NEW ZEALAND DATA SHEET

EPTIFIBATIDE VIATRIS

1. Product Name

Eptifibatide Viatris 75 mg/100 mL (0.75 mg/mL) solution for infusion.
Eptifibatide Viatris 20 mg/10 mL (2 mg/mL) solution for injection.

2. Qualitative and Quantitative Composition

Eptifibatide Viatris is a clear, colourless solution containing the acetate salt of the active ingredient, eptifibatide, a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide and one mercaptopropionyl (desamino cysteinyl) residue.

The **bolus injection** is a single dose 10 mL vial containing eptifibatide 20 mg (2 mg/mL) and the **solution for intravenous infusion** is a single dose 100 mL vial containing eptifibatide 75 mg (0.75 mg/mL).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Eptifibatide Viatris is formulated as a sterile clear, colourless solution for injection in two dosage administration forms, bolus injection and intravenous infusion.

4. Clinical Particulars

4.1 Therapeutic indications

Eptifibatide Viatris is indicated for patients undergoing non-urgent percutaneous coronary intervention (PCI) with intracoronary stenting for the reduction of death, myocardial infarction, urgent revascularisation and the need for acute antithrombotic rescue therapy.

Eptifibatide Viatris is indicated for the reduction of death and myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction (chest pain with ST-segment depression > 0.5 mm or definitive T-wave inversion > 1 mm or transient ST-segment elevation > 0.5 mm of less than 30 minutes or persistent ST-segment elevation > 0.5 mm not requiring reperfusion therapy or thrombolytic agents, or chest pain in patients without persistent ST-segment elevation with CK-MB greater than the upper limit of normal).

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

Patients with unstable angina (UA) or non-Q-wave myocardial infarction (NQMI) who are most likely to benefit from eptifibatide treatment are those at high risk of developing myocardial infarction within the first three to four days after onset of acute angina symptoms, including for instance those that are likely to undergo an early PCI.

Eptifibatide Viatris is intended for use with aspirin, heparin and clopidogrel.

4.2 Dose and method of administration

This product is for hospital use only, by specialist physicians experienced in the management of acute coronary syndromes or PCI. There has been limited study of eptifibatide in patients with severe renal insufficiency (i.e. those with CrCl < 30 mL/min) (see section 5.1).

Dose

Adults (≥ 18 years of age) undergoing percutaneous coronary intervention (PCI):

The recommended dosage of eptifibatide in patients with creatinine clearance ≥ 50 mL/min (using the Cockcroft-Gault equation)* is an intravenous bolus of 180 µg/kg administered immediately prior to the procedure, followed by a second bolus of 180 µg/kg 10 minutes after the first bolus injection. Simultaneously with the first bolus, a continuous infusion should be started at a dose of 2.0 µg/kg/min. Continue the infusion until hospital discharge or up to a maximum of 18-24 hours post-PCI. A minimum of 12 hours of infusion is recommended.

Adults (≥ 18 years of age) undergoing PCI with creatinine clearance < 50 mL/min:

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

Adults (≥ 18 years of age) presenting with unstable angina or non-Q-wave myocardial infarction (UA/NQMI):

The recommended dosage of eptifibatide in patients with creatinine clearance ≥ 50 mL/min (using the Cockcroft-Gault equation)* is an intravenous bolus of 180 µg/kg administered as soon as possible following diagnosis, followed by a continuous infusion of 2.0 µg/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 PCI is performed during eptifibatide therapy for UA/NQMI, continue the infusion for 20-24 hours post-PCI for an overall maximum duration of therapy of 96 hours.

Adults (≥ 18 years of age) presenting with UA/NQMI with creatinine clearance < 50 mL/min:

The recommended dosage of eptifibatide in patients with UA/NQMI with an estimated creatinine clearance < 50 mL/min (using the Cockcroft-Gault equation)* is an intravenous bolus of 180 µg/kg administered as soon as possible following diagnosis, immediately followed by a continuous infusion of 1.0 µg/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 PCI is performed during eptifibatide therapy for UA/NQMI, continue the infusion for 20 - 24 hours post-PCI for an overall maximum duration of therapy of 96 hours.

* Use the Cockcroft-Gault equation with actual body weight to calculate the estimated creatinine clearance in mL/min:

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

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

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.

Use with heparin and aspirin

Eptifibatide should be used in conjunction with heparin and antiplatelet doses of aspirin, unless a contraindication (such as a history of thrombocytopaenia associated with use of heparin) to the use of these medicines is present.

- Unstable angina or non-Q-wave myocardial infarction (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. Higher aPTT values may be associated with an increased risk of haemorrhage, but the risk has not been quantified.

- 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.

- Non-urgent PCI with intracoronary stenting: For those patients not treated with heparin within 6 hours before intervention, an initial heparin bolus of 60 units/kg is recommended. The target ACT during the procedure is 200-300 seconds. Additional bolus doses of heparin may be administered during the PCI procedure to maintain the ACT within this range.

Paediatric population

See section 4.4.

Method of administration

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

Before using, 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.

Physical and chemical compatibility testing indicate that eptifibatide may be administered through an intravenous line with atropine sulfate, dobutamine, heparin, lignocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, tissue plasminogen activator, or verapamil. Eptifibatide Viatris is compatible with 0.9% sodium chloride solution for injection and with dextrose 5% in Normosol R, in the presence or absence of potassium chloride.

In the absence of incompatibility studies, Eptifibatide Viatris must not be mixed with other medicinal products except those mentioned above.

As Eptifibatide Viatris does not contain any antimicrobial agent, the product is for single use only and any unused residue should be discarded.

