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

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.

If the patient requires emergency or urgent cardiac surgery during the course of 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 the Cockcroft-Gault equation with actual body weight to calculate the estimated creatinine clearance in mL/min:

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

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

Use with heparin

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

- Unstable angina or non-Q-wave myocardial infarction: 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. There may be an increased risk of bleeding if aPTT values are greater than 70 seconds.

- If PCI is to be performed in the setting of UA/NQMI, monitor the 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

This product is for hospital use only, by specialist physicians experienced in the management of acute coronary syndromes or PCI.

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

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. See section 6.6.

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;
- a 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 (< 100,000 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);
- dependency on renal dialysis;
- clinically significant hepatic impairment;
- 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

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 heparin that is given concomitantly should be stopped immediately. During the marketing of eptifibatide, very rare cases of fatal bleeding have been reported.

Because eptifibatide inhibits platelet aggregation, caution must be employed when it is used with other medicinal products that affect haemostasis, including thrombolytics, oral anticoagulants, dextran solutions, adenosine, low molecular weight heparins, sulfinpyrazone, prostacyclin, non-steroidal anti-inflammatory agents, dipyridamole, ticlopidine and clopidogrel.

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

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.

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 intra-aortic balloon pump.

If serious bleeding occurs that is not controllable with pressure, immediately stop the eptifibatide infusion 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.

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 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.

If either a confirmed platelet count decrease to < 100,000/mm^3 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.

Heparin administration

Eptifibatide should be administered in conjunction with heparin (see section 4.2) unless a contraindication to the use of this drug (such as a history of thrombocytopenia associated with use of heparin) is present.

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).

Renal impairment

Eptifibatide may be administered at the standard dose to patients with mild renal impairment (creatinine clearance ≥ 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 no clinical trial experience in patients dependant on dialysis.

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. 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, also measure the ACT.

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

Paediatric population

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.

4.5 Interaction with other medicines and other forms of interaction

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 PT > 14.5 seconds and received warfarin concomitantly did not appear to be at an increased risk of bleeding.

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, however, eptifibatide appeared to increase the risk of bleeding when administered with streptokinase in an acute myocardial infarction study.

In an acute myocardial infarction study involving 181 patients, eptifibatide (in regimens up to a bolus injection of 180 µg/kg, followed by an infusion up to 2 µg/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 µg/kg/min and 2.0 µg/kg/min) studied, eptifibatide was associated with an increased incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone.

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

See also section 4.4, Bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical studies with eptifibatide have been conducted in pregnant women. Reproduction studies in an animal species where eptifibatide shows a similar pharmacological activity as in humans are not available. Therefore, the use of eptifibatide during pregnancy is recommended only if the benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether eptifibatide is excreted in human milk. Breast feeding should be interrupted during the treatment period.

Fertility

Eptifibatide had no effect on the fertility of male and female rats at doses of 72 mg/kg/day IV. At the highest doses tested in rats and rabbits, eptifibatide demonstrated no evidence of reproductive toxicity.

4.7 Effects on ability to drive and use machines

No data available.

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 occurred 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 ≥ 9%, or a drop in haemoglobin of ≥ 3 g/dL.

PURSUIT trial (unstable angina and non-Q-wave myocardial infarction)

The most common bleeding complications were associated with cardiac invasive procedures (CABG or at femoral artery access site). Major bleeding was infrequent in the PURSUIT trial in the large majority of patients who did not undergo CABG within 30 days of enrolment.

Minor bleeding (TIMI criteria) was the most common complication of eptifibatide administration (13.1% eptifibatide vs 7.6% placebo at 30 days). CABG related events were the most common (2.8% eptifibatide vs 2.7% placebo). Minor bleeding (> 1% eptifibatide group) included genitourinary, femoral artery access, oral/oropharyngeal and gastrointestinal; haemoglobin/haematocrit decreases were reported. Bleeding events were more frequent in patients receiving concurrent heparin while undergoing PCI, when ACT exceeded 350 seconds (see section 4.2, Use with heparin).

Major bleeding (TIMI criteria) was reported more frequently in patients treated with eptifibatide (10.8% eptifibatide vs 9.3% placebo). However, eptifibatide did not appear to increase the risk for intracranial bleeding, which was reported rarely (0.1% eptifibatide vs 0.06% placebo). Bleeding incidence was not increased with eptifibatide as compared with placebo in patients who underwent CABG surgery (6.7% vs 6.5% placebo). Major bleeding (> 1% eptifibatide group) included femoral

artery access, oral/oropharyngeal, and gastrointestinal; haemoglobin/haematocrit decreases were reported. Genitourinary, retroperitoneal and intracranial bleeding was less common.

The incidence of severe or life-threatening bleeding events with eptifibatide was 1.9% eptifibatide vs 1.1% with placebo. Eptifibatide treatment modestly increased the need for blood transfusions (11.8% eptifibatide vs 9.3% placebo).

In the subgroup of patients in the PURSUIT trial, who underwent PCI, major bleeding was observed in 9.7% of eptifibatide-treated patients vs 4.6% treated with placebo.

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). 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 uncommon (1.4% eptifibatide vs 0.4% placebo (48 hours)). Eptifibatide did not increase the risk of intracranial bleeding, which was uncommon (0.2% eptifibatide vs 0.1% placebo). Bleeding incidence was not 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.

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).

Other undesirable effects

Commonly reported events (occurring in ≥ 2% across all groups) in PURSUIT were events related to the underlying disease, such as atrial fibrillation, hypotension, congestive heart failure, cardiac arrest and shock. Less common events (occurring in ≥ 1% across all groups) were phlebitis, ventricular fibrillation, atrioventricular block and ventricular tachycardia. There were rare events of cerebral ischaemia (0.4% eptifibatide vs 0.5% placebo).

Additional adverse events 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 https://nzphvc.otago.ac.nz/reporting/.

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 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 µg/kg intravenous bolus. When followed by a 2.0 µg/kg/min continuous infusion, this regimen produces a > 80% inhibition of ADP-induced *ex vivo* platelet aggregation, at physiological 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 µg/kg/min. Measurements 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 approximately 550 ng/mL and an IC_{80} (80% inhibitory concentration) of approximately 1,100 ng/mL.

Administration of eptifibatide by intravenous bolus and infusion causes up to a 5-fold increase in bleeding time. When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

5.2 Pharmacokinetic properties

Absorption

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

Distribution, Biotransformation, Elimination and Linearity/non-linearity

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. The extent of

eptifibatide binding to human plasma protein is about 25%. 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. In healthy subjects, renal excretion accounted for approximately 50% of total body clearance; approximately 50% of the amount cleared is excreted unchanged. 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).

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 pharmacological 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 pharmacological activity as in humans are not available. Consequently, these studies are not suitable to evaluate the toxicity of eptifibatide on reproductive function.

Carcinogenicity and mutagenicity

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

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

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.

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.

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

1 November 2021

Summary table of changes

Section	Summary of new information
All	Revise to SPC format
All	Product name updated to Eptifibatide Viatris
4.5	Addition of cross-reference to section 4.4
5.2	Addition of pharmacokinetic information
8	Sponsor details updated