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

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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

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93 aggregation, but the response was not maintained throughout the infusion period. The
94 onset of Abciximab-mediated platelet inhibition following a 0.25 mg/kg bolus and 0.125
95 μg/kg/min infusion was rapid and platelet aggregation was reduced to less than 20% of
96 baseline in 8 of 10 patients at 10 minutes after treatment initiation.
97
98 Low levels of GPIIb/IIIa receptor blockade are present for more than 10 days following
99 cessation of the infusion. After discontinuation of Abciximab infusion, platelet function
100 returns gradually to normal. Bleeding time returned to ≤ 12 minutes within 12 hours
101 following the end of infusion in 15 of 20 patients (75%), and within 24 hours in 18 of 20
102 patients (90%). *Ex vivo* platelet aggregation in response to 5 μM ADP returned to ≥ 50%
103 of baseline within 24 hours following the end of infusion in 11 of 32 patients (34%) and
104 within 48 hours in 23 of 32 patients (72%). In response to 20 μM ADP, *ex vivo* platelet
105 aggregation returned to ≥ 50% of baseline within 24 hours in 20 of 32 patients (62%) and
106 within 48 hours in 28 of 32 patients (88%).
107
108 **CLINICAL STUDIES:**
109 Abciximab has been studied in four Phase 3 clinical trials, all of which evaluated the
110 effect of Abciximab in patients undergoing percutaneous coronary intervention (PCI): in
111 patients at high risk for abrupt closure of the treated coronary vessel (EPIC), in a broader
112 group of patients (EPILOG), in unstable angina patients not responding to conventional
113 medical therapy (CAPTURE), and in patients suitable for either conventional
114 angioplasty/atherectomy or primary stent implantation (EPILOG Stent; EPISTENT).
115 Percutaneous intervention included balloon angioplasty, atherectomy, or stent placement.
116 All trials involved the use of various, concomitant heparin dose regimens and, unless
117 contraindicated, aspirin (325 mg) was administered orally two hours prior to the planned
118 procedure and then once daily.
119
120 EPIC was a multicenter, double-blind, placebo-controlled trial of Abciximab in patients
121 undergoing percutaneous transluminal coronary angioplasty or atherectomy (PTCA) who
122 were at high risk for abrupt closure of the treated coronary vessel (7). Patients were
123 allocated to treatment with: 1) Abciximab bolus plus infusion for 12 hours; 2) Abciximab
124 bolus plus placebo infusion, or; 3) placebo bolus plus infusion. All patients received
125 concomitant heparin (10,000 to 12,000 U bolus followed by an infusion for 12 hours).
126
127 The primary endpoint was the composite of death, myocardial infarction (MI), or urgent
128 intervention for recurrent ischemia within 30 days of randomization. The primary
129 endpoint event rates in the Abciximab bolus plus infusion group were reduced mostly in
130 the first 48 hours and this benefit was sustained through 30 days (7), 6 months (8), and
131 three years (9).
132
133 EPILOG was a randomized, double-blind, multicenter, placebo-controlled trial which
134 evaluated Abciximab in a broad population of patients undergoing PCI (excluding
135 patients with myocardial infarction and unstable angina meeting the EPIC high risk
136 criteria) (10). Study procedures emphasized discontinuation of heparin after the
137 procedure with early femoral arterial sheath removal and careful access site management
138 (*see PRECAUTIONS*). EPILOG was a three-arm trial comparing Abciximab plus

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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).