4.3 Contraindications

Eptifibatide must not be used to treat patients with:

- evidence of gastrointestinal bleeding, gross genitourinary bleeding or other active abnormal bleeding (except menstrual bleeding) within the previous 30 days of treatment;
- history of stroke within 30 days or any history of haemorrhagic stroke;
- known history of intracranial disease (neoplasm, arteriovenous malformation, aneurism);
- major surgery or severe trauma within past 6 weeks;

- a history of bleeding diathesis;
- thrombocytopaenia (< 100 x 10^9/L);
- 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);
- dependency on renal dialysis;
- clinically significant hepatic impairment;
- concomitant or planned administration of a thrombolytic agent;
- concomitant or planned administration of another parenteral GP IIb/IIIa inhibitor;
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

Bleeding

Eptifibatide is an antithrombotic agent that acts by inhibition of platelet aggregation; therefore the patient must be observed carefully for indications of bleeding during treatment (see section 4.8). Women, the elderly and patients with low body weight appear to have an increased risk of bleeding. Monitor these patients closely with regard to bleeding.

The risk of 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, genitourinary and retroperitoneal sites, and central and peripheral nervous system should be observed carefully.

If serious bleeding occurs that is not controllable with pressure, the eptifibatide infusion and any unfractionated heparin that is given concomitantly should be stopped immediately. During the marketing of eptifibatide, very rare cases of fatal bleeding have been reported.

Arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, and nasogastric tubes should be minimised. When obtaining intravenous access, non-compressible sites (e.g. subclavian or jugular veins) should be avoided.

Arterial procedures

During treatment with eptifibatide there is a significant increase in bleeding rates from arterial puncture sites. If an arterial procedure is required during eptifibatide therapy, take care to ensure that only the anterior wall of the femoral artery is punctured. If an arterial sheath is used, it should be removed only after coagulation has returned to normal (e.g. when activated partial thromboplastin time (aPTT) is less than 45 seconds. After removal of the sheath, careful haemostasis must be ensured under close observation for at least 4 hours.

Thrombocytopaenia and immunogenicity related to GP IIb/IIIa inhibitors

Eptifibatide inhibits platelet aggregation but does not appear in general to affect the viability of platelets. The incidence of thrombocytopenia was low, and similar in patients treated with eptifibatide or placebo as reported in clinical trials, and in rarely reported post-marketing instances of immune-mediated thrombocytopenia. The presence of transferable factors in plasma which appear to bind to eptifibatide GP IIb/IIIa receptor implies that an immune-mediated thrombocytopenic response may be seen in GP IIb/IIIa ligand-mimetic agent naive patients or in patients re-exposed to eptifibatide.

The mechanism, whether immune and/or non-immune mediated, by which eptifibatide may induce thrombocytopenia is not fully understood. Since either repeat exposure with any GP IIb/IIIa

ligand-mimetic agent (such as abciximab or eptifibatide) or first-time exposure to a GP IIb/IIIa inhibitor may be associated with immune-mediated thrombocytopenic responses, care should be exercised to observe for possible thrombocytopenia associated with hypotension, and/or other signs of hypersensitivity.

In the PURSUIT trial, similar proportions (4.9% each) of patients given eptifibatide or placebo developed a platelet count < 100 x 10^9/L. However, eptifibatide was associated with a small excess of patients with a ≥ 50% decrease in platelet count from baseline (5.5% vs 5.1%), a minimum platelet count < 50 x 10^9/L (0.6% vs 0.4%), and a minimum platelet count < 20 x 10^9/L (0.2% vs 0.04%). In the ESPRIT trial, 0.7% of patients given eptifibatide and 0.4% of patients given placebo developed a platelet count < 100 x 10^9/L and 0.5% of patients given eptifibatide and 0.2% of patients given placebo had ≥ 50% decrease in platelet count from baseline.

If either a confirmed platelet count decrease to < 100 x 10^9/L or acute profound thrombocytopenia is observed, discontinuation of each treatment medication having known or suspected thrombocytopenic effects, including eptifibatide, heparin and clopidogrel, should be immediately considered. Initiate supportive measures including monitoring of serial platelet counts to guide management and determine etiology. If thrombocytopenia is not attributed to eptifibatide, it may be resumed upon normalization of platelet count.

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 hours. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time aPTT.

Heparin and aspirin use

Eptifibatide should be administered in conjunction with heparin and antiplatelet doses of aspirin (see section 4.2) unless a contraindication to the use of these drugs is present.

Monitoring of laboratory values

The following laboratory tests are recommended before treatment with eptifibatide to identify pre-existing haemostatic abnormalities: prothrombin time (PT) and aPTT, serum creatinine, platelet count, haemoglobin and haematocrit levels. Thereafter, haemoglobin, haematocrit and platelet count are to be monitored 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, the ACT must be measured.

Patients must be monitored for bleeding and treated if necessary (see section 4.9).

Use in 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).

Use in renal impairment

Eptifibatide may be administered at the standard dose to patients with mild renal impairment (CrCl ≥ 50 mL/min using the Cockcroft-Gault equation*). In patients with moderate to severe renal insufficiency (creatinine clearance < 50 mL/min using the Cockcroft-Gault equation*), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled. Patients with moderate to severe renal insufficiency who receive the usual infusion dose of 2.0 µg/kg/min have an increased risk of bleeding. Therefore, the infusion dose should be reduced to 1.0 µg/kg/min in such patients (see section 4.2). There has been limited study of

eptifibatide in patients with severe renal insufficiency (i.e. those with CrCl < 30 mL/min) There has been no clinical trial experience in patients dependent on dialysis. Eptifibatide is contraindicated in patients who are dependent on renal dialysis.

Use in the elderly

See Bleeding above.

Paediatric use

Safety and efficacy in children and adolescents < 18 years of age have not been established. Therefore, use in patients younger than 18 years of age is not recommended.

Effects on laboratory tests

See section 4.8.

