ReoPro®
Abciximab

For intravenous administration
DESCRIPTION:
Abciximab, ReoPro®, is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin ($\alpha_v\beta_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells.

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.

ReoPro® is a clear, colorless, sterile, non-pyrogenic solution for intravenous (IV) use. Each single use vial contains 2 mg/mL 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 in Water for Injection. No preservatives are added.

CLINICAL PHARMACOLOGY:
General- Abciximab 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. Abciximab 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.

Abciximab binds with similar affinity to the vitronectin receptor, also known as the $\alpha_v\beta_3$ integrin. The vitronectin receptor mediates the procoagulant properties of platelets and the proliferative properties of vascular endothelial and smooth muscle cells. In *in vitro* studies using a model cell line derived from melanoma cells, Abciximab blocked $\alpha_v\beta_3$-mediated effects including cell adhesion (IC_{50} = 0.34 μg/mL). At concentrations which, *in vitro*, provide > 80% GPIIb/IIIa receptor blockade, but above the *in vivo* therapeutic range, Abciximab more effectively blocked the burst of thrombin generation that followed platelet activation than select comparator antibodies which inhibit GPIIb/IIIa alone (1). The relationship of these *in vitro* data to clinical efficacy is unknown.

Abciximab also binds to the activated Mac-1 receptor on monocytes and neutrophils (2). In *in vitro* studies, Abciximab and 7E3 IgG blocked Mac-1 receptor function as evidenced by inhibition of monocyte adhesion (3). In addition, the degree of activated Mac-1 expression on circulating leukocytes and the numbers of circulating leukocyte-platelet complexes has been shown to be reduced in patients treated with Abciximab

compared to control patients (4). The relationship of these *in vitro* data to clinical efficacy is uncertain.

Pre-clinical experience- Maximal inhibition of platelet aggregation was observed when ≥ 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 ≥ 80% by continuous intravenous infusion. The inhibitory effects of Abciximab were substantially reversed by the transfusion of platelets in 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.

Pharmacokinetics- Following intravenous bolus administration, free plasma concentrations of Abciximab decrease rapidly with an initial half-life of less than 10 minutes and a second phase half-life of about 30 minutes, probably related to rapid binding to the platelet GPIIb/IIIa receptors. Platelet function generally recovers over the course of 48 hours (5,6), although Abciximab remains in the circulation for 15 days or more in a platelet-bound state. Intravenous administration of a 0.25 mg/kg bolus dose of Abciximab followed by continuous infusion of 10 μg/min (or a weight-adjusted infusion of 0.125 μg/kg/min to a maximum of 10 μg/min) produces approximately constant free plasma concentrations throughout the infusion. At the termination of the infusion period, free plasma concentrations fall rapidly for approximately six hours then decline at a slower rate.

Pharmacodynamics- Intravenous administration in humans of single bolus doses of Abciximab 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 two hours post injection (the first time point evaluated), 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 five 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 GPIIb/IIIa receptor blockade (≥ 80%) and inhibition of platelet function (*ex vivo* platelet aggregation in response to 5 μM 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. Similar 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 weighing 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 receptor blockade and inhibition of platelet

aggregation, but the response was not maintained throughout the infusion period. The onset of Abciximab-mediated platelet inhibition following a 0.25 mg/kg bolus and 0.125 μg/kg/min infusion was rapid and platelet aggregation was reduced to less than 20% of baseline in 8 of 10 patients at 10 minutes after treatment initiation.

Low levels of GPIIb/IIIa receptor blockade are present for more than 10 days following cessation of the infusion. After discontinuation of Abciximab 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 μM 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 μM 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%).

CLINICAL STUDIES:

Abciximab has been studied in four Phase 3 clinical trials, all of which evaluated the effect of Abciximab in patients undergoing percutaneous coronary intervention (PCI): in patients at high risk for abrupt closure of the treated coronary vessel (EPIC), in a broader group of patients (EPILOG), in unstable angina patients not responding to conventional medical therapy (CAPTURE), and in patients suitable for either conventional angioplasty/atherectomy or primary stent implantation (EPILOG Stent; EPISTENT). Percutaneous intervention included balloon angioplasty, atherectomy, or stent placement. All trials involved the use of various, concomitant heparin dose regimens and, unless contraindicated, aspirin (325 mg) was administered orally two hours prior to the planned procedure and then once daily.