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160 At the six-month follow up visit, the event rate for death, MI, or repeat (urgent or
161 non-urgent) intervention remained lower in the Abciximab treatment arms (22.3% and
162 22.8%, respectively, for the standard- and low-dose heparin arms) than in the placebo
163 arm (25.8%) and the event rate for death, MI, or urgent intervention was substantially
164 lower in the Abciximab treatment arms (8.3% and 8.4%, respectively, for the standard-
165 and low-dose heparin arms) than in the placebo arm (14.7%). The treatment associated
166 effects continued to persist at the one-year follow up visit. The proportionate reductions
167 in endpoint event rates were similar irrespective of the type of coronary intervention used
168 (balloon angioplasty, atherectomy, or stent placement). Risk assessment using the
169 American College of Cardiology/American Heart Association clinical/morphological
170 criteria had large inter-observer variability. Consequently, a low risk subgroup could not
171 be reproducibly identified in which to evaluate efficacy.
172
173 The EPISTENT trial was a randomized, multicenter trial evaluating three different
174 treatment strategies in patients undergoing PCI: conventional PTCA with Abciximab plus
175 low-dose heparin, primary intracoronary stent implantation with Abciximab plus low-
176 dose heparin, and primary intracoronary stent implantation with placebo plus standard-
177 dose heparin (12). The heparin dose was weight-adjusted in all arms. The JJIS Palmaz-
178 Schatz stent was used in over 90% of the patients receiving stents. The two stent arms
179 were blinded with respect to study agent (Abciximab or placebo) and heparin dose; the
180 PCI arm with Abciximab was open-label. The Abciximab bolus plus infusion regimen
181 was the same as that used in the EPILOG trial. The standard-dose and low-dose heparin
182 regimens were the same as those used in the EPILOG trial. All patients were to receive
183 aspirin; ticlopidine, if given, was to be started prior to study agent. Patient and access
184 site management guidelines were the same as those for EPILOG, including a strong
185 recommendation for early sheath removal.
186
187 The results demonstrated benefit in both Abciximab arms (i.e., with and without stents)
188 compared with stenting alone on the composite of death, MI, or urgent intervention
189 (repeat PCI or CABG) within 30 days of PCI (12). The (Kaplan-Meier) endpoint event
190 rates at 30 days are shown in Table 2.
191

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Table 2
PRIMARY ENDPOINT EVENT RATE AT 30 DAYS - EPISTENT TRIAL

	Placebo + Stent (n=809)	Abciximab + Stent (n=794)	Abciximab + PTCA (n=796)
	Number of Patients (%)		
Death, MI, or urgent intervention[a]	87 (10.8%)	42 (5.3%)	55 (6.9%)
p-value vs. placebo		<0.001	0.007
Components of Composite Endpoint[b]			
Death	5 (0.6%)	2 (0.3%)	6 (0.8%)
Acute myocardial infarctions in surviving patients	77 (9.6%)	35 (4.4%)	40 (5.0%)
Urgent interventions in surviving patients without an acute myocardial infarction	5 (0.6%)	5 (0.6%)	9 (1.1%)

[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).

192 This benefit was maintained at 6 months: 12.1% of patients in the placebo/stent group
193 experienced death, MI, or urgent revascularization compared with 6.4% of patients in the
194 Abciximab/stent group (p<0.001 vs placebo/stent) and 9.2% in the Abciximab/PTCA
195 group (p=0.051 vs placebo/stent). At 6 months, a reduction in the composite of death,
196 MI, or all repeat (urgent or non-urgent) intervention was observed in the Abciximab/stent
197 group compared with the placebo/stent group (15.4% vs 20.4%, p=0.006); the rate of this
198 composite endpoint was similar in the Abciximab/PTCA and placebo/stent groups
199 (22.4% vs 20.4%, p=0.467). (13)
200
201 CAPTURE was a randomized, double-blind, multicenter, placebo-controlled trial of the
202 use of Abciximab in unstable angina patients not responding to conventional medical
203 therapy for whom PCI was planned, but not immediately performed (14). The CAPTURE
204 trial involved the administration of placebo or Abciximab starting 18 to 24 hours prior to
205 PCI and continuing until one hour after completion of the intervention.
206
207 Patients were assessed as having unstable angina not responding to conventional medical
208 therapy if they had at least one episode of myocardial ischemia despite bed rest and at
209 least two hours of therapy with intravenous heparin and oral or intravenous nitrates.
210 These patients were enrolled into the CAPTURE trial, if during a screening angiogram,
211 they were determined to have a coronary lesion amenable to PCI. Patients received a
212 bolus dose and intravenous infusion of placebo or Abciximab for 18 to 24 hours. At the