4.5 Interaction with other medicines and other forms of interaction

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 medications: amlodipine, atenolol, atropine, captopril, cefazolin, diazepam, digoxin, diltiazem, diphenhydramine, enalapril, fentanyl, furosemide (frusemide), heparin, lidocaine (lignocaine), lisinopril, metoprolol, midazolam, morphine, nifedipine, nitrates and warfarin, suggesting a low potential for a pharmacokinetic drug interaction between eptifibatide and these commonly used agents in patients with cardiac conditions.

Because eptifibatide inhibits platelet aggregation, it should be used cautiously with other medications that affect haemostasis, including ticlopidine, clopidogrel, thrombolytics, oral anticoagulants, dextran solutions (see section 4), adenosine, low molecular weight heparins, sulfinpyrazone, prostacyclin, non-steroidal anti-inflammatory agents 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.

There is very limited experience with eptifibatide and low molecular weight heparins. Thus, coadministration of low molecular weight heparins with eptifibatide must be done with caution.

Eptifibatide should not be used in conjunction with thrombolytic agents due to the high risk of bleeding. When the 180/2.0 dose of eptifibatide was combined with streptokinase in a clinical trial, 15% of patients developed severe bleeding and 19% required transfusion (compared with no severe bleeding or transfusion in placebo-treated patients.

Stop the eptifibatide infusion immediately if circumstances arise that necessitate thrombolytic therapy or if the patient must undergo an emergency CABG surgery or requires an intraaortic balloon pump. In a trial in patients undergoing nonurgent PCI with stenting, 95% received clopidogrel concomitantly with aspirin before PCI and daily thereafter (see section 5.1).

Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PTCA, when ACT exceeded 350 seconds (see section 4.2).

Eptifibatide is not compatible with furosemide (frusemide) in the same intravenous line. There is no data on the use of eptifibatide in combination with dextran.

In the absence of data, eptifibatide should not be mixed with medications other than those tested and found to be compatible (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical studies with eptifibatide have been conducted in pregnant women. An increased incidence of foetal loss and prematurity may be associated with maternal haemorrhage. Reproductive studies in rats and rabbits gave no evidence of fertility, embryo-foetal, or peri-/postnatal toxicity with daily eptifibatide doses of up to 72 mg/kg in rats and 36 mg/kg in rabbits (providing plasma eptifibatide concentrations similar to those expected in humans in both species); however, tissue and organ haemorrhages were seen in monkeys at plasma eptifibatide concentrations approximating those attained in humans with the recommended dose. These haemorrhages occurred despite the absence of concurrent aspirin and heparin. Because animal reproduction studies are not always predictive of human response, eptifibatide should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

Breastfeeding

It is not known whether eptifibatide is excreted in human milk. Interruption of breastfeeding during the treatment period is recommended.

Fertility

Eptifibatide had no effect on the fertility of male and female rats at doses of 72 mg/kg/day IV.

4.7 Effects on ability to drive and use machines

Eptifibatide is intended for use in hospitalised patients. There is no data in patients treated with eptifibatide outside the hospital setting.

4.8 Undesirable effects

Bleeding

The majority of undesirable effects experienced by patients treated with eptifibatide were related to bleeding, or to cardiovascular events that occurr frequently in these patient populations.

Major and minor bleeding, as classified by the criteria of the Thrombolysis in Myocardial Infarction (TIMI) study group are defined below:

Major bleeding is defined as either an intracranial haemorrhage or a clinically significant overt haemorrhage (bleeding at an observed site) associated with a drop in haematocrit ≥ 15%, or a drop in haemoglobin ≥ 5 g/dL.

Minor bleeding is defined as gross haematuria or haematemesis that does not meet the criteria for a major bleed; or, observed blood loss associated with a drop in haematocrit ≥ 10%, or a drop in haemoglobin of ≥ 3 g/dL.

PURSUIT trial (UA/NQMI)

Tables 1, 2 and 3 show the adverse events recorded during PURSUIT trial with the recommended dose of eptifibatide.

Table 1. Bleeding adverse events (%) recorded within 30 days of initiation of eptifibatide treatment		
	PURSUIT: UA/NQMI (Serious and non-serious events)	
Adverse Event	**Eptifibatide* (N=4679)**	**Placebo (N=4696)**
Major Bleeding	10.8	9.3
Type or Location of Major Bleeding		
CABG-Related	6.5	6.7
Femoral Artery Access	2.7	1.3
Oral/Oropharyngeal	1.6	0.2
Gastrointestinal	1.5	0.4
Haemoglobin/Haematocrit decrease	1.4	1.5
Genitourinary	0.8	0.3
Unidentifiable Source requiring transfusion	0.4	0.2
Brachial	0.3	0.1
Pulmonary	0.2	0.1
Retroperitoneal	0.2	0.04
Intracranial	0.1	0.06
Injection/Procedure Site	0.1	0.06
Undefined Haemorrhage	0.06	0.02
Post-Trauma Bleeding	0.02	0.02
Other Sites/Unknown	0.0	0.02
Minor Bleeding	13.1	7.6
Type or Location of Minor Bleeding		
Femoral Artery Access	3.3	1.3
CABG-Related	2.8	2.7
Genitourinary	3.9	1.6
Oral/Oropharyngeal	3.0	0.3
Gastrointestinal	2.8	0.8
Haemoglobin/Haematocrit decrease	1.4	1.4
Brachial	0.4	0.2
Pulmonary	0.4	0.1
Unidentifiable Source requiring transfusion	0.2	0.02
Undefined Haemorrhage	0.2	0.06
Injection/Procedure Site	0.1	0.0
Retroperitoneal	0.06	0.06
Other Sites/Unknown	0.04	0.04
Post-Trauma Bleeding	0.02	0.0

* IV bolus of 180 microgram/kg followed by continuous infusion of 2.0 microgram/kg/min for up to 72 hours (96 hours if PTCA performed); majority of patients received heparin and aspirin.

