PRODUCT MONOGRAPH

ReoPro®

Abciximab

Solution for Intravenous Injection (2 mg/mL)
5 mL (10 mg/5 mL)

Pharmaceutical standard (Professed)

Chimeric Monoclonal Antiplatelet Antibody

Janssen Biotech, Inc.
Horsham, Pennsylvania 19044 USA
Distributed by Eli Lilly Canada Inc.
3650 Danforth Avenue
Toronto, Ontario
M1N 2E8

Date of Authorization:
March 26, 2012

Submission Control No: 152659

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
DESCRIPTION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 11
DRUG INTERACTIONS 15
DOSAGE AND ADMINISTRATION 16
OVERDOSAGE 17
ACTION AND CLINICAL PHARMACOLOGY 17
STORAGE AND STABILITY 19
DOSAGE FORMS, COMPOSITION AND PACKAGING 19

PART II: SCIENTIFIC INFORMATION 21
PHARMACEUTICAL INFORMATION 21
CLINICAL TRIALS 22
DETAILED PHARMACOLOGY 27
TOXICOLOGY 30
REFERENCES 31

PART III: CONSUMER INFORMATION 35

ReoPro®

abciximab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Injection	Injection 2 mg/mL 5 mL (10 mg/5 mL)	Sodium phosphate, sodium chloride, polysorbate 80 *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

ReoPro® (abciximab) is the Fab fragment of the chimeric monoclonal antibody 7E3 (c7E3) containing murine variable regions and human constant regions. ReoPro® is a disulfide-linked dimer of the c7E3 IgG Fd heavy chain fragment and the intact Lκ light chain. ReoPro® is produced by continuous perfusion in mammalian cell culture. It is purified from cell culture supernatant by a series of steps involving specific viral inactivation procedures, digestion with papain and column chromatography.

INDICATIONS AND CLINICAL USE

ReoPro® (abciximab) is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications:

- in patients undergoing percutaneous coronary intervention
- in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours

ReoPro® use in patients not undergoing percutaneous coronary intervention has not been studied.

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

Geriatrics (> *65* years of age):
See *WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics*

Pediatrics (< 18 years of age):
See *WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics*

CONTRAINDICATIONS

- ReoPro® (abciximab) should not be administered to patients with known sensitivity to ReoPro®, to murine monoclonal antibodies, or to any component of the product. For a complete listing, see the *DOSAGE FORMS, COMPOSITION, AND PACKAGING* section of the product monograph.
- ReoPro® is contraindicated in the following clinical situations: active internal bleeding; recent (within six weeks) gastrointestinal or genitourinary bleeding of clinical significance; history of cerebrovascular accident (CVA) within two years or a CVA with a significant residual neurological deficit; recent (within six weeks) major surgery or trauma; intracranial neoplasm, arteriovenous malformation or aneurysm; known bleeding diathesis or severe uncontrolled hypertension; pre-existing thrombocytopenia; vasculitis; use of intravenous dextran before PTCA, or intent to use it during PTCA; administration of oral anticoagulants within seven days unless prothrombin time is ≤ 1.2 times control.

WARNINGS AND PRECAUTIONS

General

Requirement for Specialist Facilities

ReoPro® (abciximab) should only be administered in conjunction with extensive specialist medical and nursing care. In addition, there must be availability of laboratory tests of hematology function and facilities for administration of blood products.

Carcinogenesis and Mutagenesis

In vitro and *in vivo* mutagenicity studies have not demonstrated any mutagenic effect. Long-term studies in animals have not been performed to evaluate carcinogenic potential. See *TOXICOLOGY* section.

Hematologic

ReoPro® has the potential to increase the risk of bleeding, particularly in the presence of excessive anticoagulation, e.g. from heparin or thrombolytics. (See *ADVERSE REACTIONS: Bleeding*).

The risks of major bleeds due to ReoPro® therapy is increased in patients receiving thrombolytics and should be weighed against the anticipated benefits .

Should serious bleeding occur that is not controllable with pressure, the infusion of ReoPro® and any concomitant heparin should be stopped.

Bleeding Precautions

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.

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

Low-dose, Weight-adjusted 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 ≥ 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 ≥ 200 seconds is achieved. ACT should be checked prior to and a minimum of 2 minutes after each heparin bolus.

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 Bleeding Precautions: Femoral Artery Sheath Removal). In all circumstances, heparin should be discontinued at least 2 hours prior to arterial sheath removal.

2. Stabilization 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.

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 ≤ 30º
- 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 ≤ 50 seconds or ACT ≤ 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 hemostasis has been achieved

After Femoral Artery Sheath Removal

- Check groin for bleeding/hematoma and distal pulses every 15 minutes for the first hour or until stable, then hourly
- Continue complete bed rest with head of bed ≤ 30º 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/Hematoma Formation

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

- Lower head of bed to 0°
- Apply manual pressure/compression device until hemostasis has been achieved
- Any hematoma 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 hematoma 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.

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 minimized and only the anterior wall of the artery or vein should be punctured when establishing vascular access.

Pulmonary (mostly alveolar) hemorrhage

ReoPro® has rarely been associated with pulmonary (mostly alveolar) hemorrhage (6). This can present with any or all of the following in close association with ReoPro® administration: hypoxemia, alveolar infiltrates on chest x-ray, hemoptysis, or an unexplained drop in hemoglobin. If confirmed, ReoPro® and all anticoagulant and other antiplatelet drugs should immediately be discontinued.

GI Bleeding Prophylaxis

In order to prevent spontaneous GI bleeding it is recommended that patients are pretreated with H_2-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. Hemoglobin and hematocrit 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 catheterization 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.

Thrombocytopenia

To reduce the possibility of 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, (e.g. a platelet decrease to less than 100,000 cells/µL and a decrease of at least 25% from pretreatment 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/µL, heparin and acetylsalicylic acid should be discontinued. If a patient's platelet count drops below 50,000 cells/µL, platelets should be transfused.

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.

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 surgery, a bleeding time should be determined. If the bleeding time is 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.

<u>Immune</u>

Readministration

Administration of ReoPro® may result in human anti-chimeric antibody (HACA) formation (*see ADVERSE REACTIONS*) that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis), thrombocytopenia or diminished benefit upon readministration of 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 WARNINGS AND PRECAUTIONS: Thrombocytopenia and ADVERSE REACTIONS: Thrombocytopenia*), suggesting that readministration may be associated with an increased incidence and severity of thrombocytopenia.

Hypersensitivity Reactions

Anaphylactic reactions have occurred very rarely in patients treated with ReoPro®. Epinephrine, antihistamines and corticosteroids should be available for immediate use, in addition to equipment for resuscitation, in the event of a hypersensitivity reaction. Immediately, upon occurrence of anaphylaxis, administration of ReoPro® should be stopped and appropriate resuscitative measures should be initiated.

Respiratory

Pulmonary hemorrhage associated with ReoPro® use, although a very rare occurrence, can be a serious life-threatening complication that can be misdiagnosed and result in the patient not receiving timely treatment. Respiratory symptoms should be monitored closely for early detection of serious pulmonary hemorrhage in patients receiving ReoPro®.

Special Populations

Pregnant Women:
Animal reproduction studies have not been conducted with ReoPro® and the effects on fertility in male or female animals are unknown. It is also not known whether ReoPro® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ReoPro® should be given to a pregnant woman only if clearly needed.

Nursing Women:
It is not known if this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ReoPro® is administered to a nursing woman.

Pediatrics (< *18* years of age):
Safety and effectiveness of ReoPro® in children below the age of 18 have not been established.

Geriatrics (> 65 years of age):
There is insufficient clinical experience to determine whether patients aged 75 years old or greater respond differently to ReoPro® than younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Bleeding

Bleeding was classified as major or minor by the criteria of the Thrombolysis in Myocardial Infarction (TIMI) study group. Major bleeding events were defined as either an intracranial hemorrhage or decrease in hemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria or hematemesis or observed blood loss with a hemoglobin decreasing more than 3 g/dL or with a decrease in hemoglobin of at least 4 g/dL with no observed blood loss.

In the EPIC trial, in which a non-weight-adjusted, standard heparin dose regimen was used, the most common complication during ReoPro® (abciximab) therapy was bleeding during the first 36 hours. The incidences of major bleeding, minor bleeding and transfusion of blood products were approximately doubled. Approximately 70% of ReoPro®-treated patients with major bleeding had bleeding at the arterial access site in the groin. ReoPro®-treated patients also had a higher incidence of major bleeding events from gastrointestinal, genitourinary, retroperitoneal, and other sites.

In a subsequent clinical trial, EPILOG, using the heparin and ReoPro® dosing, sheath removal and arterial access site guidelines described under PRECAUTIONS, 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 (3.1%) and there was no significant increase in the incidence of intracranial hemorrhage. The reduction in bleeding observed in the EPILOG trial was achieved without loss of efficacy.

The rates of major bleeding, minor bleeding and bleeding events requiring transfusions in the EPIC, CAPTURE and EPILOG trials are shown in Table 1.

Table 1: Non-CABG Bleeding in the EPIC, EPILOG and CAPTURE Trials
Number of Patients with Bleeds (%)

EPIC:

	Placebo (n=696)	ReoPro® (Bolus+Infusion) (n=708)
Major[a]	23 (3.3)	75 (10.6)
Minor	64 (9.2)	119 (16.8)
Requiring Transfusion[b]	14 (2.0)	55 (7.8)

CAPTURE:

	Placebo (n=635)	ReoPro® (n=630)
Major[a]	12 (1.9)	24 (3.8)
Minor	13 (2.0)	30 (4.8)
Requiring Transfusion[b]	9 (1.4)	15 (2.4)

EPILOG:

	Placebo + Std-dose Heparin (n=939)	ReoPro® + Std-dose Heparin (n=918)	ReoPro® + Low-dose Heparin (n=935)
Major[a]	10 (1.1)	17 (1.9)	10 (1.1)
Minor	32 (3.4)	70 (7.6)	37 (4.0)
Requiring Transfusion[b]	10 (1.1)	7 (0.8)	6 (0.6)

[a]Patients who had bleeding in more than one classification are counted only once according to the most severe classification. Patients with multiple bleeding events of the same classification are also counted once within that classification.
[b]Packed red blood cells or whole blood

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 WARNINGS AND PRECAUTIONS: Restoration of Platelet Function*).

The total incidence of intracranial hemorrhage and non-hemorrhagic stroke across all three trials was similar, 7/2225 (0.31%) for placebo patients and 10/3112 (0.32%) for ReoPro®-treated patients. The incidence of intracranial hemorrhage was 0.13% in placebo patients and 0.19% in ReoPro® patients.

Pulmonary hemorrhage with fatal outcome following administration of ReoPro® has been reported. In many cases, patients received at least two co-suspect or concomitant medications such as heparin or aspirin. Although the outcomes of most cases were not provided, approximately 2/3 had fatal outcomes. Based on exposure data, the reporting rate for pulmonary hemorrhage is less than 1 case report per 10,000 patients. (*See WARNINGS AND PRECAUTIONS: Pulmonary Hemorrhage*)

Thrombocytopenia

In the clinical trials, patients treated with ReoPro® were more likely than patients treated with placebo to experience decreases in platelet counts. The overall rates of thrombocytopenia (platelet counts < 100,000 cells/µL) in the EPIC, EPILOG and CAPTURE trials were 0.5% for placebo-treated patients and 2.9% for patients receiving ReoPro® bolus plus infusion. The incidence of thrombocytopenia was lowest in the EPILOG trial (placebo: 1.5%; ReoPro® and standard-dose, weight-adjusted heparin: 2.6%; ReoPro® and low-dose, weight-adjusted heparin: 2.5%). The lowest rates of platelet transfusions in ReoPro®-treated patients were also observed in the EPILOG trial, (placebo: 1.1%; ReoPro® and standard-dose, weight-adjusted heparin: 1.6%; ReoPro® and low-dose, weight-adjusted heparin: 0.9%).

In a readministration registry study of patients receiving a second or subsequent exposure to ReoPro® (*See WARNINGS AND PRECAUTIONS: Readministration*) the incidence of any degree of thrombocytopenia was 5%, with an incidence of profound thrombocytopenia of 2% (<20,000 cell/µL). 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.

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 Antichimeric Antibody (HACA)

Human antichimeric antibody (HACA) may appear in response to the administration of ReoPro®. In the EPIC, EPILOG, and CAPTURE trials, positive responses occurred in approximately 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 also *WARNINGS and PRECAUTIONS: Hypersensitivity Reactions*.

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 WARNINGS AND 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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2 below shows adverse drug reactions other than bleeding, intracranial hemorrhage and thrombocytopenia from the combined EPIC, EPILOG and CAPTURE trials which occurred in ≥1% of patients in either the ReoPro® or placebo treatment arms.

Table 2 – Adverse Drug Reactions Among Treated Patients in the EPIC, EPILOG and CAPTURE Trials

	ReoPro® Bolus + Infusion n= 3111 (%)	**Placebo n= 2226 (%)**
Cardiac disorders		
Bradycardia	4.5%	3.5%
Gastrointestinal disorders		
Nausea	13.6%	11.5%
Vomiting	7.3%	6.8%
General disorders and administration site conditions		
Chest pain	11.4%	9.3%
Puncture site pain	3.6%	2.6%
Abdominal pain	3.1%	2.2%
Musculoskeletal and connective tissue disorders		
Back pain	17.6%	13.7%
Nervous system disorders		
Headache	6.4%	5.5%
Vascular disorders		
Hypotension	14.4%	10.3%
Peripheral edema	1.6%	1.1%

Less Common Clinical Trial Adverse Drug Reactions (<1%)

General disorders and administration site conditions: Injection site reaction
Immune system disorders: Allergic reactions

Post-Market Adverse Drug Reactions
Cases of anaphylaxis, sometimes fatal, have been very rarely observed and reported following marketing of ReoPro®. Gastrointestinal hemorrhage has also been very rarely reported following marketing of ReoPro®.