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213 end of the infusion period, the intervention was performed. The Abciximab or placebo
214 infusion was discontinued one hour following the intervention. Patients were treated
215 with intravenous heparin and oral or intravenous nitrates throughout the 18- to 24-hour
216 Abciximab infusion period prior to the PCI.
217
218 The Abciximab dose was a 0.25 mg/kg bolus followed by a continuous infusion at a rate
219 of 10 µg/min. The CAPTURE trial incorporated weight adjustment of the standard
220 heparin dose only during the performance of the intervention, but did not investigate the
221 effect of a lower heparin dose, and arterial sheaths were left in place for approximately 40
222 hours. The primary endpoint of the CAPTURE trial was the occurrence of any of the
223 following events within 30 days of PCI: death, MI, or urgent intervention. The 30-day
224 (Kaplan-Meier) primary endpoint event rates are shown in Table 3.
225
226

Table 3
PRIMARY ENDPOINT EVENT RATE AT 30 DAYS – CAPTURE TRIAL

	Placebo (n=635)	Abciximab (n=630)
	Number of Patients (%)	
Death, MI, or urgent intervention[a]	101 (15.9)	71 (11.3)
p-value vs. placebo		0.012
Components of Primary Endpoint[b]		
Death	8 (1.3)	6 (1.0)
MI in surviving patients	49 (7.7)	24 (3.8)
Urgent intervention in surviving patients without an 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. Urgent interventions included any unplanned PCI after the planned intervention, as well as any stent placement for immediate patency and any unplanned CABG or use of an intra-aortic balloon pump.
[b] Patients are counted only once under the most serious component (death > acute MI > urgent intervention).

227
228
229 The 30-day results are consistent with the results of the other three trials, with the greatest
230 effects on the myocardial infarction and urgent intervention components of the composite
231 endpoint. As secondary endpoints, the components of the composite endpoint were
232 analyzed separately for the period prior to the PCI and the period from the beginning of
233 the intervention through Day 30. The greatest difference in MI occurred in the
234 post-intervention period: the rates of MI were lower in the Abciximab group compared
235 with placebo (Abciximab 3.6%, placebo 6.1%). There was also a reduction in MI
236 occurring prior to the PCI (Abciximab 0.6%, placebo 2.0%). An Abciximab-associated

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reduction in the incidence of urgent intervention occurred in the post-intervention period. No effect on mortality was observed in either period. At six months of follow up, the composite endpoint of death, MI, or all repeat intervention (urgent or non-urgent) was not different between the Abciximab and placebo groups (Abciximab 31.0%, placebo 30.8%, p=0.77).

Mortality was uncommon in all four trials. Similar mortality rates were observed in all arms within each trial. Patient follow-up through one year of the EPISTENT trial suggested decreased mortality among patients treated with Abciximab and stent placement compared to patients treated with stent alone (8/794 vs. 19/809, p=0.037). Data from earlier studies with balloon angioplasty were not suggestive of the same benefit. In all four trials, the rates of acute MI were significantly lower in the groups treated with Abciximab. Most of the Abciximab treatment effect was seen in reduction in the rate of acute non-Q-wave MI. Urgent intervention rates were also lower in Abciximab-treated groups in these trials.

Anticoagulation:
EPILOG and EPISTENT: Weight-adjusted low dose heparin, weight-adjusted Abciximab, careful vascular access site management and discontinuation of heparin after the procedure with early femoral arterial sheath removal were used.

The initial heparin bolus was based upon the results of the baseline ACT, according to the following regimen:

ACT < 150 seconds: administer 70 U/kg heparin
ACT 150 - 199 seconds: administer 50 U/kg heparin
ACT ≥ 200 seconds: administer no heparin

Additional 20 U/kg heparin boluses were given to achieve and maintain an ACT of ≥ 200 seconds during the procedure.

Discontinuation of heparin immediately after the procedure and removal of the arterial sheath within six hours were strongly recommended in the trials. If prolonged heparin therapy or delayed sheath removal was clinically indicated, heparin was adjusted to keep the APTT at a target of 60 to 85 seconds (EPILOG) or 55 to 75 seconds (EPISTENT).

CAPTURE trial: Anticoagulation was initiated prior to the administration of Abciximab. Anticoagulation was initiated with an intravenous heparin infusion to achieve a target APTT of 60 to 85 seconds. The heparin infusion was not uniformly weight adjusted in this trial. The heparin infusion was maintained during the Abciximab infusion and was adjusted to achieve an ACT of 300 seconds or an APTT of 70 seconds during the PCI. Following the intervention, heparin management was as outlined above for the EPILOG trial.