EPIC was a multicenter, double-blind, placebo-controlled trial of Abciximab in patients undergoing percutaneous transluminal coronary angioplasty or atherectomy (PTCA) who were at high risk for abrupt closure of the treated coronary vessel (7). Patients were allocated to treatment with: 1) Abciximab bolus plus infusion for 12 hours; 2) Abciximab bolus plus placebo infusion, or; 3) placebo bolus plus infusion. All patients received concomitant heparin (10,000 to 12,000 U bolus followed by an infusion for 12 hours).

The primary endpoint was the composite of death, myocardial infarction (MI), or urgent intervention for recurrent ischemia within 30 days of randomization. The primary endpoint event rates in the Abciximab bolus plus infusion group were reduced mostly in the first 48 hours and this benefit was sustained through 30 days (7), 6 months (8), and three years (9).

EPILOG was a randomized, double-blind, multicenter, placebo-controlled trial which evaluated Abciximab in a broad population of patients undergoing PCI (excluding patients with myocardial infarction and unstable angina meeting the EPIC high risk criteria) (10). Study procedures emphasized discontinuation of heparin after the procedure with early femoral arterial sheath removal and careful access site management (see PRECAUTIONS). EPILOG was a three-arm trial comparing Abciximab plus standard-dose heparin, Abciximab plus low-dose heparin, and placebo plus standard-dose heparin. Abciximab and heparin infusions were weight-adjusted in all arms. The Abciximab bolus plus infusion regimen was: 0.25 mg/kg bolus followed by a 0.125 μg/kg/min infusion (to a maximum of 10 μg/min) for 12 hours. The heparin regimen was either a standard-dose regimen (initial 100 U/kg bolus, target ACT ≥ 300 seconds) or a low-dose regimen (initial 70 U/kg bolus, target ACT ≥ 200 seconds).

The primary endpoint of the EPILOG trial was the composite of death or MI occurring within 30 days of PCI. The composite of death, MI, or urgent intervention was an important secondary endpoint. The endpoint events in the Abciximab treatment group were reduced mostly in the first 48 hours and this benefit was sustained through 30 days and six months (10) and one year (11). The (Kaplan-Meier) endpoint event rates at 30 days are shown in Table 1.

Table 1
ENDPOINT EVENT RATES AT 30 DAYS - EPILOG TRIAL

	Placebo + Standard Dose Heparin (n=939)	Abciximab + Standard Dose Heparin (n=918)	Abciximab + 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		<0.001	<0.001
Death, MI, or urgent intervention[a]	109 (11.7)	49 (5.4)	48 (5.2)
p-value vs. placebo		<0.001	<0.001
Components of Composite Endpoints[b]			
Death	7 (0.8)	4 (0.4)	3 (0.3)
Acute myocardial infarctions in surviving patients	78 (8.4)	34 (3.7)	32 (3.4)
Urgent interventions in surviving patients without an acute myocardial infarction	24 (2.6)	11 (1.2)	13 (1.4)

[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).

At the six-month follow up visit, the event rate for death, MI, or repeat (urgent or non-urgent) intervention remained lower in the Abciximab treatment arms (22.3% and 22.8%, respectively, for the standard- and low-dose heparin arms) than in the placebo arm (25.8%) and the event rate for death, MI, or urgent intervention was substantially lower in the Abciximab treatment arms (8.3% and 8.4%, respectively, for the standard- and low-dose heparin arms) than in the placebo arm (14.7%). The treatment associated effects continued to persist at the one-year follow up visit. The proportionate reductions in endpoint event rates were similar irrespective of the type of coronary intervention used (balloon angioplasty, atherectomy, or stent placement). Risk assessment using the American College of Cardiology/American Heart Association clinical/morphological criteria had large inter-observer variability. Consequently, a low risk subgroup could not be reproducibly identified in which to evaluate efficacy.

The EPISTENT trial was a randomized, multicenter trial evaluating three different treatment strategies in patients undergoing PCI: conventional PTCA with Abciximab plus low-dose heparin, primary intracoronary stent implantation with Abciximab plus low-

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