DRUG INTERACTIONS

Formal drug interaction studies with ReoPro® have not been conducted. ReoPro® has been administered to patients with ischemic heart disease treated concomitantly with a broad range of medications used in the treatment of angina, myocardial infarction and hypertension. These medications have included heparin, warfarin, beta-adrenergic receptor blockers, calcium channel antagonists, angiotensin converting enzyme inhibitors, intravenous and oral nitrates, and acetylsalicylic acid. Heparin, other anticoagulants, thrombolytics, and antiplatelet agents are associated with an increase in bleeding. Because ReoPro® inhibits platelet aggregation, caution should be employed when used with other drugs affecting hemostasis.

Patients with HACA titers may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents
Because ReoPro® inhibits platelet aggregation, caution should be employed when used with other drugs affecting hemostasis such as heparin, oral anticoagulants such as warfarin, thrombolytics and antiplatelet agents other than acetylsalicylic acid, such as dipyridamole, ticlopidine or low molecular weight dextrans.

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 randomized patients with acute myocardial infarction to treatment with combined ReoPro® and half-dose Reteplase, or full-dose Reteplase alone (7). 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). This increase was more pronounced in patients above age 75. Also noted in this age group, but not in other age groups, was a trend towards increased incidence of intracranial hemorrhage in those patients receiving ReoPro® and half-dose Reteplase versus those receiving Reteplase alone.

If urgent intervention is required for refractory symptoms, it is recommended that PTCA using ReoPro® be attempted first to salvage the situation. Should PTCA and any other appropriate procedures fail, and should the angiographic appearance suggest that the etiology is due to thrombosis, consideration may be given to the administration of adjunctive thrombolytic therapy

via the intracoronary route. Prior to surgical interventions, the bleeding time should be determined by the Ivy method and should be 12 minutes or less (see *WARNINGS AND PRECAUTIONS: Restoration of Platelet Function*).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The safety and efficacy of ReoPro® (abciximab) have only been investigated with concomitant administration of heparin and acetylsalicylic acid.
- Acetylsalicylic acid should be administered orally at a daily dose of 300 to 325 mg.
- For heparin anticoagulation guidelines see *WARNINGS AND PRECAUTIONS: Bleeding Precautions: Heparin*.
- In patients with failed PTCAs, the continuous infusion of ReoPro® should be stopped because there is no evidence for ReoPro® efficacy in that setting.
- In the event of serious bleeding that cannot be controlled by compression, ReoPro® and heparin should be discontinued immediately (*see WARNINGS AND PRECAUTIONS: Restoration of Platelet Function*).

Recommended Dose and Dosage Adjustment

Adults
The recommended dose of ReoPro® is a 0.25 mg/kg intravenous bolus followed by a 0.125 µg/kg/min (to a maximum of 10 µg/min) continuous intravenous infusion.

For the stabilization 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 ischemic cardiac complications in patients undergoing percutaneous coronary intervention, and who are not currently receiving a ReoPro® infusion, the bolus should be administered 10-60 minutes prior to the intervention, followed by the infusion for twelve (12) hours.

Administration

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. Epinephrine, 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 and appropriate treatment given.
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 0.2 or 0.22 µm filter (Millipore SLGV025LS or equivalent).
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 or 0.22 µm syringe filter (Millipore SLGV025LS or equivalent) or upon administration using an in-line, sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 µm filter (Abbott #4524 or equivalent).
6. Discard the unused portion at the end of the infusion.
7. Although incompatibilities have not been observed 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.
8. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets.

OVERDOSAGE

There has been no experience of overdosage with ReoPro® (abciximab) in human clinical trials. However, refer to Reversal of Antiplatelet Effects in the *WARNINGS AND PRECAUTIONS* section.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ReoPro® (abciximab) is the Fab fragment of the chimeric monoclonal antibody 7E3. It selectively binds to the glycoprotein IIb/IIIa (GPIIb/IIIa) 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 with similar affinity to the vitronectin ($\alpha_v\beta_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells. The vitronectin receptor mediates pro-coagulant properties of platelets and proliferative properties of vascular endothelial cells and smooth muscle cells.

Pharmacodynamics

Intravenous administration in humans of single bolus doses of ReoPro® from 0.15 mg/kg to 0.30 mg/kg resulted in a dose-dependent blockade of platelet GPIIb/IIIa receptors and produced dose-dependent inhibition of platelet function as measured by *ex vivo* platelet aggregation in response to 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 μM 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.

Intravenous administration in humans of a single bolus dose of 0.25 mg/kg followed by a continuous infusion of 10 μg/min for periods of 12 to 96 hours produced sustained high-grade platelet inhibition (ex vivo platelet aggregation in response to 5 or 20 μM 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 μg/kg/min to a maximum of 10 μg/min) was used in patients up to 80 kg. Results in patients who received the 0.25 mg/kg bolus followed by a 5 μg/min infusion for 24 hours showed a similar initial inhibition of platelet aggregation, but the response was not maintained throughout the infusion period. Following cessation of the infusion, platelet function typically returned to baseline values over a period of 24 to 48 hours.

Pharmacokinetics

Following intravenous administration of ReoPro®, free plasma concentrations decreased very rapidly with an initial half-life of several 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 (approximately 80,000 to 100,000 GPIIb/IIIa receptors on the surface of each platelet).

After a single bolus injection of ReoPro®, the inhibitory effects on platelet function, as measured by inhibition of platelet aggregation, were evident within 10 minutes. The antibody remains in the circulation for 15 days or more in a platelet-bound state. Its disappearance follows a monoexponential time course.

Intravenous administration of a 0.25 mg/kg bolus dose of ReoPro® followed by continuous infusion of 5 or 10 μg/min for periods of 12 to 96 hours produced relatively constant total plasma concentrations from the first time point measured (usually 2 hours) for all infusion rates and durations. However, although the total plasma concentrations resulting from the 5 μg/min infusion were only slightly lower than those from the 10 μg/min infusion, the 5 μg/min infusion was ineffective in inhibiting platelet function over the whole infusion period. At the termination of the infusion period, plasma concentrations fell rapidly for approximately 6 hours, then declined at a much slower rate.

STORAGE AND STABILITY

Vials should be stored at 2 to 8°C (36 to 46°F). Do not freeze. Do not shake. Do not use beyond the expiration date. Discard any unused portion left in the vial.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ReoPro® (abciximab) is available in solution for intravenous injection and supplied in a 5 mL (10 mg) vial in packages of single vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: abciximab (ReoPro®)

Chemical name: abciximab

Molecular mass: 47,615 daltons

Physicochemical properties: ReoPro® is a clear, colorless, sterile, non-pyrogenic solution for intravenous (IV) use. Each mL contains 2 mg of abciximab in a buffered solution (pH 7.2) of 0.01 M sodium phosphate, 0.15 M sodium chloride and 0.001% polysorbate 80. No preservatives are added.