Overall, serious and non-serious non-bleeding adverse events were reported at a similar rate in patients treated with eptifibatide and those treated with placebo (Tables 1 and 2).

Commonly reported events (occurring in ≥ 2% across all groups) were events related to the underlying disease, such as atrial fibrillation, hypotension, congestive heart failure, cardiac arrest and shock.

Table 2. PURSUIT study: UA/NQMI Serious non-bleeding adverse events* (%)		
Adverse Event	**Eptifibatide (N=4679)**	**Placebo (N=4696)**
Any Non-Bleeding Adverse Event	19.0	18.7
Cardiovascular		
Hypotension	6.9	6.2
Atrial Fibrillation	6.3	6.4
Congestive Heart Failure	5.1	5.5
Shock	2.6	2.5
Cardiac Arrest	2.3	2.7
Atrioventricular Block	1.5	1.3
Phlebitis	1.4	1.5
Ventricular Fibrillation	1.3	1.4
Ventricular Tachycardia	1.1	1.1
Haem/Lymphatic		
Thrombocytopenia	0.2	<0.1
Neurological		
Cerebral ischaemia	0.4	0.5

* Causality has not been determined for all adverse events.

Table 3. PURSUIT study: UA/NQMI Non-serious, non-bleeding adverse events*					
Adverse Event	**INTEGRILIN**			**Placebo**	
Digestive					
Nausea	25	(1.0%)		25	(1.0%)
Whole Body					
Headache	83	(3.2%)		83	(3.2%)
Fever	41	(1.6%)		26	(1.0%)
Pain (unspecified)	30	(1.2%)		32	(1.2%)
Abdominal Pain	24	(0.9%)		27	(1.0%)
Chest Pain	21	(0.8%)		31	(1.2%)

* Data for non-serious, non-bleeding events were not collected in study centres outside Europe.

Events with a frequency < 1% are not tabulated.

Injection site reaction has also been reported with the use of eptifibatide during clinical trials.

ESPRIT trial (non-urgent PCI with intracoronary stenting)

Minor bleeding (TIMI criteria) was the most common complication of eptifibatide administration (2.8% eptifibatide vs 1.8% placebo, at 48 hours) (Table 4). Minor bleeding events (> 1% eptifibatide group) included femoral artery access and haematuria. Less frequently occurring (< 1% eptifibatide group) were haematemesis and other gastrointestinal related events.

Major bleeding (TIMI criteria) events were higher with eptifibatide than placebo (1.3% eptifibatide vs 0.4% placebo, at 48 hours). Eptifibatide did not significantly increase the risk of intracranial bleeding, which was uncommon (0.2% eptifibatide vs 0.1% placebo). Bleeding incidence was not significantly increased with eptifibatide as compared with placebo in patients who underwent CABG surgery (33% vs 50% placebo). Major bleeding (< 1% eptifibatide group) included femoral artery access, retroperitoneal, intracranial, hematuria, haematemesis and genitourinary.

Table 4. ESPRIT study: Bleeding adverse events [n(%)] Recorded within 48 hours* of initiation of eptifibatide treatment		
Adverse Event	**Eptifibatide (N = 1040)**	**Placebo (N = 1024)**
Major bleeding (TIMI)	**13 (1.3%)**	**4 (0.4%)**
Type or location of major bleeding**		
Access site	8 (0.8%)	1(0.1%)
Intracranial	2 (0.2%)	1 (0.1%)
Haematuria	1 (0.1%)	0 (0%)
Hematemesis	1 (0.1%)	0 (0%)
Retroperitoneal	3 (0.3%)	0 (0%)
Other GU site	1 (0.1%)	0 (0%)
Other	4 (0.4%)	2 (0.2%)
Minor bleeding (TIMI)	**29 (2.8%)**	**18 (1.8%)**
Type or location of minor bleeding**		
Access site	10 (1.0%)	8 (0.9%)
Haematuria	14 (1.4%)	8 (0.9%)
Hematemesis	6 (0.6%)	4 (0.4%)
Other GI	1 (0.1%)	2 (0.2%)
Other	5 (0.5%)	2 (0.2%)

Note: Denominator is based on patients in whom data are available
* or discharge, whichever occurred first
** Note: Patients may have bleeding at more than one site.

The incidence of severe or life-threatening bleeding events in patients was 0.7% eptifibatide vs 0.5% placebo. Eptifibatide treatment modestly increased the need for red blood cell transfusions (1.4% eptifibatide vs 1.0% placebo). The most common serious adverse events (excluding death) which occurred within 30 days of treatment with eptifibatide are shown in Table 5.

Table 5. ESPRIT study: Most common* serious treatment emergent adverse events within 30 Days (excluding deaths)		
Adverse Event	**Eptifibatide (N = 1040)**	**Placebo (N = 1024)**
All patients who had a serious adverse event, other than death, within 30 days of randomization	100 (9.6%)	71 (6.9%)
By type of serious adverse event:		
Chest pain	22 (2.1%)	18 (1.8%)
Groin Hematoma	8 (0.8%)	3 (0.3%)
Arterial Anomaly	7 (0.7%)	3 (0.3%)
GI Bleed	8 (0.8%)	1 (0.1%)
Haemorrhage	3 (0.3%)	5 (0.5%)
Retroperitoneal Haemorrhage	7 (0.7%)	1 (0.1%)
Cardiac Arrest	3 (0.3%)	4 (0.4%)
Atrial Fibrillation	3 (0.3%)	3 (0.3%)
Myocardial Infarction	1 (0.1%)	5 (0.5%)
Heart Failure	0 (0.0%)	5 (0.5%)
Coronary Occlusion	3 (0.3%)	2 (0.2%)
Pericardial Effusion	1 (0.1%)	3 (0.3%)
Allergic Reaction	2 (0.2%)	1 (0.1%)
Dyspepsia	1 (0.1%)	2 (0.2%)
Intracranial Haemorrhage	2 (0.2%)	1 (0.1%)
Pneumonia	1 (0.1%)	2 (0.2%)
Renal Dysfunction	2 (0.2%)	1 (0.1%)
Stroke	2 (0.2%)	1 (0.1%)
Coronary Artery Disease	1 (0.1%)	1 (0.1%)

