
REOPRO[®]

abciximab (rnc)

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

REOPRO[®] abciximab (rnc) 2 mg/mL solution for injection vials.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REOPRO vial 5 mL contains 10 mg abciximab (rnc).

Excipient(s) with known effect

The total sodium content is approximately 3.45 mg/mL.

For a full list of excipients, see **section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

REOPRO is a clear, colourless, sterile solution for intravenous use.

REOPRO is formulated in a buffered aqueous solution (pH 7.2).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REOPRO is indicated as an adjunct to heparin and aspirin for:

1. Percutaneous coronary intervention: The prevention of ischaemic cardiac complications (death, myocardial infarction or need for urgent intervention) in patients during or following percutaneous coronary intervention (balloon angioplasty, atherectomy and stent placement).
2. Unstable angina: The stabilisation of unstable angina patients not responding to conventional medical therapy who may be candidates for percutaneous coronary intervention.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

The recommended dose of REOPRO is a 0.25 mg/kg intravenous bolus immediately followed by a 0.125 µg/kg/min (to a maximum of 10 µg/min) continuous intravenous infusion. For the stabilisation of unstable angina patients, the bolus dose followed by the infusion should be started up to 24 hours prior to the possible intervention.

For the prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention, and who are not currently receiving a REOPRO infusion, the bolus should be administered 10 to 60 minutes prior to the intervention followed by the infusion for 12 hours.

Children or Patients Aged Over 80 Years

There is no experience on the use of REOPRO in children or in patients aged over 80 years.

Administration Instructions

DO NOT SHAKE VIALS.

1. Parenteral medicine products should be inspected visually for particulate matter prior to administration. Preparations of REOPRO containing visibly opaque particles should NOT be used.
2. Hypersensitivity reactions should be anticipated whenever protein solutions such as REOPRO are administered. Adrenaline, dopamine, theophylline, antihistamines and corticosteroids should be available for immediate use. If symptoms of an allergic reaction or anaphylaxis appear, the infusion should be stopped immediately. Subcutaneous administration of 0.3 to 0.5 mL of aqueous adrenaline (1:1000 dilution), and use of corticosteroids, respiratory assistance and other resuscitative measures are essential.
3. As with all parenteral medicine products, aseptic procedures should be used during the administration of REOPRO.
4. Withdraw the necessary amount of REOPRO for the bolus injection into a syringe. Filter the bolus injection using a sterile, non-pyrogenic, low protein-binding 0.2/0.22 µm or 5.0 µm syringe filter. The bolus should be administered over one (1) minute.
5. Withdraw the necessary amount of REOPRO for the continuous infusion into a syringe. Inject into an appropriate container of sterile 0.9% saline or 5% dextrose and infuse at the calculated rate via a continuous infusion pump. The continuous infusion should be filtered either upon admixture using a sterile, non-pyrogenic, low protein-binding 0.2/0.22 µm or 5.0 µm syringe filter or upon administration using an in-line, sterile, non-pyrogenic, low protein-binding 0.2 µm or 0.22 µm filter. Discard the unused portion at the end of the infusion period.
6. Although incompatibilities have not been shown with intravenous infusion fluids or commonly used cardiovascular medicines, it is recommended that REOPRO be administered in a separate intravenous line whenever possible and not mixed with other medications.
7. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags or administration sets.

4.3 CONTRAINDICATIONS

REOPRO should not be administered to patients with known sensitivity to abciximab, to any component of the product or to murine monoclonal antibodies.

Because inhibition of platelet aggregation increases the risk of bleeding, REOPRO is contraindicated in the following clinical situations: active internal bleeding; history of cerebrovascular accident within two years; recent (within two months) intracranial or intraspinal surgery or trauma; recent (within two months) major surgery; intracranial neoplasm, arteriovenous malformation or aneurysm; known bleeding diathesis or severe uncontrolled hypertension; pre-existing thrombocytopenia; vasculitis; hypertensive or diabetic retinopathy; severe hepatic or severe renal failure.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Administration of REOPRO may be associated with an increase in bleeding events, rarely including those with a fatal outcome. Careful assessment of risk:benefit should be made in individual patients before commencing therapy with REOPRO.

Requirement for Specialist Facilities: REOPRO should only be administered in conjunction with extensive specialist medical and nursing care. In addition, there must be availability of laboratory tests of haematology function and facilities for administration of blood products.

Concomitant Aspirin and Heparin Therapy

REOPRO should be used as an adjunct to aspirin and heparin therapy.

Aspirin

Aspirin should be administered orally at a daily dose of approximately but not less than 300 mg.

Heparin

1. Percutaneous Coronary Intervention

Heparin Bolus Pre-PTCA

If a patient's activated clotting time (ACT) is less than 200 seconds prior to the start of the PTCA procedure, an initial bolus of heparin should be given upon gaining arterial access according to the following algorithm:

ACT < 150 seconds: administer 70 U/kg

ACT 150-199 seconds: administer 50 U/kg

The initial heparin bolus dose should not exceed 7,000 U.

ACT should be checked a minimum of 2 minutes after the heparin bolus. If the ACT is < 200 seconds, additional heparin boluses of 20 U/kg may be administered. Should the ACT remain < 200 seconds, additional 20 U/kg boluses are to be given until an ACT greater than or equal to 200 seconds is achieved.

Should a situation arise where higher doses of heparin are considered clinically necessary in spite of the possibility of a greater bleeding risk, it is recommended that heparin be carefully titrated using weight-adjusted boluses and that the target ACT not exceed 300 seconds.

Heparin Bolus during PTCA

During the PTCA procedure, ACT should be checked every 30 minutes. If ACT is < 200 seconds, additional heparin boluses of 20 U/kg may be administered. Should the ACT remain < 200 seconds, additional 20 U/kg boluses may be given until an ACT greater than or equal to 200 seconds is achieved. ACT should be checked prior to and a minimum of 2 minutes after each heparin bolus.

As an alternative to giving additional boluses as described above, a continuous heparin infusion may be initiated after the initial heparin bolus doses achieve the ACT target greater than or equal to 200 seconds at a rate of 7 U/kg/hour and continued for the duration of the procedure.

Heparin Infusion after PTCA

Discontinuation of heparin immediately following completion of the procedure, with removal of the arterial sheath within 6 hours, is *strongly recommended*. In individual patients, if prolonged heparin therapy after PTCA or later sheath removal is used, then an initial infusion rate of 7 U/kg/hr is recommended (see **section 4,4 Special warnings and precautions for use - Bleeding Precautions, Femoral Artery Sheath Removal**). In all circumstances, heparin should be discontinued at least 2 hours prior to arterial sheath removal.

2. Stabilisation of Unstable Angina

Anticoagulation should be initiated with heparin to a target APTT of 60-85 seconds. The heparin infusion should be maintained during the REOPRO infusion. Following angioplasty, heparin management is outlined above under 1. Percutaneous Coronary Intervention.

Bleeding Precautions

Femoral Artery Access Site

REOPRO is associated with an increase in bleeding rate particularly at the site of arterial access for femoral artery sheath placement. The following are specific recommendations for access site care:

Femoral Artery Sheath Insertion

- When appropriate, place only an arterial sheath for vascular access (avoid venous sheath placement)
- Puncture only the anterior wall of the artery or vein when establishing vascular access
- The use of a through and through technique to identify the vascular structure is *strongly discouraged*

While Femoral Artery Sheath Is In Place

- Check sheath insertion site and distal pulses of affected leg(s) every 15 minutes for 1 hour, then hourly for 6 hours
- Maintain complete bed rest with head of bed less than or equal to 30°
- Maintain affected leg(s) straight via sheet tuck method or soft restraint
- Medicate for back/groin pain as necessary
- Educate patient on post-PTCA care via verbal instructions

Femoral Artery Sheath Removal

- Heparin should be discontinued at least 2 hours prior to arterial sheath removal
- Check APTT or ACT prior to arterial sheath removal: do not remove sheath unless APTT less than or equal to 50 seconds or ACT less than or equal to 175 seconds
- Apply pressure to access site for at least 30 min following sheath removal, using either manual compression or a mechanical device
- Apply pressure dressing after haemostasis has been achieved

After Femoral Artery Sheath Removal

Check groin for bleeding/haematoma and distal pulses every 15 minutes for the first hour or until stable, then hourly for 6 hours following sheath removal

- Continue complete bed rest with head of bed less than or equal to 30° and affected leg(s) straight for 6-8 hours following femoral artery sheath removal, 6-8 hours following discontinuation of REOPRO or 4 hours following discontinuation of heparin, whichever is later
- Remove pressure dressing prior to ambulation
- Continue to medicate for discomfort

Management of Femoral Access Site Bleeding/Haematoma Formation

In the event of groin bleeding with or without haematoma formation, the following procedures are recommended:

- Lower head of bed to 0°
- Apply manual pressure/compression device until haemostasis has been achieved
- Any haematoma should be measured and monitored for enlargement
- Change pressure dressing as needed
- If heparin is being given, obtain APTT and adjust heparin as needed
- Maintain intravenous access if sheath has been removed

If groin bleed continues or the haematoma expands during REOPRO infusion despite the above measures, the REOPRO infusion should be immediately discontinued and the arterial sheath removed according to the guidelines listed above. After sheath removal intravenous access should be maintained until bleeding is controlled (see **section 4.9 Overdose – Uncontrolled bleeding**).

Potential Bleeding Sites

Careful attention should be paid to all potential bleeding sites, including arterial and venous puncture sites, catheter insertion sites, cutdown sites, and needle puncture sites.

Retroperitoneal Bleeding

REOPRO is associated with an increased risk of retroperitoneal bleeding in association with femoral vascular puncture. The use of venous sheaths should be minimised and only the anterior wall of the artery or vein should be punctured when establishing vascular access (see **section 4.4 Special warnings and precautions for use – Bleeding Precautions, Femoral Artery Access Site**).

GI Bleeding Prophylaxis

In order to prevent spontaneous GI bleeding it is recommended that patients are pretreated with H₂-histamine receptor antagonists or liquid antacids. Antiemetics should be given as needed to prevent vomiting.

General Nursing Care

Unnecessary arterial and venous punctures, intramuscular injections, routine use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs should be avoided. When obtaining intravenous access, non-compressible sites (e.g. subclavian or jugular veins) should be avoided. Saline or heparin locks should be considered for blood drawing. Vascular puncture sites should be documented and monitored. Gentle care should be provided when removing dressings.

Patient Monitoring

Before administration of REOPRO, platelet count, ACT, prothrombin time (PT) and APTT should be measured to identify pre-existing coagulation abnormalities. Haemoglobin and haematocrit measurements should be obtained prior to the REOPRO administration, at 12 hours following the REOPRO bolus injection, and again at 24 hours following the bolus injection. Twelve lead electrocardiograms (ECG) should be obtained prior to the bolus injection of REOPRO, and repeated once the patient has returned to the hospital ward from the catheterisation laboratory, and at 24 hours after the bolus injection of REOPRO. Vital signs (including blood pressure and pulse) should be obtained hourly for the first 4 hours following the REOPRO bolus injection, and then at 6, 12, 18 and 24 hours following the REOPRO bolus injection.

Restoration of Platelet Function

Transfusion of donor platelets has been shown to restore platelet function following REOPRO administration in animal studies and transfusions of fresh random donor platelets have been given empirically to restore platelet function in humans. In the event of serious uncontrolled bleeding or the need for emergency surgery, REOPRO should be discontinued. In the majority of patients, bleeding time returns to 12 minutes within 12 hours. A bleeding time should be determined by the Ivy method (see below). If the bleeding time remains greater than 12 minutes, 10 units of platelets may be given. REOPRO may be displaced from endogenous platelet receptors and subsequently bind to platelets which have been transfused. Nevertheless, a single transfusion may be sufficient to reduce receptor blockade to 60% to 70% at which level platelet function is restored. Repeat platelet transfusions may be required to maintain the bleeding time at or below 12 minutes.

Ivy Method for Determination of Bleeding Time

Using an automated incision template, make a small incision on the lateral volar surface of the forearm while maintaining 40 mmHg pressure on the arm with a sphygmomanometer cuff. Determine the time for bleeding to stop with a stopwatch. Every 15 to 30 seconds a filter

paper should be used to capture the blood from the incision but should not come in contact with the incision.

Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents

Because REOPRO inhibits platelet aggregation, caution should be employed when used with other medicines affecting haemostasis such as heparin, oral anticoagulants such as warfarin, thrombolytics and antiplatelet agents other than aspirin, such as dipyridamole, ticlopidine or low molecular weight dextrans (see **section 4.5 Interaction with other medicines and other forms of interaction**).

There are limited data on the use of REOPRO in patients receiving thrombolytic agents. However, these data suggest an increase in the risk of bleeding when REOPRO is administered to patients treated with thrombolytics at doses sufficient to produce a systemic fibrinolytic state. If urgent intervention is required for refractory symptoms in a patient receiving REOPRO (or who has received the medicine in the previous 48 hours), it is recommended that PTCA be attempted first to salvage the situation. Prior to further surgical interventions, the bleeding time should be determined by the Ivy method (see above) and should be 12 minutes or less. Should PTCA and any other appropriate procedures fail, and should the angiographic appearance suggest that the aetiology is due to thrombosis, consideration may be given to the administration of adjunctive thrombolytic therapy via the intracoronary route. A systemic fibrinolytic state should be avoided.

Thrombocytopenia

Thrombocytopenia, including severe thrombocytopenia, has been observed with REOPRO administration (see **section 4.8 Undesirable effects**). To reduce the possibility of thrombocytopenia, platelet counts should be monitored prior to treatment, 2 to 4 hours following the bolus dose of REOPRO, at 24 hours, and periodically for 2 weeks. If a patient experiences an acute platelet decrease, additional platelet counts should be determined. These platelet counts should be drawn in three separate tubes containing ethylenediaminetetraacetic acid (EDTA), citrate and heparin, respectively, to exclude pseudothrombocytopenia due to *in vitro* anticoagulant interaction. If true thrombocytopenia is verified, REOPRO should be immediately discontinued and the condition appropriately monitored and treated. A daily platelet count should be obtained until it returns to normal. If a patient's platelet count drops to 60,000 cells/ μ L, heparin and aspirin should be discontinued. If a patient's platelet count drops below 50,000 cells/ μ L, platelets should be transfused.

Readministration

There are limited data concerning readministration of REOPRO. Human antichimeric antibody (HACA) appears, generally as a low titre, in approximately 5% to 6% of patients after single administrations of REOPRO (see **section 4.8 Undesirable effects**). Available evidence suggests that human antibodies to other monoclonal antibodies do not cross-react with REOPRO. Readministration of REOPRO to 29 patients known to be HACA-negative has not led to any change in REOPRO pharmacokinetics or to any reduction in antiplatelet potency. Nevertheless, the possibility of allergic or hypersensitivity reactions or diminished benefit cannot be excluded when REOPRO is administered to patients who have previously received monoclonal antibody therapy.

Renal Disease and Peripheral Vascular Disease

Benefits may be reduced in patients with renal disease or peripheral vascular disease.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

REOPRO has been formally studied as an adjunct to heparin and aspirin treatment. In the presence of REOPRO, heparin is associated with an increase in the incidence of bleeding. Although there have been no formal studies of REOPRO with other commonly used cardiovascular medicines, in clinical studies there have been no adverse medicine reactions associated with concomitant use of other medications used in the treatment of angina, myocardial infarction or hypertension nor with common intravenous infusion fluids. These medications have included warfarin (before and following but not during PTCA), beta-adrenergic receptor blockers, calcium channel antagonists, angiotensin converting enzyme (ACE) inhibitors, and intravenous and oral nitrates.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Animal reproduction studies have not been conducted with REOPRO. It is also not known whether REOPRO can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. REOPRO should be given to a pregnant woman only if clearly needed.

Breastfeeding Breast feeding of infants should be discontinued in nursing mothers since the secretion of abciximab in animal or human breast milk has not been studied.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable

4.8 UNDESIRABLE EFFECTS

In the EPIC trial, in which a non-weight-adjusted, standard heparin dose regimen was used, the most common complication during REOPRO therapy was bleeding during the first 36 hours. The incidences of major bleeding¹, minor bleeding² and transfusion of blood products were approximately doubled. In patients who had major bleeding, 67% had bleeding associated with the arterial access site in the groin.

In a subsequent clinical trial, EPILOG, using the heparin regimen, sheath removal and femoral access care guidelines outlined in the section on Warnings and Precautions, the incidence of major bleeding in patients treated with REOPRO (1.8%) was not significantly different from patients receiving placebo (3.1%) and there was no significant increase in the incidence of intracranial haemorrhage. The reduction in major bleeding observed in the EPILOG trial was achieved without loss of efficacy.

Although data are limited, REOPRO treatment was not associated with excess major bleeding in patients who underwent CABG surgery. Some patients with prolonged bleeding times received platelet transfusions to correct the bleeding time prior to surgery (see **section 4.4 Special warnings and precautions for use – Restoration of Platelet Function**).

The total incidence of intracranial haemorrhage and non-haemorrhagic stroke in all three pivotal trials was similar, 7/2225 (0.31%) for placebo patients and 10/3112 (0.32%) for REOPRO treated patients. The incidence of intracranial haemorrhage was 0.13% in placebo patients and 0.19% in REOPRO patients.

The most frequent adverse events are back pain, hypotension, nausea, chest pain, vomiting, headache pain, bradycardia, fever, puncture site pain, thrombocytopenia, abdominal pain and peripheral oedema. Human antichimeric antibody (HACA) appears, generally as a low titre, in approximately 5% to 6% of patients after 2 to 4 weeks. Hypersensitivity or allergic reactions have been observed rarely following treatment with REOPRO. Nevertheless, anaphylaxis may

potentially occur at any time during administration (see **section 4.2 Dose and method of administration – Administration Instructions**).

¹ Decrease in haemoglobin > 5 g/dL

² Spontaneous gross haematuria or haematemesis, or observed blood loss with a haemoglobin decrease > 3 g/dL or with a decrease in haemoglobin greater than or equal to 4 g/dL with no observed blood loss

Postmarketing experience

In addition to the clinical trials safety data described above, spontaneous adverse events from the worldwide postmarketing experience with REOPRO are listed below. The spontaneous adverse drug reactions are ranked by frequency according to the following convention: Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1 000, <1/100); Rare (>1/10 000, <1/1 000); Very rare (<1/10 000 including isolated reports). The frequency provided is a reflection of reporting rates for spontaneous adverse drug reactions and does not represent true incidence or frequency as seen with clinical trials or epidemiologic studies.

Blood and Lymphatic System Disorders: rare – fatal bleeding

Gastrointestinal Disorders: very rare – gastrointestinal haemorrhage NOS

Immune System Disorders: very rare – anaphylactic reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

There has been no experience of adverse events associated with overdosage. However, in the event of acute allergic reactions, thrombocytopenia or uncontrolled bleeding the administration of REOPRO should be immediately discontinued. In the event of thrombocytopenia or uncontrolled bleeding, platelet transfusion is recommended.

For advice on the management of overdose please contact the National Poisons Center on 0800 POISON (0800 764766).

Allergic reactions

See **section 4.4 Special warnings and precautions for use – Administration Instructions**.

Thrombocytopenia

See **section 4.4 Special warnings and precautions for use**.

Uncontrolled Bleeding

(Specific guidelines for access site bleeding are given above under **section 4.4 Special warnings and precautions for use – Bleeding Precautions, Femoral Artery Access Site**.) When considering the need to transfuse patients, the patient's intravascular volume should be assessed. If hypovolaemic, intravascular volume should be adequately restored with crystalloids. In asymptomatic patients, normovolaemic anaemia (haemoglobin 7-10 g/dL) can be well tolerated; transfusion is not indicated unless a deterioration in vital signs is seen or unless the patient develops signs and symptoms. In symptomatic patients (e.g., syncope, dyspnoea, postural hypotension, tachycardia), crystalloids should be used to replace intravascular volume. If symptoms persist, the patient should receive transfusions with packed red blood cells or whole blood on a unit-by-unit basis to relieve symptoms; one unit may be sufficient. Transfusion of donor platelets has been shown to restore platelet function following REOPRO administration in animal studies and transfusions of fresh random donor platelets have been given empirically to restore platelet function in humans. In the event of serious

uncontrolled bleeding or the need for emergency surgery, REOPRO should be discontinued. In the majority of patients, bleeding time returns to 12 minutes within 12 hours. If the bleeding time remains greater than 12 minutes, 10 units of platelets may be given. REOPRO may be displaced from endogenous platelet receptors and subsequently bind to platelets which have been transfused. Nevertheless, a single transfusion may be sufficient to reduce receptor blockade to 60% to 70% at which level platelet function is restored. Repeat platelet transfusions may be required to maintain the bleeding time at or below 12 minutes.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antithrombotic agents, platelet aggregation inhibitors excl. heparin ATC code: B01AC13

Mechanism of action

REOPRO is the Fab fragment of the chimeric monoclonal antibody 7E3. It is directed against the glycoprotein (GP) IIb/IIIa ($\alpha_{IIb}\beta_3$) receptor located on the surface of human platelets. REOPRO inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets. REOPRO also binds to the vitronectin ($\alpha_v\beta_3$) receptor found on platelets and endothelial cells. The vitronectin receptor mediates the pro-coagulant properties of platelets and proliferative properties of vessel wall endothelial and smooth muscle cells. Because of its dual specificity, REOPRO more effectively blocks the burst of thrombin generation that follows platelet activation than agents which inhibit GPIIb/IIIa alone.

Intravenous administration in humans of single bolus doses of REOPRO from 0.15 mg/kg to 0.30 mg/kg produced rapid dose-dependent inhibition of platelet function as measured by *ex vivo* platelet aggregation in response to adenosine diphosphate (ADP) or by prolongation of bleeding time. At the two highest doses (0.25 and 0.30 mg/kg) at 2 hours post injection, over 80% of the GPIIb/IIIa receptors were blocked and platelet aggregation in response to 20 μ M ADP was almost abolished. The median bleeding time increased to over 30 minutes at both doses compared with a baseline value of approximately 5 minutes. The 80% level of receptor blockade was selected as a target for pharmacological efficacy because animal models of severe coronary stenosis have shown that platelet inhibition associated with this degree of blockade prevents platelet thrombosis.

Intravenous administration in humans of a single bolus dose of 0.25 mg/kg followed by a continuous infusion of 10 μ g/min for periods of 12 to 96 hours produced sustained high-grade GPIIb/IIIa receptor blockade (greater than or equal to 80%) and inhibition of platelet function (*ex vivo* platelet aggregation in response to 20 μ M ADP less than 20% of baseline and bleeding time greater than 30 minutes) for the duration of the infusion in most patients. Equivalent results were obtained when a weight adjusted infusion dose (0.125 μ g/kg/min to a maximum of 10 μ g/min) was used in patients up to 80 kg. Results in patients who received the 0.25 mg/kg bolus followed by a 5 μ g/min infusion for 24 hours showed a similar initial receptor blockade and inhibition of platelet aggregation, but the response was not maintained throughout the infusion period. Although low levels of GPIIb/IIIa receptor blockade are present for more than 10 days following cessation of the infusion, platelet function typically returned to normal over a period of 24 to 48 hours.

In clinical trials, REOPRO has demonstrated marked effects in reducing the thrombotic complications of coronary interventions such as balloon angioplasty, atherectomy and stent placement. These effects were observed within hours of the intervention and sustained for 30 days in the EPIC, EPILOG and CAPTURE trials. In the EPIC and EPILOG trials, in which the infusion dose was continued for 12 hours after the procedure, the reduction in the composite endpoint of death, MI or urgent intervention was sustained for the period of

follow-up, 3 years and 6 months, respectively. In the CAPTURE trial in patients with unstable angina not responding to medical therapy, REOPRO was administered as a bolus plus infusion starting up to 24 hours before the procedure until 1 hour after completion of the procedure. This regimen demonstrated stabilisation of patients prior to angioplasty, as shown for example by a reduction in MIs, and the reduction in thrombotic complications was sustained at the 30-day endpoint but not at 6 months.

5.2 PHARMACOKINETIC PROPERTIES

Following intravenous bolus administration of REOPRO, free plasma concentrations decrease very rapidly with an initial half life of less than 10 minutes and a second phase half life of about 30 minutes, probably related to rapid binding to the platelet GPIIb/IIIa receptors. Platelet function generally recovers over the course of 48 hours, although REOPRO remains in the circulation for 15 days or more in a platelet-bound state. Intravenous administration of a 0.25 mg/kg bolus dose of REOPRO followed by continuous infusion of 10 µg/min (or a weight adjusted infusion of 0.125 µg/kg/min to a maximum of 10 µg/min) produces relatively constant free plasma concentrations throughout the infusion. At the termination of the infusion period, free plasma concentrations fall rapidly for approximately 6 hours then decline at a slower rate.

5.3 PRECLINICAL SAFETY DATA

Animal toxicity studies in rats and monkeys did not elicit information on the benefit/risk evaluation of REOPRO beyond that determined from the clinical trials in man. REOPRO was generally well tolerated. Signs of bleeding considered an exaggerated pharmacological response were observed at high doses in monkeys. Repeated daily doses in monkeys led to a significant monkey anti-chimeric antibody response as might be expected following repeated doses of a foreign protein. As a result of this response, thrombocytopenia was induced with consequential haemorrhage and anaemia. *In vitro* and *in vivo* mutagenicity studies have not demonstrated any mutagenic effect. Long-term studies in animals have not been performed to evaluate the carcinogenic potential or effects on fertility in male or female animals.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Dibasic sodium phosphate dihydrate

Monobasic sodium phosphate monohydrate;

Sodium chloride,

Polysorbate 80

Water for injection

Trace amounts of papain resulting from the production process may be present.

6.2 INCOMPATIBILITIES

No incompatibilities have been shown with intravenous infusion fluids or commonly use cardiovascular drugs. Nevertheless, it is recommended that REOPRO be administered in a separate intravenous line whenever possible and not mixed with other medications (see **section 6.6 Special precautions for disposal and other handling**).

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

REOPRO should be stored in a refrigerator at between 2° and 8°C. Do not freeze.

REOPRO does not contain a preservative and is for single use only. Unused portions should be discarded. When intended for use by intravenous infusion, REOPRO should be used promptly after dilution.

6.5 NATURE AND CONTENTS OF CONTAINER

REOPRO is supplied in 5 mL (10 mg) glass vials with rubber stoppers and aluminium crimps protected by a plastic cap.

Each 5 mL vial is supplied separately.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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

No incompatibilities have been observed with glass bottles or polyvinyl chloride bags or administration sets (see **section 6.2 Incompatibilities**).

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland

NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

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9. DATE OF FIRST APPROVAL

21 September 1995

10. DATE OF REVISION OF THE TEXT

8 February 2019

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
All	Datasheet reformat
4.4	Updated information relating to thrombocytopenia.