Product Characteristics

ReoPro® (abciximab) is a chimeric Fab fragment that binds to platelet glycoprotein IIb/IIIa. Abciximab is generated by papain cleavage of the intact chimeric monoclonal antibody 7E3 comprising antigen-binding variable regions of murine monoclonal antibody 7E3 and constant regions of human $IgG_{1\kappa}$.

CLINICAL TRIALS

Study demographics and trial design

Table 3- Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% Female)
EPIC Trial	Multicenter, double-blind, placebo-controlled	ReoPro® bolus (0.25 mg/kg)/ ReoPro® infusion (10 µg/min) for 12 hours			
		Bolus + Infusion	708	60.0±10.6 (26, 83)	27.9%
		Bolus	695		
		Placebo	696		
EPILOG Trial	Randomized, double-blind, multicenter, placebo-controlled	ReoPro® bolus (0.25 mg/kg)/ ReoPro® infusion (0.125 µg/kg/min – maximum 10 µg/min) for 12 hours + heparin			
		ReoPro® + Low-Dose Heparin	935	59.7±11.0 (29, 89)	27.9%
		ReoPro® + Standard Dose Heparin	918		
		Placebo + Standard Dose Heparin	939		

The EPIC Trial

The Evaluation of c7E3 to Prevent Ischemic Complications (EPIC) trial was a multicenter, double-blind, placebo-controlled trial of ReoPro® (abciximab) in patients undergoing percutaneous transluminal coronary angioplasty or atherectomy (PTCA) (1-3). 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: 1) a ReoPro® bolus (0.25 mg/kg) followed by a ReoPro® infusion (10 µg/min) for twelve hours (bolus plus infusion group); 2) a ReoPro® bolus (0.25 mg/kg) followed by a placebo infusion (bolus group), or; 3) a placebo bolus followed by a placebo infusion (placebo group). Patients at high risk during or following PTCA were defined as those with unstable angina or a non-Q-wave myocardial infarction (n=489), those with an acute Q-wave myocardial infarction within twelve hours of

symptom onset (n=66), and those who were at high risk because of coronary morphology and/or clinical characteristics (n=1544). Treatment with study agent in each of the three arms was initiated 10-60 minutes before the onset of PTCA. 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 twelve hours to maintain a therapeutic elevation of activated partial thromboplastin time (APTT, 1.5-2.5 times normal). Unless contraindicated, acetylsalicylic acid (325 mg) was administered orally two hours prior to the planned procedure and then once daily.

The EPILOG Trial
A second trial (Evaluation of PTCA to Improve Long-term Outcome by c7E3 GPIIb/IIIa Receptor Blockade or EPILOG), also a randomized, double-blind, multicenter, placebo-controlled trial, evaluated ReoPro® in a broad population of PTCA patients (but excluding patients myocardial infarction and unstable angina meeting the EPIC high risk criteria) (4). 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[1], ReoPro® plus low dose, weight-adjusted heparin[2] 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[3]. 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 randomized patients are shown in Table 5. The EPILOG trial also achieved the objective of lowering the bleeding rate: in the ReoPro® treatment arms major bleeding was reduced to the level of placebo (see *ADVERSE REACTIONS: Bleeding*).

Study results

The EPIC Trial
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 ischemia (i.e. 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 events for each treatment group by intention-to-treat analysis of all randomized patients are shown in Table 4. 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

[1] Bolus administration of 100 U/kg weight-adjusted heparin to achieve an activated clotting time (ACT) of ≥ 300 seconds (maximum initial bolus 10,000 units).
[2] Bolus administration of 70 U/kg weight-adjusted heparin to achieve an activated clotting time (ACT) of 200 seconds (maximum initial bolus 7,000 units).
[3] Bolus administration of 0.25 mg/kg ReoPro 10 to 60 minutes before PTCA immediately followed by a 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 hours.

angina, patients presenting within twelve hours of the onset of symptoms of an acute myocardial infarction, 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 subgroup.

Table 4: Primary Endpoint Events at 30-Days -EPIC Trial

Event	Placebo (n=696)	Bolus (n=695)	Infusion (n=708)
	Number of Patients (%)		
Primary Endpoint[a]	89 (12.8)	79 (11.5)	59 (8.3)
p-value vs. placebo		0.428	0.008
Components of Primary Endpoint[b]			
Death	12 (1.7)	9 (1.3)	12 (1.7)
Acute myocardial infarctions in surviving patients	55 (7.9)	40 (5.8)	31 (4.4)
Urgent interventions in surviving patients without an acute myocardial infarction	22 (3.2)	30 (4.4)	16 (2.2)

[a] Patients who experienced more than one event in the first 30 days are counted only once.
[b] Patients are counted only once under the most serious component (death > acute MI > urgent intervention).

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 (1), 6 months (2) and 3 years (3). 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).

The EPILOG Trial

The 30-day Kaplan-Meier primary endpoint events for each treatment group by intention-to-treat analysis of all 2792 randomized patients are shown in Table 5. The EPILOG trial also achieved the objective of lowering the bleeding rate: in the ReoPro® treatment arms major bleeding was reduced to the level of placebo (see *ADVERSE REACTIONS: Bleeding*).

Table 5: Primary Endpoint Events at 30 Days -EPILOG Trial

Event	Placebo + Standard Dose Heparin (n=939)	ReoPro® + Standard Dose Heparin (n=918)	ReoPro® + Low Dose Heparin (n=935)
	Number of Patients (%)		
Death or MI[a]	85 (9.1)	38 (4.2)	35 (3.8)
p-value vs. Placebo		<0.0001	<0.0001
Death, MI or urgent intervention[a]	109 (11.7)	49 (5.4)	48 (5.2)
p-value vs. Placebo		<0.0001	<0.0001
Endpoint components[b]			
Death	7 (0.8)	4 (0.4)	3 (0.3)
MI in surviving	78 (8.4)	34 (3.7)	32 (3.4)

patients			
Urgent intervention in surviving patients without acute MI	24 (2.6)	11 (1.2)	13 (1.4)

[a] Patients who experienced more than 1 event in the first 30 days are counted only once.
[b] Patients are counted only once under the most serious component (death > acute MI > urgent intervention)

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 myocardial infarctions was significantly lower in the groups treated with ReoPro®. While most myocardial infarctions 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

Study demographics and trial design

Table 6- Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% Female)
CAPTURE Trial	Randomized, double-blind, multicenter, placebo-controlled	ReoPro® bolus (0.25 mg/kg)/ ReoPro® infusion (10 µg/min)			
		ReoPro®	630	60.8±10.0	27.3%
		Placebo	635	(32, 80)	

The CAPTURE Trial
The CAPTURE (Chimeric Anti-Platelet Therapy in Unstable angina Refractory to standard medical therapy) trial was a randomized, double-blind, multicenter, placebo-controlled trial designed to determine if potent antiplatelet therapy would reduce ischemic complications and stabilize unstable angina patients not responding to conventional therapy who were candidates for percutaneous coronary intervention (5). In contrast to the EPIC and EPILOG trials, the CAPTURE trial involved the administration, in addition to conventional therapy, of placebo or ReoPro® starting up to 24 hours prior to PTCA and continuing until 1 hour after completion of PTCA. The ReoPro® dose was a 0.25 mg/kg bolus followed by a continuous infusion at a rate of 10 µg/min. The CAPTURE trial did incorporate weight adjustment of the standard heparin dose, but did not investigate the effect of a lower heparin dose, and arterial sheaths were left in place for approximately 40 hours.

Study results

The CAPTURE Trial
The 30-day Kaplan-Meier primary endpoint events for each treatment group by intention-to-treat analysis of all 1265 randomized patients are shown in Table 7.

Table 7: Primary Outcome Events at 30 Days -CAPTURE Trial

Event	Placebo (n=635) Number of Patients (%)	ReoPro® (n=630)
Death, MI or urgent intervention[a]	101 (15.9%)	71 (11.3%)
p-value vs. placebo		(p=0.012)
Endpoint components[b]		
Death	8 (1.3%)	6 (1.0%)
MI in surviving patients	49 (7.7%)	24 (3.8%)
Urgent intervention in surviving patients without acute MI	44 (6.9%)	41 (6.6%)

[a] Patients who experienced more than one event in the first 30 days are counted only once.
[b] Patients are counted only once under the most serious component (death>acute MI>urgent intervention).

Figure 1 shows the Kaplan-Meier event rate curves for myocardial infarction for the periods from randomization to angioplasty and from angioplasty through 24 hours post angioplasty. A reduction in myocardial infarction is apparent both pre-and post-angioplasty. The 30-day results are consistent with the EPIC and EPILOG trials, with the greatest effects on the myocardial infarction and urgent revascularization components of the composite endpoint.

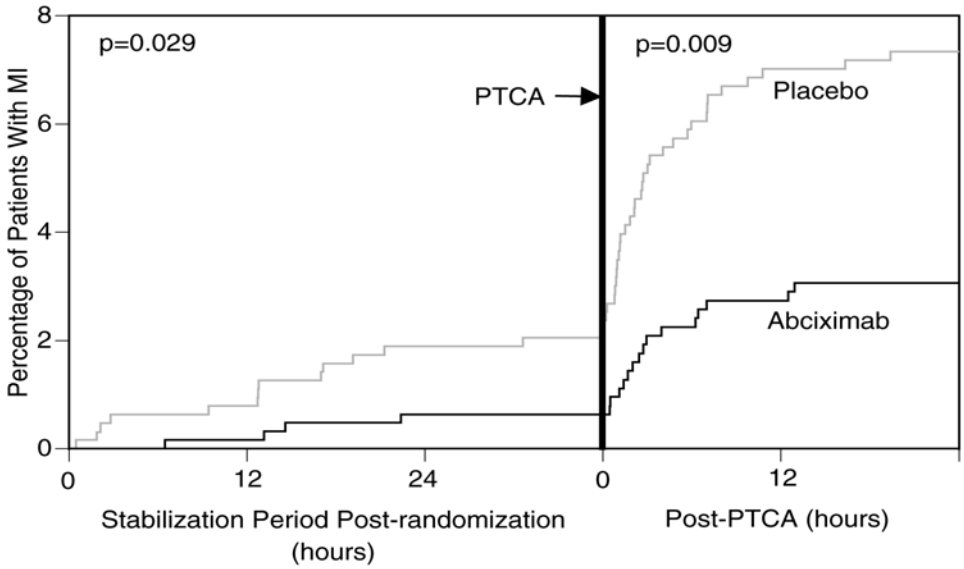

Figure 1. Kaplan-Meier event rates for myocardial infarction before and after PTCA.

DETAILED PHARMACOLOGY

In vitro Studies

c7E3 Fab has been studied extensively with regard to both antigen binding and functional ability to inhibit platelet aggregation. Using platelets from humans, cynomolgus monkey, and baboons, the chimeric 7E3 Fab fragment displayed a dose-dependent inhibition of platelet aggregation. Similar binding characteristics were observed to affinity-isolated human GPIIb/IIIa receptors.

Animal Studies

To determine whether the ability of 7E3 to inhibit platelet aggregation correlates with therapeutic potential in the treatment of vascular disease, 7E3 has been investigated in several animal models of vaso-occlusive disease. Dogs, monkeys, and baboons were employed in these studies because 7E3 cross-reacts with the GPIIb/IIIa receptor on canine and nonhuman primate platelets. Because the m7E3 $F(ab')_2$ and Fab fragments and the c7E3 Fab fragment are functionally equivalent with respect to platelet GPIIb/IIIa binding and inhibition of platelet aggregation, preclinical efficacy studies with any of these test materials provide valid data for determining potential clinical utility associated with 7E3 inhibition of platelet aggregation.

Establishment of In Vivo Dose-Response: A dose-response study in dogs established that doses of 0.81 mg/kg of m7E3 $F(ab')_2$ blocked 85% of GPIIb/IIIa receptors and almost completely abolished platelet aggregation in response to ADP 30 minutes after infusion (8). Both the inhibition of platelet aggregation and the number of blocked GPIIb/IIIa sites progressively decreased over the next days. No obvious ill effects were detected; there was no spontaneous bleeding and no evidence of coagulopathy.

In Vivo Equivalence of 7E3 Fab and $F(ab')_2$: A direct comparison of the *in vivo* activity of 7E3 Fab and m7E3 $F(ab')_2$ was performed in cynomolgus monkeys (9). Both fragments of m7E3 were found to inhibit ADP-induced platelet aggregation to a similar degree. Blockade of platelet GPIIb/IIIa receptors was also comparable in the two groups. To explore the comparative

immunogenicity of the Fab and the $F(ab')_2$ fragments of m7E3, animals were administered several follow-up injections of antibody. The results of this comparative study established that while the *in vivo* antiplatelet activities of m7E3 Fab and m7E3 $F(ab')_2$ were comparable, Fab fragment exhibited decreased immunogenicity (9).

Prevention of Thrombosis at Sites of Vessel Wall Injury: The m7E3 $F(ab')_2$ fragment was tested *in vivo* models of platelet thrombus formation in stenosed coronary arteries in dogs and carotid arteries of monkeys developed by Folts (10, 11). This model was specifically designed to simulate the situation in partially stenosed vessels with underlying atherosclerotic lesions when patients suffer acute intermittent ischemia from injured (ruptured or fissured) atherosclerotic plaques, as in unstable angina and post-PTCA abrupt closure (cardiac circulation) or transient ischemic attacks (cerebral circulation) (12). An intravenous dose (0.8 mg/kg) of m7E3 $F(ab')_2$, which completely inhibits *ex vivo* platelet aggregation, not only abolished thrombotic cycles, but also protected against their return by a variety of provocations. On occasion, a dose as low as 0.1 mg/kg, which produced only 41% platelet inhibition, could also abolish thrombus formation. More recent work in monkeys has demonstrated that both m7E3 Fab and c7E3 Fab are as effective as the m7E3 $F(ab')_2$ fragment in abolishing *in vivo* thrombus formation in the Folts mode (13).

Direct Current Internal Injury Model of Thrombosis: Mickelson et al. (14) confirmed that 7E3 $F(ab')_2$ prevents coronary artery thrombosis in an experimental dog model of vascular wall injury. In this model dose intimal injury is induced at the site of stenosis by delivery of anodal direct current which results in spontaneous oscillations in coronary blood flow preceding a final complete thrombotic occlusion. Compared to controls, a dose of 0.8 mg/kg $F(ab')_2$: 1) prevented thrombotic left circumflex coronary artery occlusion, 2) inhibited platelet aggregation, 3) minimized platelet deposition on injured vascular endothelium and in established thrombi, and 4) stabilized left circumflex coronary artery blood flow for 5 hours after injury.

The 7E3 antibody has also been investigated in a model of acute thrombosis following injury induced by coronary angioplasty in dogs (15). This investigation established an effective model of acute occlusion that was dependent on platelet deposition following balloon-induced deep arterial injury. Treatment with m7E3 $F(ab')_2$ prior to angioplasty prevented the formation of either occlusive or non-occlusive thrombi in 8 dogs. Acetylsalicylic acid, in contrast, was only partially effective.

Coronary Angioplasty Model: Studies by Bates et al. (15) examined whether m7E3 $F(ab')_2$ could prevent acute thrombosis following coronary angioplasty in a canine model. Coronary angioplasty was performed in the left anterior descending coronary artery of dogs pretreated with a bolus injection of either 0.8 mg/kg of 7E3 $F(ab')_2$, 325 mg acetylsalicylic acid or saline control. This study demonstrated that m7E3 $F(ab')_2$ was superior to acetylsalicylic acid in inhibiting platelet aggregation, thrombosis and acute closure.

Enhancement of Thrombolytic Efficacy: Several studies have examined the combination of 7E3

with thrombolytic agents in promoting thrombolysis using different models of arterial thrombosis in dogs and primates. All have reported that the addition of 7E3 to a standard thrombolytic regiment enhances thrombolysis and prevents reocclusion.

Instilled Coronary Model: To test the role of 7E3 in enhancing the action of recombinant tissue-type plasminogen activator (rt-PA), Yasuda *et al.* (16) used a localized coronary thrombosis model in open chest dogs. A performed thrombus was placed at a site of intimal damage, immediately proximal to a constricted segment of the left anterior descending coronary artery in heparinized animals. Intravenous infusion of rt-PA at a rate of 15 µg/kg/minute (two-chain rt-PA) or 30 µg/kg/minute (single chain rt-PA) alone for 30-60 minutes failed to prevent reocclusion despite heparin anticoagulation. Intravenous injection of 0.8 mg/kg of m7E3 $F(ab')_2$ in addition to rt-PA prevented reocclusion during a 2-hour observation period. The antibody abolished ADP-induced platelet aggregation and prolonged bleeding time.

In another study, Gold *et al.* (17), using the canine model described above, administered intravenous bolus doses of rt-PA alone and in combination with m7E3 $F(ab')_2$ to determine whether thrombolysis could be accelerated in addition to preventing reocclusion. In this model, reocclusion occurred in animals treated with 450 µg/kg rt-PA alone. In contrast, accelerated thrombolysis without reocclusion was observed when bolus injections of 0.8 mg/kg m7E3 $F(ab')_2$ alone, without rt-PA.

Ziskind *et al.* demonstrated similar benefit of adding m7E3 $F(ab')_2$ to the combined thrombolytic regimen of rt-PA and single-chain urokinase-type plasminogen activator (scu-PA) in the same dog coronary thrombosis model (18). Although various dosage combinations of rt-PA and scu-PA produced synergistic effects in achieving thrombolysis, all animals experienced reocclusion. Reocclusion was abolished by combining a single pretreatment dose of 0.6 mg/kg m7E3 $F(ab')_2$.

Everted Coronary Artery Model: The ability of m7E3 $F(ab')_2$ to enhance rt-PA thrombolysis was also examined in a dog model of platelet-rich coronary artery thrombus using eversion of a circumflex coronary artery segment (19). In this model of highly resistant coronary thrombolysis, in which no animals treated with rt-PA alone had enduring successful thrombolysis, m7E3 $F(ab')_2$ was able to facilitate and maintain reperfusion with reduced doses of rt-PA. Again, occasional animals achieved sustained reperfusion with infusion of m7E3 $F(ab')_2$ alone, without rt-PA.

Direct Current Intimal Injury Model: The efficacy of m7E3 $F(ab')_2$ as an adjunct to thrombolytic therapy was demonstrated by Fitzgerald *et al.* (20) using an electrical current intimal injury model of coronary thrombosis in dogs. Coadministrations of several adjunctive antiplatelet regimens with 10 µg/kg/minute rt-PA were compared. Compared to prostacyclin (PGl2), acetylsalicylic acid, or thromboxane, At (TXA2) at doses sufficient to inhibit platelet aggregation, only m7E3 $F(ab')_2$ achieved accelerated thrombolysis without reocclusion, using reduced thrombolytic doses.

Instilled Femoral Artery Thrombus Model in Baboons: Chimeric 7E3 Fab was investigated in a baboon model of thrombin-induced thrombus formation (21) similar to the dog model developed by Gold *et al.* (22). An occlusive thrombus was instilled in the femoral artery after which intravenous bolus doses of rt-PA were administered to heparinized animals in combination with either c7E3 Fab or acetylsalicylic acid. Administration of c7E3 Fab in combination with rt-PA produced a more rapid and more stable reperfusion of the baboon femoral artery with a lower total dose of rt-PA in comparison to acetylsalicylic acid administered in combination with rt-PA.

TOXICOLOGY

Acute Intravenous Studies

Single Dose Studies: Sprague-Dawley rats were injected with saline or 26.4 mg/kg c7E3 Fab. No mortality or drug related signs of toxicity were observed. Necropsy revealed no gross pathological changes.

Single intravenous dose studies in cynomolgus monkeys revealed that c7E3 Fab was well tolerated at doses up to 8 µg/kg. Transient gingival bleeding, epistaxis and bruising were observed post-dosing.

Multiple-Day Intravenous Studies

One-month Rat: rats were given c7E3 Fab once daily at 0, 0.5, 5.0, or 10.0 mg/kg/day for 30 days. No deaths or signs of toxicity considered to be c7E3 Fab-related were observed during the study.

Two-day Monkey: c7E3 Fab was given to cynomolgus monkeys as a 0.3 mg/kg bolus followed immediately by a 0.45 µg/kg/minute infusion. No signs of toxicity considered to be c7E3 Fab-related were observed.

Four-day Monkey: c7E3 Fab as a 0.6 µg/kg bolus injection immediately followed by a 0.8 µg/kg/minute I.V. infusion over 96 hours was well tolerated in rhesus monkeys.

Two-week Monkey: Cynomolgus monkeys given c7E3 Fab once daily intravenously for fourteen days at doses up to 1 µg/kg/day tolerated the drug well for the first week of treatment. On days 11 through 13, significant signs of toxicity in all treatment groups became severe and frequent, especially in the high-dose animals. Due to the deteriorating condition and adverse hematological findings for some of the monkeys, treatment was discontinued. As expected following repeat bolus intravenous doses of a foreign protein, a monkey anti-chimeric antibody response was detected in the serum of animals in all c7E3 Fab treatment groups, which induced thrombocytopenia and consequent hemorrhaging and anemia during the second week of

treatment. Following a 2-week recovery period, evidence of reversibility of effects was observed.

Interaction with Other Drugs

Concomitant administration of c7E3 Fab (0.3 µg/kg bolus dose followed by 0.45 or 0.5 µg/kg/min infusion for 48 hours) with heparin (100 U/kg bolus doses followed by 50 U/kg/hr infusion for 48 hours), rt-PA (1.25 mg/kg dose of Activase® over 3 hours or Streptokinase at 30,000 U/kg over 1 hour) and acetylsalicylic acid (25 mg/day oral dose) was well tolerated in rhesus monkeys.

***In Vitro* Human Tissue Cross-reactivity Studies**

Immunohistochemical studies demonstrated that Murine 7E3 Fab and c7E3 Fab reacted with platelets from blood smears and megakaryocyte in the bone marrow at 3 different antibody dilutions. No cross-reactivity was observed with any other tissues or organs.

***In Vitro* and *In Vivo* Mutagenicity Studies**

The mutagenic potential of c7E3 Fab was evaluated in three separate assays. c7E3 Fab did not exhibit mutagenic activity in the *in vitro* mammalian forward gene mutation assay (Chinese hamster ovary cells/hypoxanthine-guanine phosphoribosyl transferase; CHO/HPRT), *in vitro* chromosomal aberration analysis (CHO cells), or *in vivo* mouse micronucleus test.

REFERENCES

1. EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Eng J Med* 1994; 300:956-961.

2. Topol EJ, Califf RM, Weisman HF, et al: Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994:343:881-886.

3. Topol EJ, Ferguson JJ, Weisman HF, et al. for the EPIC Investigators. Long term protection from myocardial ischemic events in a randomized trial of brief integrin blockade with percutaneous coronary intervention. *JAMA* 1997;278:479-484.

4. EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low dose heparin during percutaneous coronary revascularization. *N Eng J Med*. 1997;336:1689-1696.

5. CAPTURE Investigators. Randomized placebo-controlled trial of abciximab before,

during and after coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;349:1429-1435.

6. Kalra S, Bell MR, Rihal CS. Alveolar Hemorrhage as a Complication of Treatment with Abciximab. *Chest* 2001;120:126-131.

7. Data on file.

8. Coller BS, Scudder LE. Inhibition of dog platelet function by *in vivo* infusion of $F(ab')_2$ fragments of a monoclonal antibody. *Blood* 1985;66:1456-1459.

9. Jordan RE, Wagner CL, McAleer MF, Spitz MS, Mattis JA. Evaluation of the potency and immunogenicity of 7E3 $F(ab')_2$ and Fab fragments in monkeys. *Circ* (Suppl III) 1990;82:661.

10. Coller BS, Folts JD, Scudder LE, Smith SR. Antithrombotic effect of a monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor in an experimental animal model. *Blood* 1986;68:783-786.

11. Coller BS, Folts JD, Smith SR, Scudder LE, Jordan R. Abolition of *in vivo* platelet thrombus formation in primates with monoclonal antibodies to the platelet GPIIb/IIIa receptor. *Circ* 1989;80:1766-1773.

12. Sherman CT, Litvock F, Grundfest W, Lee M, Hickey A, Chaux A, Kass R, Blanche C, Matloff J, Morgenstern L, Ganz W, Swan HJC, Forrester J. Coronary angioscopy in patients with unstable angina pectoris. *N Eng J Med* 1986;315:913-919.

13. Folts Jd, University of Wisconsin, Madison, WI. Personal Communication.

14. Mickelson JK, Simpson PJ, Lucchesi BR. Antiplatelet monoclonal $F(ab')_2$ antibody directed against the platelet GPIIb/IIIa receptor complex prevents coronary artery thrombosis in the canine heart. *J Mol Cell Cardiol* 1989;21:393-405.

15. Bates ER, McGillem MJ, Mickelson JK, Pitt B, Mancini GBJ. A monoclonal antibody against the platelet glycoprotein IIb/IIIa receptor complex prevents platelet aggregation and thrombosis in a canine model of coronary angioplasty. *Circ* 1991;84:2463-2469.

16. Yasuda T, Gold HK, Fallon JT, Leinbach RC, Guerrero JL, Scudder LE, Kanke M, Shealy D, Ross MJ, Collen D, Coller BS. Monoclonal antibody against the platelet glycoprotein (GP) IIb/IIIa receptor prevents coronary artery reocclusion after reperfusion with recombinant tissue-type plasminogen activator in dogs. *J Clin Invest* 1988;81:1284-1291.

17. Gold HK, Coller BS, Yasuda T, Saito T, Fallon JT, Guerrero JL, Leinbach RC, Ziskind AA, Collen D. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet GPIIb/IIIa antibody in a canine preparation. *Circ* 1988;77:670-677.

18. Ziskind AA, Gold HK, Yasuda T, Kanke M, Guerrero JL, Fallon JT, Saito T, Collen D. Synergistic combinations of recombinant human tissue-type plasminogen activator and human single-chain urokinase-type plasminogen activator. *Circ* 1989;79:393-399.

19. Yasuda T, Gold HK, Leinbach RC, Saito T, Guerrero JL, Jang I-K, Holt R, Fallong JT, Collen D. Lysis of plasminogen activator-resistant platelet-rich coronary artery thrombus with combined bolus injection of recombinant tissue-type plasminogen activator and antiplatelet GPIIb/IIIa antibody. *J Am Coll Card* 1990;16:1728-1735.

20. Fitzgerald DJ, Wright F, Fitzgerald GA. Increased thromboxane biosynthesis during coronary thrombolysis. *Circ Res* 1989;65:83-94.

21. Kohmura C, Gold HK, Yasuda T, Holt R, Nedelman MA, Guerrero JL, Weisman HF, Collen D. A chimeric murine/human antibody Fab fragment directed against the platelet GPIIb/IIIa receptor enhances and sustains arterial thrombolysis with recombinant tissue-type plasminogen activator in baboons. *Artherio Thromb* 1993;13:1837-1842.

22. Gold HK, Gimple LW, Yasuda T, Leinbach RC, Werner W, Jordan R, Berger H, Collen D, Coller B. Pharmacodynamic study of $F(ab')_2$ fragments of murine monoclonal antibody 7E3 directed against human platelet glycoprotein IIb/IIIa in patients with unstable angina pectoris. *J Clin Invest* 1990;86:651-659.

PART III: CONSUMER INFORMATION

ReoPro®
abciximab

This leaflet is part III of a three-part "Product Monograph" published when ReoPro® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ReoPro®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ReoPro® is used when you undergo an operation known as angioplasty (see "What is an angioplasty operation?" below) for the following purposes:

- ReoPro® is used (together with heparin and aspirin) to prevent the formation of blood clots in the heart during or after an angioplasty operation.