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281
282 **INDICATIONS AND USAGE:**
283 Abciximab is indicated as an adjunct to percutaneous coronary intervention for the
284 prevention of cardiac ischemic complications
285 - in patients undergoing percutaneous coronary intervention
286 - in patients with unstable angina not responding to conventional medical therapy
287 when percutaneous coronary intervention is planned within 24 hours
288
289 Safety and efficacy of Abciximab use in patients not undergoing percutaneous coronary
290 intervention have not been established.
291
292 Abciximab is intended for use with aspirin and heparin and has been studied only in that
293 setting, as described in CLINICAL STUDIES.
294
295 **CONTRAINDICATIONS:**
296 Because Abciximab may increase the risk of bleeding, Abciximab is contraindicated in
297 the following clinical situations:
298 - Active internal bleeding
299 - Recent (within six weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of
300 clinical significance.
301 - History of cerebrovascular accident (CVA) within two years, or CVA with a
302 significant residual neurological deficit
303 - Bleeding diathesis
304 - Administration of oral anticoagulants within seven days unless prothrombin time is
305 ≤ 1.2 times control
306 - Thrombocytopenia (< 100,000 cells/μL)
307 - Recent (within six weeks) major surgery or trauma
308 - Intracranial neoplasm, arteriovenous malformation, or aneurysm
309 - Severe uncontrolled hypertension
310 - Presumed or documented history of vasculitis
311 - Use of intravenous dextran before PCI, or intent to use it during an intervention
312
313 Abciximab is also contraindicated in patients with known hypersensitivity to any
314 component of this product or to murine proteins.
315
316 **WARNINGS:**
317
318 **Bleeding Events**
319
320 Abciximab has the potential to increase the risk of bleeding events, rarely including those
321 with a fatal outcome, particularly in the presence of anticoagulation, e.g., from heparin,
322 other anticoagulants, or thrombolytics (*see ADVERSE REACTIONS: Bleeding*).
323
324 The risk of major bleeds due to Abciximab therapy is increased in patients receiving
325 thrombolytics and should be weighed against the anticipated benefits.
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327 Should serious bleeding occur that is not controllable with pressure, the infusion of
328 Abciximab and any concomitant heparin should be stopped.
329
330 **Allergic Reactions (including anaphylaxis)**

331 Allergic reactions, some of which were anaphylaxis (sometimes fatal), have been
332 reported rarely in patients treated with ReoPro. Patients with allergic reactions should
333 receive appropriate treatment. Treatment of anaphylaxis should include immediate
334 discontinuation of ReoPro administration and initiation of resuscitative measures.
335
336 **PRECAUTIONS:**
337 **Bleeding Precautions-** To minimize the risk of bleeding with Abciximab, it is important
338 to use a low-dose, weight-adjusted heparin regimen, a weight-adjusted Abciximab bolus
339 and infusion, strict anticoagulation guidelines, careful vascular access site management,
340 discontinuation of heparin after the procedure and early femoral arterial sheath removal.
341
342 Therapy with Abciximab requires careful attention to all potential bleeding sites
343 including catheter insertion sites, arterial and venous puncture sites, cutdown sites, needle
344 puncture sites, and gastrointestinal, genitourinary, pulmonary (alveolar), and
345 retroperitoneal sites.
346
347 Arterial and venous punctures, intramuscular injections, and use of urinary catheters,
348 nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs should be
349 minimized. When obtaining intravenous access, non-compressible sites (e.g., subclavian
350 or jugular veins) should be avoided. Saline or heparin locks should be considered for
351 blood drawing. Vascular puncture sites should be documented and monitored. Gentle
352 care should be provided when removing dressings.
353
354 *Femoral artery access site:* Arterial access site care is important to prevent bleeding.
355 Care should be taken when attempting vascular access that only the anterior wall of the
356 femoral artery is punctured, avoiding a Seldinger (through and through) technique for
357 obtaining sheath access. Femoral vein sheath placement should be avoided unless
358 needed. While the vascular sheath is in place, patients should be maintained on complete
359 bed rest with the head of the bed ≤ 30° and the affected limb restrained in a straight
360 position. Patients may be medicated for back/groin pain as necessary.
361
362 Discontinuation of heparin immediately upon completion of the procedure and removal
363 of the arterial sheath within six hours is strongly recommended if APTT ≤ 50 sec or
364 ACT ≤ 175 sec (*see PRECAUTIONS: Laboratory Tests*). In all circumstances, heparin
365 should be discontinued at least two hours prior to arterial sheath removal.
366
367 Following sheath removal, pressure should be applied to the femoral artery for at least 30
368 minutes using either manual compression or a mechanical device for hemostasis. A
369 pressure dressing should be applied following hemostasis. The patient should be
370 maintained on bed rest for six to eight hours following sheath removal or discontinuation
371 371 of Abciximab, or four hours following discontinuation of heparin, whichever is later.
372 The pressure dressing should be removed prior to ambulation. The sheath insertion site

