium chloride solution for infusion and with dextrose 5 % in Normosol R with or without potassium chloride. Please refer to the Normosol R Summary of Product Characteristics for details on its composition.

Single use only.

Physiological compatibility studies were performed at a concentration of 0.2 mg/mL for 96 hours at 2°C-8°C & 25°C.

Before use, inspect the vial contents. Do not use if particulate matter or discoloration is present. Protection of eptifibatide solution from light is not necessary during administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Limited
Station close, Potters Bar,
Hertfordshire EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PA405/86/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT