NAME OF THE MEDICINE
ReoPro® (abciximab)

The active ingredient is abciximab.

DESCRIPTION
ReoPro (abciximab rmc) is the Fab fragment of the chimeric monoclonal antibody 7E3 (c7E3 Fab). The chemical description of abciximab is:

Immunoglobulin G (human-mouse monoclonal c7E3 clone p7E3V, hCH, Fab fragment anti-human glycoprotein IIb/IIIa receptor), disulfide with human-mouse monoclonal c7E3 clone p7E3V, kH, light chain.

The chimeric 7E3 antibody is produced by continuous perfusion in mammalian cell culture. The 47,615 dalton Fab fragment is purified from cell culture supernatant by a series of steps involving specific viral inactivation and removal procedures, digestion with papain and column chromatography.

Each 5 mL single-use vial contains 10 mg abciximab, 6.75 mg dibasic sodium phosphate dihydrate, 1.65 mg monobasic sodium phosphate (monohydrate), 43.85 mg sodium chloride, 0.05 mg polysorbate 80 and water for injections, qs to 5.0 mL. No preservatives are added.

CLINICAL PHARMACOLOGY
ReoPro binds to the intact platelet GPIIb/IIIa receptor, which is a member of the integrin family of adhesion receptors and the major platelet surface receptor involved in platelet aggregation. 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. The mechanism of action is thought to involve steric hindrance and/or conformational effects to block access of large molecules to the receptor rather than direct interaction with the RGD (arginine-glycine-aspartic acid) binding site of GPIIb/IIIa.

ReoPro binds with similar affinity to the related integrin, \( \alpha_v\beta_3 \), also known as the vitronectin receptor. The \( \alpha_v\beta_3 \) receptor is present on a wide variety of cell types including platelets and vessel wall endothelial and smooth muscle cells. ReoPro effectively blocks \( \alpha_v\beta_3 \)-mediated effects including cell adhesion (IC\text{50} = 0.34 mcg/mL). 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.

Preclinical Experience
Maximal inhibition of platelet aggregation was observed in vivo when \( \geq 80\% \) of GPIIb/IIIa receptors were blocked by abciximab. In non-human primates, abciximab bolus doses of 0.25 mg/kg generally achieved a blockade of at least 80\% of platelet receptors and fully inhibited platelet aggregation. Inhibition of platelet function was temporary following a bolus dose but receptor blockade could be sustained at \( \geq 80\% \) by continuous intravenous infusion. The inhibitory effects of abciximab were substantially reversed by transfusion of platelets in ReoPro (abciximab)- Product Information v2.0
monkeys. The antithrombotic efficacy of prototype antibodies [murine 7E3 Fab and F(ab’)2] and abciximab was evaluated in dog, monkey and baboon models of coronary, carotid and femoral artery thrombosis. Doses of the murine version of 7E3 or abciximab sufficient to produce high-grade (≥ 80%) GPIIb/IIIa receptor blockade prevented acute thrombosis and yielded lower rates of thrombosis compared with aspirin and/or heparin.

Pharmacodynamics

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 mcM 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 mcg/min for periods of 12 to 96 hours produced sustained high-grade GPIIb/IIIa receptor blockade (≥ 80%) and inhibition of platelet function (ex vivo platelet aggregation in response to 5 mcM or 20 mcM 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 mcg/kg/min to a maximum of 10 mcg/min) was used in patients up to 80 kg. Results in patients who received the 0.25 mg/kg bolus followed by a 5 mcg/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. Following cessation of the infusion, platelet function typically returned to normal over a period of 24 to 48 hours.

Low levels of GPIIb/IIIa receptor blockade are present for more than 10 days following cessation of the infusion. After discontinuation of ReoPro infusion, platelet function returns gradually to normal. Bleeding time returned to ≤ 12 minutes within 12 hours following the end of infusion in 15 of 20 patients (75%) and within 24 hours in 18 of 20 patients (90%). Ex vivo platelet aggregation in response to 5 mcM ADP returned to ≥ 50% of baseline within 24 hours following the end of infusion in 11 of 32 patients (34%) and within 48 hours in 23 of 32 patients (72%). In response to 20 mcM ADP, ex vivo platelet aggregation returned to ≥ 50% of baseline within 24 hours in 20 of 32 patients (62%) and within 48 hours in 28 of 32 patients (88%).

Pharmacokinetics

Following intravenous bolus administration of ReoPro, plasma levels decrease very rapidly with an initial phase half-life of less than 10 minutes and a second phase half-life of about 30 minutes. This disappearance from the plasma is probably related to rapid binding to the platelet GPIIb/IIIa receptors. ReoPro remains in the circulation for 15 days or more in a platelet-bound state, although platelet function recovers over the course of 48 hours. Intravenous administration of a 0.25 mg/kg bolus dose of ReoPro followed by continuous infusion of 10 mcg/min (or a weight adjusted infusion of 0.125 mcg/kg/min to a maximum of 10 mcg/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. Recovery of platelet function after ReoPro (abciximab)- Product Information v2.0
cessation of infusion is independent of the total time of infusion and is similar to that observed following a bolus dose.

Clinical Experience

ReoPro has been studied in three pivotal clinical trials: to reduce ischaemic cardiac complications in high risk angioplasty patients (EPIC), to reduce ischaemic cardiac complications in low as well as high risk angioplasty patients (EPILOG) and to stabilise unstable angina patients not responding to conventional medical therapy who are scheduled for angioplasty (CAPTURE). All trials involved the use of various heparin dose regimens and unless contraindicated, aspirin (325 mg) was administered orally 2 hours prior to the planned procedure and then once daily.

Percutaneous Coronary Intervention (PCI)

The EPIC (Evaluation of c7E3 to Prevent Ischaemic Complications) trial was a multicentre, double-blind, placebo-controlled trial of ReoPro in patients undergoing percutaneous transluminal coronary angioplasty or arterectomy (PTCA). In the EPIC trial, 2099 patients between 26 and 83 years of age who were at high risk for abrupt closure of the treated coronary vessel were randomly allocated to one of three treatments: (i) ReoPro bolus (0.25 mg/kg) followed by ReoPro infusion (10 mcg/min) for 12 hours (bolus plus infusion group); (ii) ReoPro bolus (0.25 mg/kg) followed by placebo infusion (bolus group) or (iii) a placebo bolus followed by a placebo infusion (placebo group). All patients initially received an intravenous heparin bolus (10,000 to 12,000 units) and boluses of up to 3,000 units thereafter to a maximum of 20,000 units during PTCA. Heparin infusion was continued for 12 hours to maintain a therapeutic elevation of activated partial thromboplastin time (APTT, 1.5 - 2.5 times normal).

The primary endpoint was the occurrence of any of the following events within 30 days of PTCA: death, myocardial infarction (MI) or the need for urgent intervention for recurrent ischaemia (ie. urgent PTCA, urgent coronary artery bypass graft (CABG) surgery, a coronary stent or an intra-aortic balloon pump). The 30-day (Kaplan-Meier) primary endpoint event rates for each treatment group by intention-to-treat analysis of all randomised patients are: placebo = 12.8% (89/696), bolus = 11.5% [(79/695); p-value vs placebo 0.428] and bolus plus infusion = 8.3% [(59/708); p-value vs placebo 0.008]. The 4.5% lower incidence of the primary endpoint in the bolus plus infusion treatment group, compared with the placebo group, was statistically significant, whereas the 1.3% lower incidence in the bolus treatment group was not. A lower incidence of the primary endpoint was observed in the bolus plus infusion treatment arm for all three high-risk subgroups; patients with unstable angina, patients presenting within 12 hours of the onset of symptoms of an acute MI and patients with other high-risk clinical and/or morphologic characteristics. The treatment effect was largest in the first two subgroups and smallest in the third sub-group.

The primary endpoint events in the bolus plus infusion treatment group were reduced mostly in the first 48 hours and this benefit was sustained through blinded evaluations at 30 days, 6 months and 3 years. At the 6 months follow-up visit, this event rate remained lower in the bolus plus infusion arm (12.3%) than in the placebo arm (17.6%) (p = 0.006 vs placebo). At 3 years, the absolute reduction in events was maintained with an event rate of 19.6% in the bolus plus infusion arm and 24.4% in the placebo arm (p = 0.027 vs placebo).

A second trial, EPILOG (Evaluation of PTCA to Improve Long-term Outcome by c7E3 GPIIb/IIa Receptor Blockade) was also a randomised, double-blind, multicentre, placebo-controlled trial, which evaluated ReoPro in a broad population of PTCA patients (but ReoPro (abciximab)- Product Information v2.0
excluding patients with MI and unstable angina meeting the EPIC high risk criteria). EPILOG tested the hypothesis that use of a low dose, weight adjusted heparin regimen, early sheath removal, better access site management and weight adjustment of the ReoPro infusion dose could significantly lower the bleeding rate yet maintain the efficacy seen in the EPIC trial. EPILOG was a three treatment-arm trial of ReoPro plus standard dose, weight adjusted heparin; ReoPro plus low dose, weight adjusted heparin; and placebo plus standard dose, weight adjusted heparin. The ReoPro dose regimen was the same as that used in the EPIC trial, except that the continuous infusion dose was weight adjusted in patients up to 80 kg. Improved patient and access site management as well as a strong recommendation for early sheath removal were also incorporated into the trial. The 30-day (Kaplan-Meier) primary endpoint events for each treatment group by intention-to-treat analysis of all 2792 randomised patients are: death or MI: placebo + standard dose heparin = 9.1% (85/939), ReoPro + standard dose heparin = 4.2% [(38/918); p-value vs placebo < 0.0001] and ReoPro + low dose heparin = 3.8% [(35/935); p-value vs placebo <0.0001] and death, MI or urgent intervention: placebo + standard dose heparin = 11.7% (109/939), ReoPro + standard dose heparin = 5.4% [(49/918); p-value vs placebo < 0.0001] and ReoPro + low dose heparin = 5.2% [(48/935); p-value vs placebo <0.0001]. In the EPILOG trial, there was a lowering of the bleeding rate: in the ReoPro treatment arms, major bleeding was reduced to the level of placebo (see ADVERSE REACTIONS - Bleeding).

As seen in the EPIC trial, the endpoint events in the ReoPro treatment groups were reduced mostly in the first 48 hours and this benefit was sustained through blinded evaluations at 30 days and 6 months. At the 6 month follow-up visit, the event rate for death, MI or urgent intervention remained lower in the combined ReoPro treatment arms (8.3% and 8.4% respectively, for the standard and low dose heparin arms) than in the placebo arm (14.7%) (p<0.001 for both treatment arms vs placebo).

The proportionate reductions in the composite endpoints death and MI, and death, MI and urgent intervention were similar in high and low risk patients, although overall event rates were higher in high risk patients. The proportionate reductions in endpoints were also similar irrespective of the type of coronary intervention used (balloon angioplasty, atherectomy or stent placement).

Mortality was uncommon in both the EPIC and EPILOG trials. Similar mortality rates were observed in all arms in the EPIC trial: mortality rates were lower in the ReoPro treatment arms than the placebo treatment arm in the EPILOG trial. In both trials, the rate of acute MI was significantly lower in the groups treated with ReoPro. While most MI in both studies were non-Q-wave infarctions, patients in the ReoPro treated groups experienced a lower incidence of both Q-wave and non-Q-wave infarctions. Urgent intervention rates were also lower in the groups treated with ReoPro, mostly because of lower rates of emergency PTCA and to a lesser extent, emergency CABG surgery.

**Unstable Angina**

The CAPTURE (Chimeric Anti-Platelet Therapy in Unstable angina Refractory to standard medical therapy) trial was a randomised, double-blind, multicentre, placebo-controlled trial designed to determine if potent antiplatelet therapy would reduce ischaemic complications in unstable angina patients not responding to conventional therapy who were candidates for PCI.

In contrast to the EPIC and EPILOG trials, the CAPTURE trial involved the administration of placebo or ReoPro starting up to 24 hours prior to PTCA and continuing until 1 hour after completion of PTCA in addition to conventional therapy. The ReoPro dose was a 0.25 mg/kg ReoPro (abciximab)- Product Information v2.0
bolus followed by a continuous infusion at a rate of 10 mcg/min. The CAPTURE trial incorporated weight adjustment of the standard heparin dose, but did not investigate the effect of a lower heparin dose. During CAPTURE arterial sheaths were left in place for approximately 40 hours. The 30-day (Kaplan-Meier) primary endpoint events for each treatment group by intention-to-treat analysis of all 1265 randomised patients are: death, MI or urgent intervention: placebo 15.9% (101/635) and ReoPro = 11.3% [(71/630); p-value vs placebo = 0.012]. The 30-day results are consistent with EPIC results, with the greatest effects on the MI and urgent intervention components of the composite endpoint.

As secondary endpoints, the components of the composite endpoint were analysed separately for the period prior to PCI and the period from the beginning of the intervention through Day 30. The greatest difference in MI occurred in the post-intervention period: the rates of MI were lower in the ReoPro group compared with placebo (ReoPro 3.6%, placebo 6.1%). There was also a reduction in MI occurring prior to PCI (ReoPro 0.6%, placebo 2.0%). A ReoPro associated reduction in the incidence of urgent intervention occurred in the post-intervention period.

INDICATIONS

ReoPro is indicated for Percutaneous Coronary Intervention (PCI): the prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention (balloon angioplasty, atherectomy and stent placement). In patients with unstable angina refractory to conventional treatment, where PCI is planned, ReoPro may be used 18 to 24 hours prior to the planned intervention.

ReoPro is intended for use with aspirin and heparin and has been studied only in that setting.

CONTRAINDICATIONS

ReoPro should not be administered to patients with known sensitivity to abciximab, to any component of the product or to murine proteins.

Because inhibition of platelet aggregation increases the risk of bleeding, ReoPro is contra-indicated in the following clinical situations: active internal bleeding; recent (within 6 weeks) gastrointestinal (GI) or genitourinary bleeding of clinical significance; history of cerebrovascular accident (CVA) within two years or CVA with a significant residual neurological deficit; bleeding diathesis; administration of oral anticoagulants within seven days unless prothrombin time is \( \leq 1.2 \) times control; thrombocytopenia (< 100,000 cells/mcL); recent (within 6 weeks) major surgery or trauma; intracranial neoplasm, arteriovenous malformation or aneurysm; severe uncontrolled hypertension; presumed or documented history of vasculitis; use of intravenous dextran before PTCA or intent to use it during PTCA.

PRECAUTIONS

Bleeding

ReoPro has the potential to increase the risk of bleeding, particularly in the presence of excessive anticoagulation, eg. from heparin or thrombolytics (see ADVERSE REACTIONS - Bleeding). Results of the EPILOG clinical trial show that bleeding can be reduced to the level of placebo by the use of low dose, weight adjusted heparin regimens, early sheath removal, careful patient and access site management and weight adjustment of the ReoPro infusion dose.
Should serious bleeding occur that cannot be controlled by pressure, the infusion of ReoPro and any concomitant heparin should be stopped (see PRECAUTIONS - Reversal of antiplatelet effects).

Therapy with ReoPro requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, needle puncture sites, and gastrointestinal, genitourinary, pulmonary (alveolar) and retroperitoneal sites).

**Femoral Artery Access Site**
Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Femoral vein sheath placement should be avoided unless needed. While the vascular sheath is in place, patients should be maintained on complete bed rest with head of bed ≤ 30° and the affected limb restrained in a straight position. Patients may be medicated for back/groin pain as necessary. Discontinuation of heparin immediately upon completion of the procedure and removal of the arterial sheath within 6 hours is strongly recommended. In all circumstances, heparin should be discontinued at least 2 hours prior to arterial sheath removal. The APTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless APTT ≤ 50 seconds or ACT ≤ 175 seconds. Following sheath removal, pressure should be applied to the femoral artery for at least 30 minutes using either manual compression or a mechanical device for haemostasis. A pressure dressing should be applied following haemostasis. The patient should be maintained on bed rest for 6 to 8 hours following sheath removal or discontinuation of ReoPro, or 4 hours following discontinuation of heparin, which ever is later. The pressure dressing should be removed prior to ambulation.

The sheath insertion site and distal pulses of affected leg(s) should be frequently checked while the femoral artery sheath is in place and for 6 hours after femoral artery sheath removal. Any haematoma should be measured and monitored for enlargement.

**General Nursing Care**
Arterial and venous punctures, intramuscular injections and use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs should be minimised. When obtaining intravenous access, non-compressible sites (eg. 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.

**Anticoagulation**
Before infusion of ReoPro, platelet count, prothrombin time, ACT and APTT should be measured to identify pre-existing haemostatic abnormalities.

**Percutaneous Coronary Intervention (PCI)**
If a patient's activated clotting time (ACT) is < 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. Additional heparin boluses of 20 U/kg may be administered during the procedure to achieve and maintain an ACT \( \geq 200 \) seconds.

It is strongly recommended that heparin be discontinued immediately upon completion of the procedure. However, if prolonged heparin therapy or later sheath removal is clinically indicated, heparin should be started at a rate of 7 U/kg/hr and heparin infusion adjusted to keep the APTT at a target of 60-85 seconds.

During and following ReoPro treatment, platelet counts and extent of heparin anticoagulation, as assessed by activated clotting time or APTT, should be monitored closely.

**Unstable Angina Patients when PCI is Planned**

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 *Percutaneous Coronary Intervention (PCI)*.

**Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents**

In the EPIC, EPILOG and CAPTURE trials, ReoPro was used concomitantly with heparin and aspirin (see CLINICAL PHARMACOLOGY - Clinical Experience). Aspirin should be administered at a daily dose of not less than 300 mg commencing at least 2 hours before the procedure. Because ReoPro inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect haemostasis, including thrombolytics; oral anticoagulants; non-steroidal anti-inflammatory drugs, and other antiplatelet agents other than aspirin.

Because of concern about observed synergistic effects on bleeding, ReoPro therapy should be used judiciously in patients who have received systemic thrombolytic therapy. The GUSTO V trial randomised patients with acute MI to treatment with combined ReoPro and half-dose reteplase, or full-dose reteplase alone. In this trial, the incidence of moderate or severe nonintracranial bleeding was increased in those patients receiving ReoPro and half-dose reteplase versus those receiving reteplase alone (4.6% versus 2.3%, respectively).

If urgent intervention is required for refractory symptoms in a patient receiving ReoPro (or who has received the drug in the previous 48 hours), it is recommended that PTCA be attempted first to salvage the situation. 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 lytic state should be avoided.

In clinical studies, there is limited experience with the administration of ReoPro with low molecular weight dextran. In the 11 patients who received low molecular weight dextran with ReoPro, five had major bleeding events and four had minor bleeding events. None of the five placebo patients treated with low molecular weight dextran had a major or minor bleeding event.

**Thrombocytopenia**

Platelet counts should be monitored prior to treatment, 2 to 4 hours following the bolus dose of ReoPro and at 24 hours or prior to discharge, whichever is first. If a patient experiences an acute platelet decrease (eg. a platelet decrease to < 100,000 cells/mcL and a decrease of ReoPro (abciximab)- Product Information v2.0
at least 25% from pre-treatment value), 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/mcL, heparin and aspirin should be discontinued. In the EPIC study, if a patient’s platelet count dropped below 50,000 cells/mcL, platelets were transfused. Most cases of severe thrombocytopenia (≤ 50,000 cells/mcL) occur within the first 24 hours of administration.

In a registry study of ReoPro readministration, a history of thrombocytopenia associated with prior use of ReoPro was predictive of an increased risk of recurrent thrombocytopenia. Readministration within 30 days was associated with an increased incidence and severity of thrombocytopenia, as was a positive human anti-chimeric antibody (HACA) test at baseline, compared to the rates seen in studies with first administration.

**Readministration**

Human anti-chimeric antibody (HACA) appears, generally as a low titre, in approximately 5% to 6% of patients after single administrations of ReoPro (see **ADVERSE REACTIONS**). 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.

Readministration of ReoPro to patients undergoing PCI was assessed in a registry that included 1342 treatments in 1286 patients. Most patients were receiving their second ReoPro exposure; 15% were receiving the third or subsequent exposure. The overall rate of HACA positivity prior to the readministration was 6% and increased to 27% post-readministration. There were no reports of serious allergic reactions or anaphylaxis. Thrombocytopenia was observed at higher rates in the readministration study than in the phase 3 studies of first-time administration (see **Precautions: Thrombocytopenia and Adverse Reactions: Thrombocytopenia**), suggesting that readministration may be associated with an increased incidence and severity of thrombocytopenia.

**Reversal of antiplatelet effects**

Transfer 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 surgery during infusion of ReoPro, the infusion of ReoPro should be discontinued and transfusion of 10 units of platelets should be considered. If serious uncontrolled bleeding or need for surgery occurs during the 24 hour period following ReoPro infusion, a bleeding time should be determined; if the bleeding time is greater than 12 minutes, 10 units of platelets may be given.

**Allergic Reactions**

Anaphylactic reactions have occurred very rarely in patients treated with ReoPro. Immediately upon occurrence of anaphylaxis, administration of ReoPro should be stopped and appropriate resuscitative measures should be initiated.
Drug Interactions

ReoPro has been 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. The risk of major bleeding due to ReoPro is increased in patients receiving thrombolytics (see Precautions – Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents.) Although there have been no formal studies with ReoPro with other commonly used cardiovascular drugs, in clinical studies there have been no adverse drug reactions associated with concomitant use of other medications used in the treatment of angina, MI 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.

Use in Pregnancy

Pregnancy category C. 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. An increased incidence of foetal loss and prematurity may be associated with maternal haemorrhage.

Use in Lactation

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

Paediatric Use

Safety and effectiveness in children have not been studied.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Abciximab did not show any mutagenic or clastogenic activity in in vitro studies with mammalian cells and was not clastogenic in an in vivo study in mice. Long-term studies in animals have not been performed to evaluate the carcinogenic potential of abciximab. The effects of abciximab on fertility in male or female animals have not been investigated.

ADVERSE REACTIONS

Bleeding

Bleeding was classified as major or minor by the criteria of the Thrombolysis in MI study group. Major bleeding events were defined as either an intracranial haemorrhage or a decrease in haemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross haematuria, spontaneous haematemesis, observed blood loss with a haemoglobin decrease of more than 3 g/dL or a decrease in haemoglobin of at least 4 g/dL without an identified bleeding site.

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 bleeding, minor bleeding and transfusion of blood products were approximately doubled. The incidence of intracranial haemorrhage was similar in all ReoPro (abciximab)- Product Information v2.0
three treatment groups. In patients who had major bleeding, 67% had bleeding associated with the arterial access site in the groin. ReoPro treated patients also had a higher incidence of major bleeding events from GI, genitourinary, retroperitoneal and other sites.

In a subsequent clinical trial, EPILOG, using the heparin and ReoPro dosing, sheath removal and arterial access site guidelines (see PRECAUTIONS – Bleeding), the incidence of major bleeding in patients treated with ReoPro and low dose, weight adjusted heparin (1.8%) was not significantly different from patients receiving placebo and standard dose, weight adjusted heparin (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, when given with low dose, weight adjusted heparin, 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 PRECAUTIONS - Reversal of Antiplatelet Effects).

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.

Potentially serious pulmonary alveolar haemorrhage and cardiac tamponade have been rarely reported during use of ReoPro. Pulmonary alveolar haemorrhage can present with any or all of the following in close association with ReoPro administration: hypoxaemia, alveolar infiltrates on chest x-ray, haemoptysis, or an unexplained drop in haemoglobin.

**Thrombocytopenia**

In the clinical trials, patients treated with ReoPro were more likely than patients receiving placebo to experience decreases in platelet counts. The rate of thrombocytopenia and transfusions were lower in the subsequent CAPTURE and EPILOG trials:

**Patients with decrease of platelets to 50,000 cells/mcL**  In EPIC: placebo + standard dose heparin = 0.7% (5/690), ReoPro + standard dose heparin = 1.6% (11/708); in CAPTURE: placebo + standard dose heparin = 0.3% (2/635), ReoPro + standard dose heparin = 1.7% (11/630); and in EPILOG: placebo + standard dose heparin = 0.4% (4/939), ReoPro + standard dose heparin = 0.9% (8/918); and ReoPro + low dose heparin = 0.4% (4/935).

**Patients with decrease of platelets to 100,000 cells/mcL**  In EPIC: placebo + standard dose heparin = 3.4% (24/690), ReoPro + standard dose heparin = 5.2% (37/708); in CAPTURE: placebo + standard dose heparin = 1.3% (8/635), ReoPro + standard dose heparin = 5.6% (35/630); and in EPILOG: placebo + standard dose heparin = 1.5% (14/939), ReoPro + standard dose heparin = 2.6% (24/918); and ReoPro + low dose heparin = 2.5% (23/935).

**Patients who received platelet transfusions**  In EPIC: placebo + standard dose heparin = 2.6% (18/690), ReoPro + standard dose heparin = 5.5% (39/708); in CAPTURE: placebo + standard dose heparin = 0.3% (2/635), ReoPro + standard dose heparin = 2.1% (13/630); and in EPILOG: placebo + standard dose heparin = 1.1% (10/939), ReoPro + standard dose heparin = 1.6% (15/918); and ReoPro + low dose heparin = 0.9% (8/935).
Patients who received ReoPro more than one time In a readministration registry study of patients receiving a second or subsequent exposure to ReoPro the incidence of any degree of thrombocytopenia was 5%, with an incidence of profound thrombocytopenia of 2% (<20,000 cell/mcL). Factors associated with an increased risk of thrombocytopenia were a history of thrombocytopenia on previous ReoPro exposure, readministration within 30 days, and a positive HACA assay prior to the readministration (see Precautions: Readministration).

Among 14 patients who had thrombocytopenia associated with a prior exposure to ReoPro, 7 (50%) had recurrent thrombocytopenia. In 130 patients with a readministration interval of 30 days or less, 25 (19%) developed thrombocytopenia. Severe thrombocytopenia occurred in 19 of these patients. Among the 71 patients who had a positive HACA assay at baseline, 11 (15%) developed thrombocytopenia, 7 of which were severe.

Human Anti-Chimeric Antibody Development

Human anti-chimeric antibody (HACA) may appear in response to the administration of ReoPro. In the EPIC, EPILOG and CAPTURE trials, positive responses occurred in 5.8% of the ReoPro treated patients. There was no excess of hypersensitivity or allergic reactions related to ReoPro treatment compared with placebo treatment (see PRECAUTIONS - Allergic Reactions). Such development of anti-chimeric antibodies may predispose patients to untoward reactions after future treatment with any protein of murine origin.

In a study of readministration of ReoPro to patients (see Precautions: Readministration) the overall rate of HACA positivity prior to the readministration was 6% and increased post-readministration to 27%. Among the 36 subjects receiving a fourth or greater ReoPro exposure, HACA positive assays were observed post-readministration in 16 subjects (44%). There were no reports of serious allergic reactions or anaphylaxis. HACA positive status was associated with an increased risk of thrombocytopenia (see Precautions: Thrombocytopenia).

The data reflect the percentage of patients whose test results were considered positive for antibodies to ReoPro using an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ReoPro with the incidence of antibodies to other products may be misleading.

Allergic Reactions:
There have been rare reports of allergic reactions, and very rare reports of anaphylaxis (see PRECAUTIONS). Although very rare, anaphylaxis may potentially occur at any time during administration (see DOSAGE AND ADMINISTRATION – Administration Instructions).

Other Adverse Reactions

The following body/organ systems show adverse events which occurred at an incidence of at least 0.5% in the combined ReoPro treatment in patients receiving ReoPro bolus plus infusion (n=3111) in the EPIC, EPILOG and CAPTURE trials compared to the patients receiving placebo (n=2226) in these trials [note: the placebo figure is in brackets].

Cardiovascular System: hypotension 14.4% (10.3%), chest pain 11.4% (9.3%), bradycardia 4.5% (3.5%), atrial fibrillation/ flutter 1.6% (2.2%), hypertension 1.9% (1.9%), peripheral oedema 1.6% (1.1%), angina pectoris 1.4% (1.8%), ventricular tachycardia 1.4% ReoPro (abciximab)- Product Information v2.0
(1.3%), cardiac failure 1.2% (2.1%), tachycardia 0.9% (1.1%), pulmonary oedema 0.5% (0.9%), ventricular fibrillation 0.5% (0.8%), palpitation 0.5% (0.4%).

**Gastrointestinal:** nausea 13.6% (11.5%), vomiting 7.3% (6.8%), dyspepsia 2.1% (1.8%), diarrhoea 1.1% (0.7%), constipation 1.2% (1.2%), flatulence 0.8% (0.9%).

**Haemic and Lymphatic:** thrombocytopenia 3.5% (1.2%), anaemia 1.3% (1.0%), haematoma 0.7% (0.3%), puncture site haematoma 0.7% (1.0%), leukocytosis 0.5% (0.1%).

**Nervous:** anxiety 1.7% (1.4%), confusion 0.6% (0.0%), abnormal thinking 1.3% (0.9%), dizziness 2.9% (2.8%), agitation 0.7% (0.5%), hypoesthesia 0.6% (0.5%), coma 0.4% (0.3%), brain ischaemia 0.3% (0.1%), insomnia 1.0% (1.0%).

**Respiratory:** dyspnoea 3.1% (3.3%), coughing 0.6% (0.6%), respiratory insufficiency 0.6% (0.8%).

**Urogenital:** urinary tract infection 1.0% (1.3%), urinary retention 0.7% (0.5%), renal failure 0.9% (1.2%).

**Miscellaneous:** back pain 17.6% (13.7%), headache 6.4% (5.5%), pain 5.4% (5.3%), fever 4.0% (5.1%), puncture site pain 3.6% (2.6%), abdominal pain 3.1% (2.2%), fatigue 1.8% (1.9%), rash 1.0% (1.3%), increased sweating 1.0% (0.9%), pseudoaneurysm 0.8% (0.6%), asthenia 0.7% (0.4%), incisional pain 0.6% (0.4%), infection 0.5% (0.7%), pruritus 0.5% (0.4%).

**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 (>1/1000, <1/100), Rare (>1/10,000, <1/1000), 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.

**Gastrointestinal Disorders:** very rare – gastrointestinal haemorrhage NOS

**Immune System Disorders:** very rare – anaphylactic reactions

**ANIMAL TOXICOLOGY**

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.
ReoPro is for intravenous (I.V.) administration in adults (including elderly patients).

**Adults:** In patients undergoing PCI, the recommended dose of ReoPro is a 0.25 mg/kg intravenous bolus 10-60 minutes prior to the intervention followed by a 0.125 mcg/kg/min (to a maximum of 10 mcg/min) continuous intravenous infusion for 12 hours.

In patients with unstable angina refractory to conventional treatment, who require PCI and in whom such intervention needs to be deferred for 18-24 hours, the following dosage regimen may be used:

A bolus dose of 0.25 mg/kg and infusion of 10 mcg/min, commencing 18 to 24 hours before the planned intervention and ceasing 1 hour after the completion of the intervention.

There are no safety data available on the infusion of ReoPro for periods greater than 25 hours in total.

**Children:** There is no experience on the use of ReoPro in children.

**Administration Instructions**

Use in one patient on one occasion only. ReoPro contains no antimicrobial agent. Use once only and discard any residue. When intended for use by intravenous infusion, ReoPro should be used promptly after dilution.

1. Parenteral drug 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), corticosteroids, respiratory assistance and other resuscitative measures are essential.

3. As with all parenteral drug products, aseptic procedures should be used during the administration of ReoPro.

4. Withdraw the necessary amount of ReoPro for bolus injection into a syringe. Filter the bolus injection using a sterile, non-pyrogenic, low protein-binding 0.20/0.22 micron or 5.0 micron 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% glucose 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 0.20/0.22 micron or 5.0 micron syringe filter or upon administration using an in-line, sterile, non-pyrogenic, low protein-binding 0.20 micron or 0.22 micron filter. Discard the unused portion at the end of the infusion.
6. Although incompatibilities have not been shown with intravenous infusion fluids or commonly used cardiovascular drugs, 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 (PVC) bags or administration sets. However, ReoPro should not be used with filters composed of an acrylic polymer of PVC and polyethylene cast on a non-woven nylon substrate.

**Incompatibilities**

No incompatibilities have been shown with intravenous infusion fluids or commonly used cardiovascular drugs. Nevertheless, it is recommended that ReoPro be administered in a separate intravenous line whenever possible and not mixed with other medications. No incompatibilities have been observed with PVC bags or administration sets.

**OVERDOSE**

There has been no experience of overdosage, however see **PRECAUTIONS** - Reversal of Antiplatelet Effects.

**PRESENTATION AND STORAGE CONDITIONS**

ReoPro (abciximab) 2 mg/mL is a clear, colourless, solution for injection, supplied in 5 mL glass vials with rubber stoppers and aluminium crimps protected by a plastic cap. Store at 2°C to 8°C. Do not freeze. Do not shake. Do not use beyond the expiration date.

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**POISON SCHEDULE OF THE MEDICINE**

S4 – Prescription only medicine

**DATE OF APPROVAL**

TGA Approval: 08 June 2005
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