Table 5. ESPRIT study: Most common* serious treatment emergent adverse events within 30 Days (excluding deaths)		
Adverse Event	**Eptifibatide (N = 1040)**	**Placebo (N = 1024)**
Decreased HGB/HCT	1 (0.1%)	1 (0.1%)
Dyspnoea	2 (0.2%)	0 (0.0%)
Epistaxis	2 (0.2%)	0 (0.0%)
Hypertension	2 (0.2%)	0 (0.0%)
Hypotension	0 (0.0%)	2 (0.2%)
Infection	1 (0.1%)	1 (0.1%)
Respiratory Disease	2 (0.2%)	0 (0.0%)
Ventricular Tachycardia	1 (0.1%)	1 (0.1%)
Arterial Thrombus	2 (0.2%)	0 (0.0%)
Thrombocytopenia	2 (0.2%)	0 (0.0%)
Deep Thrombophlebitis	1 (0.1%)	1 (0.1%)

* Occurring in at least two patients.

Post-marketing experience

Additional adverse events reported during use of eptifibatide include anaphylaxis, rash and application site disorders such as urticaria. Rare cases of acute profound thrombocytopenia and very rare cases of pulmonary haemorrhage and fatal bleeding have also been reported.

Laboratory values

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 and placebo in values for liver function (SGOT/AST, SGPT/ALT, bilirubin, alkaline phosphatase) or renal function (serum creatinine, blood urea nitrogen).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, ATC code: B01AC16

Mechanism of action

Eptifibatide belongs to the class of RGD (arginine-glycine-aspartate)-mimetics and binds to the platelet receptor glycoprotein (GP) IIb-IIIa of human platelets. It reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the glycoprotein (GP) IIb/IIIa receptors.

When administered intravenously, eptifibatide inhibits *ex vivo* platelet aggregation in a dose- and concentration-dependent manner. Measurement of ADP-induced *ex vivo* platelet aggregation at physiological calcium concentrations (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone [PPACK] as the anticoagulant) in patients presenting with unstable angina (UA) or non-Q-wave myocardial infarction (NQMI) showed a concentration-dependent inhibition with an IC_{50} (50% inhibitory concentration) of 557 ng/mL and a mean IC_{80} (80% inhibitory concentration) of 1107 ng/mL.

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 *ex vivo* platelet aggregation at physiological calcium concentrations in more than 80% of patients. Platelet aggregation inhibition is reversible following cessation of the eptifibatide infusion (see Table 6).

Table 6. Platelet inhibition and bleeding time after a 180 microgram/kg bolus followedby a 2.0 microgram/kg/min infusion (PURSUIT study).

Time point	Inhibition of platelet aggregation	Prolongation of bleeding time
15 min after bolus	84%	-
At steady state	>90%	< 5×
4h after stopping infusion	<50%	-
6h after stopping infusion	-	1.4×

Clinical trials

Eptifibatide has not been directly compared with abciximab or any other GPIIb-IIIa inhibitor in clinical trials.

Clinical pharmacology trials

The pharmacodynamic and pharmacokinetic properties of eptifibatide were studied in subjects with various degrees of renal function[1]. The purpose of this study was to determine appropriate dose adjustment in patients with decreased renal function. Tolerability of eptifibatide when administered to patients with reduced renal function was also assessed.

Subjects were divided into four groups according to renal function based on estimated CrCl using the Cockcroft-Gault equation (refer to section 4.2). Subjects with differing renal function (normal [Group 1, CrCl >80 mL/min], mild renal impairment [Group 2, CrCl 51-80 mL/min], moderate renal impairment [Group 3, CrCl 30-50 mL/min], or severe renal impairment [Group 4, CrCl <30 mL/min]), received a 24- hour eptifibatide infusion of 2.0 µg/kg/min (Groups 1, 2, and 3) or 1.0 µg/kg/min (Group 4).

A strong correlation was found between eptifibatide clearance and CrCl. In patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min), clearance rates and steady state concentrations of

eptifibatide were approximately 50 % lower and almost 2-fold higher respectively, than in patients with normal renal function or mild renal impairment (CrCl >50 mL/min) (see Table 7). These findings support adjustment of the infusion dose of eptifibatide from 2.0 µg/kg/min to 1.0 µg/kg/min in patients with moderately or severely impaired renal function (see sections 4.2, 4.4 and 5.2).

Table 7. Pharmacokinetic (PK) properties of eptifibatide in subjects with various degrees of renal function. (All values expressed as mean [SD]).

PK Parameter	Group 1 (n=7)	Group 2 (n=8)	Group 3 (n=7)	Group 4 (n=5)
C_{ss}, mg/L	2.04 (0.62)	2.28 (1.02)	3.71 (0.85)	4.08 (1.83)†
C_{max}, mg/L	2.59 (1.75)	2.24 (0.85)	3.44 (0.57)	3.74 (1.06)†
Cl_{total}, L/h	5.73 (1.84)	5.63 (1.84)	3.04 (0.38)	2.72 (0.58)
Cl_{renal}, L/h	3.44 (1.30)	2.54 (0.91)	1.10 (0.38)	0.56 (0.21)
$AUC_{0-\infty}$, mg/L/h	43.08 (10.07)	51.97 (23.99)	77.89 (11.88)	77.52 (10.00)†
	(n=8)	(n=8)	(n=8)	(n=7)
$T_{½}$, h‡	4.18 (3.31)	4.74 (1.92)	6.16 (2.59)	6.63 (1.36)
V_l, L‡	6.38 (6.72)	10.45 (10.68)	8.67 (11.13)	6.92 (9.21)
V_{ss}, L‡	13.73 (15.05)	21.73 (18.50)	18.08 (12.48)	19.29 (15.64)
Baseline CrCl, mL/min	95.4 (24.6)	64.6 (8.8)	41.7 (6.7)	21.7 (6.9)