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373 and distal pulses of affected leg(s) should be frequently checked while the femoral artery
374 sheath is in place and for six hours after femoral artery sheath removal. Any hematoma
375 should be measured and monitored for enlargement.
376
377 The following conditions have been associated with an increased risk of bleeding and
378 may be additive with the effect of Abciximab in the angioplasty setting: PCI within 12
379 hours of the onset of symptoms for acute myocardial infarction, prolonged PCI (lasting
380 more than 70 minutes) and failed PCI.
381
382 **Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents-** In the EPIC,
383 EPILOG, CAPTURE, and EPISTENT trials, Abciximab was used concomitantly with
384 heparin and aspirin. For details of the anticoagulation algorithms used in these clinical
385 trials, see *CLINICAL STUDIES: Anticoagulation*. Because Abciximab inhibits platelet
386 aggregation, caution should be employed when it is used with other drugs that affect
387 hemostasis, including thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory
388 drugs, dipyridamole, and ticlopidine.
389
390 In the EPIC trial, there was limited experience with the administration of Abciximab with
391 low molecular weight dextran. Low molecular weight dextran was usually given for the
392 deployment of a coronary stent, for which oral anticoagulants were also given. In the 11
393 patients who received low molecular weight dextran with Abciximab, five had major
394 bleeding events and four had minor bleeding events. None of the five placebo patients
395 treated with low molecular weight dextran had a major or minor bleeding event (*see*
396 *CONTRAINDICATIONS*).
397
398 Because of observed synergistic effects on bleeding, Abciximab therapy should be used
399 judiciously in patients who have received systemic thrombolytic therapy. The GUSTO V
400 trial randomized patients with acute myocardial infarction to treatment with combined
401 Abciximab and half-dose Reteplase, or full-dose Reteplase alone (15). In this trial, the
402 incidence of moderate or severe nonintracranial bleeding was increased in those patients
403 receiving Abciximab and half-dose Reteplase versus those receiving Reteplase alone
404 (4.6% versus 2.3%, respectively).
405
406 **Thrombocytopenia-** Thrombocytopenia, including severe thrombocytopenia, has been
407 observed with Abciximab administration (*see ADVERSE REACTIONS:*
408 *Thrombocytopenia*). Platelet counts should be monitored prior to, during, and after
409 treatment with Abciximab. Acute decreases in platelet count should be differentiated
410 between true thrombocytopenia and pseudothrombocytopenia (*see PRECAUTIONS:*
411 *Laboratory Tests*). If true thrombocytopenia is verified, Abciximab should be
412 immediately discontinued and the condition appropriately monitored and treated.
413
414 In clinical trials, patients who developed thrombocytopenia were followed with daily
415 platelet counts until their platelet count returned to normal. Heparin and aspirin were
416 discontinued for platelet counts below 60,000 cells/μL and platelets were transfused for a
417 platelet count below 50,000 cells/μL. Most cases of severe thrombocytopenia (< 50,000
418 cells/μL) occurred within the first 24 hours of Abciximab administration.