- ReoPro® is also used (together with heparin and aspirin) to lower the short term risk of getting a heart attack before an angioplasty operation, which is planned to take place within the next 1-month. This is for patients who have chest pain due to low blood supply to the heart (unstable angina) and have not responded to the usual therapy.

What is an angioplasty operation?
An angioplasty operation aims to open blocked arteries around the heart. A doctor will carefully guide a special instrument through an artery (which is usually in the groin) to reduce or remove the blockage.
There are three types of angioplasty operations where ReoPro® can be used:

- Using an inflatable balloon to compress an artery blockage (balloon angioplasty)
- Using a cutting device to open a blocked artery (atherectomy)
- Inserting an expandable metal sheath to keep an artery open (stent)

What it does:
The active ingredient, abciximab, is a 'fragment of murine/human chimeric monoclonal antibody'. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. ReoPro® belongs to a group of medicines known as antithrombotics and binds to platelets in your blood to help to prevent blood clots.

When it should not be used:
Your doctor will review your medical history to see if you are at an increased risk for any side effects associated with being given ReoPro®.
To prevent risks of increased bleeding ReoPro® must not be given:

- if you have internal bleeding
- if you have bleeding in the intestines. Symptoms may include vomiting blood, blood in feces or black feces.
- if you have had a stroke within the last two years
- if you have had any head, spinal surgery (or trauma) or other major surgery in the last two months
- if you have brain cancer
- if you have serious bleeding problems or have very low amounts of platelets in your blood
- if you have uncontrolled high blood pressure
- if you have an abnormal bulge in one of your blood vessels (aneurysm)
- if you have serious problems with your liver
- if you are on dialysis for kidney failure

ReoPro® must not be given if you are allergic (hypersensitive):

- to abciximab, to any of the other ingredients of ReoPro® or to a group of medicines known as 'murine monoclonal antibodies'.

If you think that you fit into any of the categories described above, it is important that you discuss it with your doctor. ReoPro® must not be given in these situations.

What the medicinal ingredient is:
abciximab

What the important nonmedicinal ingredients are:
Sodium phosphate, sodium chloride, polysorbate 80. No preservative are added.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
What ReoPro® contains

- ReoPro® 2 mg/mL is supplied as a solution for injection or infusion containing 10 milligrams of abciximab (active ingredient) dissolved in 5 milliliters of water for injection.

What ReoPro® looks like and contents of the pack
ReoPro® 2 mg/mL pack contains a 10 mL labeled glass vial filled with colourless and clear ReoPro® liquid.

WARNINGS AND PRECAUTIONS

BEFORE you use ReoPro® talk to your doctor or pharmacist if:

- if you are taking blood-thinning medicines or any other medicines that affect blood clotting or blood platelets (see "INTERACTIONS WITH THIS MEDICATION" section).

- if you have previously received ReoPro®, since this could be associated with higher risk of reduction in blood platelets or allergic reactions (hypersensitivity).

- If you think that you fit into any of the categories described above, it is important that you discuss it with your doctor.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ReoPro® include:
Blood-thinning medicines, or any other medicines that affect blood clotting ('anticoagulants') or blood platelets ('anti-platelet medicines'). It is particularly important that you tell your doctor if 'thrombolytic' medicines have been given to unblock your arteries. Being given ReoPro® together with these medicines may put you at risk of increased bleeding.

PROPER USE OF THIS MEDICATION

Usual dose:
Your nurse or doctor will inject ReoPro® liquid from a syringe into one of your veins. This is known as a 'bolus injection'.

After you have had the injection, your nurse, doctor or pharmacist will put more diluted ReoPro® liquid into a bag which is connected by a tube to a needle which goes into one of your veins. This is known as a 'drip' or 'infusion'. Depending on your condition ReoPro® will be given to you as follows:

If you are about to undergo an angioplasty operation, your doctor will give you the bolus injection 10 to 60 minutes before the operation begins. After the bolus injection your doctor will start the infusion. The infusion will continue for 12 hours after the operation is completed.

If you have unstable angina (chest pain due to low blood supply to the heart) and are scheduled for an angioplasty operation, your doctor will give you the bolus injection up to 24 hours before the scheduled operation. After the bolus injection your doctor will start the infusion. The infusion will continue for 12 hours after the operation is completed.

Dosage
Your doctor will calculate the dose of ReoPro® to give to you as follows:

The dose of the bolus injection will be based on your body weight. The dose is 0.25 milligrams for every kilogram of your body weight.

The infusion dose will also be based on your body weight. The dose is 0.125 micrograms per kilogram per minute up to a maximum of 10 micrograms per minute.

After the operation
After the angioplasty operation your doctor or nurse will gently press a dressing on the artery to stop any bleeding. Total bed rest is required by the patient and the leg on which the angioplasty has been performed must be kept in a straight position for at least 6 to 8 hours. You will also be carefully observed by your doctor and nurse and your blood pressure and pulse will be measured several times. Regular blood tests will also be performed to monitor your blood cell count.

Overdose:
There has been no experience with ReoPro® in human trials.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ReoPro® can cause side effects, although not everybody gets them. If you notice any of the below side effects, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	Bleeding (including bruising, purple skin rash, nose bleed, vaginal bleeding, blood in urine and feces)		√
	Low blood platelet count. Symptoms include easy or excessive bruising, bleeding under the skin, bleeding from nose or gums.		√
	Chest pain		√
	Pain in the abdomen		√
	Slow heart rate		√
	Nausea or vomiting		√
	Pain at the injection site	√	
	Back pain	√	
	Headache	√	
	Swelling of arms and legs		√
	Very low blood pressure. Symptoms include dizziness or feeling faint		√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Uncommon	Bleeding in the skull. Symptoms include pain in the head; speech, visual or hearing difficulties; numbness or lack of feeling; problems with movement or balance		√
	Build up of blood around the heart. Symptoms are a combination of rapid heartbeat, chest pain, shortness of breath, sweating and fatigue.		√
	Bleeding in the lungs. Symptoms include coughing blood, wheezing, rapid breathing, airway obstruction.		√
	Serious restriction in breathing capacity. Symptoms include shortness of breath, rapid and shallow breathing.		√
	Bleeding in the intestines. Symptoms include vomiting blood, blood in faeces or black faeces.		√
	Allergic reactions. Symptoms include skin rash, itchy and swollen skin, difficulty in breathing		√

This is not a complete list of side effects. For any unexpected effects while taking ReoPro®, contact your doctor or pharmacist.

HOW TO STORE IT

Your doctor or other healthcare professionals will take care of handling and storing ReoPro® according to the following instructions:

- Keep out of the reach and sight of children.
- Store in a refrigerator (2°C and 8°C).
- Do not freeze.
- Do not shake.
- Do not use ReoPro® after the expiry date which is stated on the carton and vial label after the letters EXP. The expiry date refers to the last day of that month.
- Do not use ReoPro® if you notice discoloring of the liquid or opaque particles in the liquid.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.lilly.ca
or by contacting the sponsor, Eli Lilly Canada, Inc.
at: 1-888-545-5972

This leaflet was prepared by
Janssen Inc.

Last revised: March 12, 2012.