C_{ss} = steady-state plasma eptifibatide concentration (calculated); C_{max} = maximal plasma drug concentration; Cl_{total} = total body clearance; Cl_{renal} = renal eptifibatide clearance; $AUC_{0-\infty}$ = areaunder the plasma concentration-time curve from time 0 to infinity; $T_{½}$ = terminal plasma half- life; V_l = apparent volume of distribution; V_{ss} = apparent steady-state central volume of distribution.

†Corrected for a 2.0 µg/kg/min infusion (actual values were 50 % of those reported in table)

‡Compartmental estimate

[1] Gretler DD *et al*. Pharmacokinetic and pharmacodynamic properties of eptifibatide in subjects with normal or impaired renal function. *Clinical Therapeutics* 2004;26:390-398.

PURSUIT trial: (UA/NQM)

Dose-ranging studies using clinical efficacy endpoints have not been conducted. The recommended dose of eptifibatide has been extrapolated from *in vitro* data and was shown to be effective in the PURSUIT trial.

The pivotal clinical trial for unstable angina (UA)/non-Q-wave myocardial infarction (NQMI) was PURSUIT. This study was a 726-centre, 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 ischaemia at rest (≥ 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 re-perfusion therapy or thrombolytic agents, T-wave inversion (> 1 mm),
- or increased CK-MB (serum concentration of the myocardial band isoenzyme of creatine kinase).

Patients were randomised to either placebo, eptifibatide 180 µg/kg bolus followed by a 2 µg/kg/min infusion (180/2.0) or eptifibatide 180 µg/kg bolus followed by a 1.3 µg/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 percutaneous coronary intervention (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.

This was a “real world” study; each patient was managed according to the usual standards of the investigational site, therefore, the frequencies of angiography, PCI and CABG differed widely from site to site and from country to country. Eptifibatide was used in combination with standard

medical therapies and/or percutaneous coronary intervention (PCI). 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 infusion).

The vast 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 U followed by a continuous infusion of 1000 U/hour. A target aPTT of 50-70 seconds was recommended. A total of 1250 patients underwent PCI within 72 hours after randomisation, in which case they received intravenous 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, CEC) within 30 days of randomisation.

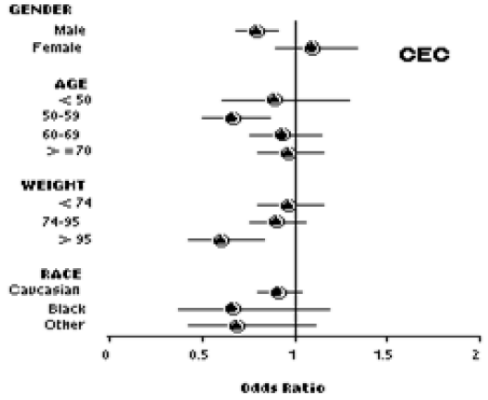
Compared to placebo, eptifibatide administered as 180/2.0 significantly reduced the incidence of endpoint events at 96 hours, 7 days and 30 days (Table 8).

Although there was no CEC assessment of myocardial infarction after 30 days, analysis of the incidence of death/investigator-assessed myocardial infarction revealed a sustained reduction of clinical events at 6 months (see Table 9 and Figure 2).

The difference in efficacy between eptifibatide and placebo was due primarily to differences in the rate of myocardial infarction, with a relatively small contribution from reduced mortality.

Results by gender, age, weight and race are provided in Figure 1 below. Significant clinical benefit was not demonstrated in women, patients under the age of 50 and those weighing less than 74 kg.

Fig 1. Odds ratios and 95% confidence intervals for incidence of death and CEC Adjudicated MI at 30 days by gender, age (y) weight (kg) and race: Eptifibatide vs placebo (treated as randomised data set).



Compared to placebo, eptifibatide was associated with an excess of major bleeding episodes (10.8% vs 9.3%), minor bleeding episodes (13.1% vs 7.6%) and transfusions (12.8% vs 10.4%).

CEC-assessed myocardial infarctions were identified by a computer program which flagged elevated CK test results as well as other variables (e.g., patient symptoms, ECG data). As a result, approximately half the myocardial infarctions in the endpoint "CEC-assessed MI" were not clinically evident.

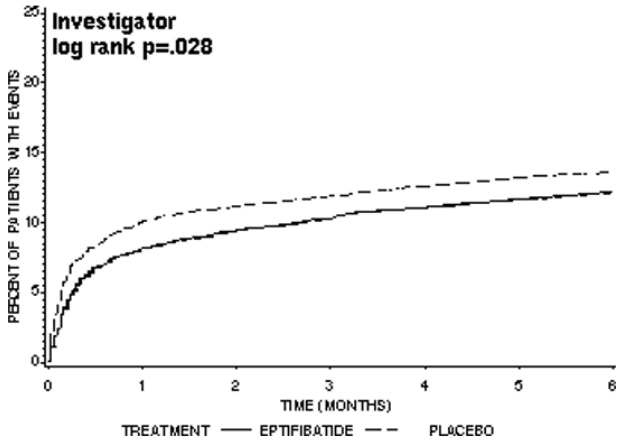
Table 8. Incidence of death/CEC-assessed MI ("treated as randomised" data set)				
Time	Placebo (n=4697)	Eptifibatide (n=4680)	p-Value	95% CI[b]
96 hours	427 (9.1%)	356 (7.6%)	0.009[a]	0.711 to 0.954
7 days	550 (11.7%)	472 (10.1%)	0.012[a]	0.742 to 0.963
30 days	743 (15. 8%)	667 (14.3%)	0.034[a]	0.790 to 0.991

a: Pearson's chi-square test of difference between placebo and eptifibatide.
b: Confidence Intervals (CIs) are for the odds ratios; ratios less than 1 favour eptifibatide.

Table 9. Incidence of death/investigator-assessed MI ("treated as randomised" data set)				
Time	Placebo (n=4697)	Eptifibatide (n=4680)	p-Value	95% CI
96 hours	236 (5.0%)	156 (3.3%)	<0.001[a]	0.530 to 0.801[d]
7 days	320 (6.8%)	226 (4.8%)	<0.001[a]	0.582 to 0.827[d]
30 days	471 (10.0%)	378 (8.1%)	0.001[a]	0.684 to 0.909[d]
6 months	636 (13.6%)[b]	567 (12.2%)[b]	0.028[c]	0.787 to 0.987[e]

a: Pearson's chi-square test of difference between placebo and eptifibatide.
b: Kaplan-Meier estimate of incidence using available information from each patient from randomisation to time of last contact.
c: Log-rank test based on Kaplan-Meier estimates.
d: Confidence Intervals (CIs) are for the odds ratios; ratios less than 1 favour eptifibatide.
e: Confidence Interval (CI) is for the Kaplan-Meier hazard ratio; a ratio less than 1 favours eptifibatide.

Fig 2. Kaplan-Meier plot of time to death/MI after enrolment as assessed by the investigators for 6 months (treated as randomised data set).



ESPRIT trial: (PCI with stenting)

ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Eptifibatide Therapy) was a pivotal trial for nonurgent PCI with intracoronary stenting. This was a 92-centre, double- blind, randomised, placebo-controlled trial conducted in the United States and Canada in 2,064 patients scheduled to undergo non-urgent PCI with stent implantation in native coronary vessels. Patients were excluded from the trial if treatment had been planned with a GP IIb/IIIa inhibitor prior to the PCI. Other reasons for exclusion were: if the patient had a myocardial infarction within the previous 24 hours before randomisation, ongoing chest pain (or anginal equivalent) leading to urgent referral, PCI within the previous 90 days before randomisation or prior stent in the target lesion.

All patients received routine standard of care. Patients were randomised to either placebo or eptifibatide, two bolus doses of 180 µg/kg and a continuous infusion until discharge from hospital

or a maximum of 18-24 hours. The first bolus injection and the infusion were started simultaneously, immediately before the PCI procedure. The second bolus was administered 10 minutes after the first bolus. The rate of infusion was 2.0 µg/kg/min for patients with serum creatinine < 175 µmol/L or 1.0 µg/kg/min for serum creatinine > 175 up to 350 µmol/L. Additionally, for any patient considered to be at high risk of bleeding, the infusion rate was allowed to be decreased to 0.5 µg/kg/min; however the standard infusion dose was to have been continued for at least 12 hours. In addition, investigators had the option to discontinue study medication and start open-label eptifibatide in the event of procedural complications, such as abrupt closure, no reflow or coronary thrombosis (defined as acute antithrombotic rescue therapy). A kit was provided that contained blinded trial drug for bolus administration, enabling investigators to switch their patients to open-label eptifibatide without unblinding the initial treatment regimen.

The vast majority of patients received concomitant aspirin (162 - 325 mg before the procedure and daily thereafter) and the majority received a loading dose of clopidogrel (or ticlopidine) before the PCI. All patients received clopidogrel 75 mg daily or ticlopidine 250 mg twice daily after stent implantation.

The ESPRIT trial used a simplified regimen of heparin dosing during PCI as compared to the PURSUIT trial where urgent PCI was performed. For those patients not treated with heparin in the 6 hours before PCI, an initial bolus of 60 U/kg was recommended. The target ACT during the procedure was 200-300 seconds. A heparin infusion regimen after the PCI was discouraged and the early removal of the vascular access sheath (approximately 4 hours after PCI) was suggested. In patients requiring a heparin infusion after PCI however, heparin was administered at a rate of 10 U/kg/hour or 800 U/hour, whichever was less. An aPTT was obtained within 4 hours of starting the heparin infusion with an aPTT target of 50-70 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. An independent, blinded Clinical Events Committee was responsible for adjudicating suspected endpoint events, including MI, UTVR and acute antithrombotic rescue therapy.

During this trial, MI was defined as an “enzymatic” or “adjudicated investigator” MI.

Enzymatic MI was identified per the CK/CK-MB core laboratory criteria. Within 24 hours after the index PCI procedure, MI occurred if there was at least two CK-MB values ≥ 3x the upper limit of normal. Myocardial infarction meeting this criterion were not adjudicated.

Adjudicated MI is an investigator reported MI, confirmed as MI after adjudication by the CEC. [The investigators were blinded to the results of the core CK-MB values.]

Eptifibatide significantly reduced the incidence of the primary endpoint (Table 10). This benefit occurred early (within 12 hours) and was principally attributed to a reduction in MI.

Secondary endpoints of the trial included D, MI, UTVR and RT at 30 days, and D and MI at 30 days (Table 10).

The reduction in individual components, D, MI, UTVR, of the endpoints at 48 hours and 30 days is shown in Table 11. For the individual components, statistical significance between eptifibatide and placebo was reached for MI only.

Table 10. Events (%) at 48 hours, seven days and 30 days			
Time	**Placebo** N = 1,024	**Eptifibatide** N = 1,040	**p-Value**
Primary End-Point (D, MI, UTVR/RT)			
48 Hours	10.5 % (108)	6.6 % (69)	0.0015
7 days	11.1 % (114)	7.2 % (75)	0.002
30 days	11.7 % (120)	7.25 % (78)	0.001
D and / or MI only			
48 Hours	9.2 % (94)	5.5 % (57)	0.0013
7 days	9.7 % (99)	6.1 % (63)	0.002
30 days	10.2 % (104)	6.3 % (66)	0.002
D/MI/UTVR			
30 days	10.4 % (107)	6.8 % (71)	0.0034

Table 11. Individual components of the endpoints at 48 hours and 30 days			
Time	**Placebo** N = 1,024	**Eptifibatide** N = 1,040	**p-Value**
Death			
48 Hours	0.2 % (2)	0.1 % (1)	0.5544
30 days	0.6% (6)	0.4 % (4)	0.5102
MI			
48 Hours	9.0 % (92)	5.4 % (56)	0.0015
30 days	9.7 % (99)	6.2 % (64)	0.0031
UTVR			
48 hours	1.0 % (10)	0.6% (6)	0.3006
30 days	1.7 % (17)	1.1 % (11)	0.2368

An independent data safety monitoring committee (DSMC) for the ESPRIT Trial recommended that the trial be terminated prematurely because the data demonstrated overwhelming efficacy in the absence of a safety concern.

5.2 Pharmacokinetic properties

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.

Absorption

Eptifibatide is dosed intravenously and therefore is immediately and completely bioavailable.

Distribution

In patients with coronary artery disease, the volume of distribution of approximately 185 to 260 mL/kg. During administration of the recommended treatment regimen, plasma concentrations of eptifibatide peak immediately after the 180 microgram/kg bolus and decline to a mean steady state level of 2.2 microgram/mL within 4-6 hours after commencement of the 2.0 microgram/kg/min infusion. The extent of eptifibatide binding to human plasma protein is about 25%.

Metabolism

No major metabolites have been detected in human plasma, but deamination takes place in the urine.

Excretion

In patients with coronary artery disease, the mean plasma clearance of eptifibatide is estimated to be 55 to 80 mL/kg/hr and plasma elimination half-life is approximately 2.5 hours, In healthy subjects, renal excretion accounted for approximately 50% of total body clearance.

A modest increase in half-life and volume of distribution is seen with increased age, decreased weight (< 74 kg) and/or decreased creatinine clearance (CrCl). The pharmacokinetics are unaffected by dose and gender. No dose adjustment of the bolus or infusion is required in the case of mild renal impairment (CrCl ≥ 50 mL/min using the Cockcroft-Gault equation*). Dose adjustment is recommended for cases of moderate to severe renal impairment (CrCl < 50 mL/min using the Cockcroft-Gault equation*). In patients with moderate to severe renal insufficiency (CrCl < 50 mL/min), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels are approximately doubled (see sections 4.4 and 4.2).

Pre-clinical data

In vitro studies of the inhibition of ADP-induced platelet aggregation by eptifibatide showed marked species differences, with much higher concentrations of eptifibatide required for inhibition of platelet aggregation in rats and rabbits than in monkeys and humans.

Toxicology studies conducted with eptifibatide included single dose studies in the rat, rabbit and monkey, repeat-dose studies in the rat and monkey, reproduction studies in the rat and rabbit, and irritation, hypersensitivity and antigenicity studies.

The preclinical acute and repeat dose toxicity studies have been conducted in only one animal species possessing a suitable GPIIb-IIIa receptor, namely the monkey. No unexpected toxic effects for an agent with this pharmacological profile were observed and findings were predictive of clinical experience, with bleeding and haemorrhages occurring in monkeys at high doses of eptifibatide. There were no effects in rats and rabbits. In the monkey, tissue and organ haemorrhages were seen at plasma eptifibatide concentrations approximating those attained in humans during therapy with the recommended dose.

Preclinical studies of the concurrent use of eptifibatide with heparin and aspirin were not conducted.

5.3 Preclinical safety data

Genotoxicity

Eptifibatide showed no evidence of genotoxicity in a series of assays for gene mutations and chromosomal damage.

Carcinogenicity

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

6. Pharmaceutical Particulars

6.1 List of excipients

Eptifibatide Viatris also contains:

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

6.2 Incompatibilities

Eptifibatide is not compatible with furosemide.

There are no data on the use of eptifibatide in combination with dextran.

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

3 years.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze.) Protect from light until administration.

6.5 Nature and contents of container

Type I glass vial with rubber closure and crimp seal.
Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements. Discard any unused material after opening.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

10 November 2016

10. Date of Revision of the Text

16 January 2024

Summary table of changes

Section	Summary of new information
4.2	Reworded sections. Additional information on use with aspirin. Relocated information from Method of administration to beginning of section and included statement on limited study in patients with severe renal insufficiency.

	Additional information on administration (relocated from section 6.6). Statement added on mixing with other medicinal products. Statement added about single use only.
4.3	Addition of concomitant or planned administration of a thrombolytic agent.
4.4	Addition of prolongation of bleeding time. Additional information under Thrombocytopaenia and immunogenicity related to GP IIb/IIIa inhibitors. Reworded sections.
4.5	Additional information on low potential for interaction with common used agents in patients with cardiac conditions. Additional caution with ticlopidine and clopidogrel.
4.6	Addition of increased incidence of foetal loss and prematurity may be associated with maternal haemorrhage. Additional information on reproductive studies in animals.
4.7	Addition of eptifibatide is intended for use in hospitalised patients.
4.8	Addition of adverse events tables from clinical studies. Updated reporting URL for suspected adverse reactions.
5.1	Reworded sections. Additional information related to clinical studies.
5.2	Additional information on distribution, metabolism and excretion. Additional pre-clinical data.
5.3	Removed animal toxicology and teratology study information as covered under section 4.6.
6.6	Relocated administration information to section 4.2.
10	Updated date of revision of text.