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419
420 In a registry study of Abciximab readministration, a history of thrombocytopenia
421 associated with prior use of Abciximab was predictive of an increased risk of recurrent
422 thrombocytopenia (*see ADVERSE REACTIONS: Thrombocytopenia*). Readministration
423 within 30 days was associated with an increased incidence and severity of
424 thrombocytopenia, as was a positive human anti-chimeric antibody (HACA) test at
425 baseline, compared to the rates seen in studies with first administration.
426
427 **Restoration of Platelet Function-** In the event of serious uncontrolled bleeding or the
428 need for emergency surgery, Abciximab should be discontinued. If platelet function does
429 not return to normal, it may be restored, at least in part, with platelet transfusions.
430
431 **Laboratory Tests-** Before infusion of Abciximab, prothrombin time, ACT, APTT, and
432 platelet count should be measured to identify pre-existing hemostatic abnormalities.
433
434 Based on an integrated analysis of data from all studies, the following guidelines may be
435 utilized to minimize the risk for bleeding:
436
437 When Abciximab is initiated 18 to 24 hours before PCI, the APTT should be maintained
438 between 60 and 85 seconds during the Abciximab and heparin infusion period.
439
440 During PCI the ACT should be maintained between 200 and 300 seconds.
441
442 If anticoagulation is continued in these patients following PCI, the APTT should be
443 maintained between 55 and 75 seconds.
444
445 The APTT or ACT should be checked prior to arterial sheath removal. The sheath should
446 not be removed unless APTT $\leq$ 50 seconds or ACT $\leq$ 175 seconds.
447
448 Platelet counts should be monitored prior to treatment, two to four hours following the
449 bolus dose of Abciximab and at 24 hours or prior to discharge, whichever is first. If a
450 patient experiences an acute platelet decrease (e.g., a platelet decrease to less than
451 100,000 cells/µL and a decrease of at least 25% from pre-treatment value), additional
452 platelet counts should be determined. Platelet monitoring should continue until platelet
453 counts return to normal.
454
455 To exclude pseudothrombocytopenia, a laboratory artifact due to *in vitro* anticoagulant
456 interaction, blood samples should be drawn in three separate tubes containing
457 ethylenediaminetetraacetic acid (EDTA), citrate and heparin, respectively. A low platelet
458 count in EDTA but not in heparin and/or citrate is supportive of a diagnosis of
459 pseudothrombocytopenia.
460
461 **Readministration-** Administration of Abciximab may result in the formation of HACA
462 that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis),
463 thrombocytopenia or diminished benefit upon readministration of Abciximab (*see*
464 *WARNINGS: Allergic Reactions; see ADVERSE REACTIONS: Immunogenicity*).

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465
466 Readministration of Abciximab to patients undergoing PCI was assessed in a registry that
467 included 1342 treatments in 1286 patients. Most patients were receiving their second
468 Abciximab exposure; 15% were receiving the third or subsequent exposure. The overall
469 rate of HACA positivity prior to the readministration was 6% and increased to 27% post-
470 readministration. There were no reports of serious allergic reactions or anaphylaxis (*see*
471 *WARNINGS: Allergic Reactions*). Thrombocytopenia was observed at higher rates in the
472 readministration study than in the phase 3 studies of first-time administration (*see*
473 *PRECAUTIONS: Thrombocytopenia and Adverse Reactions: Thrombocytopenia*),
474 suggesting that readministration may be associated with an increased incidence and
475 severity of thrombocytopenia.
476
477
478 **Drug Interactions-** Formal drug interaction studies with Abciximab have not been
479 conducted. Abciximab has been administered to patients with ischemic heart disease
480 treated concomitantly with a broad range of medications used in the treatment of angina,
481 myocardial infarction and hypertension. These medications have included heparin,
482 warfarin, beta-adrenergic receptor blockers, calcium channel antagonists, angiotensin
483 converting enzyme inhibitors, intravenous and oral nitrates, ticlopidine, and aspirin.
484 Heparin, other anticoagulants, thrombolytics, and antiplatelet agents are associated with
485 an increase in bleeding. Patients with HACA titers may have allergic or hypersensitivity
486 reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
487
488 **Carcinogenesis, Mutagenesis and Impairment of Fertility-** *In vitro* and *in vivo*
489 mutagenicity studies have not demonstrated any mutagenic effect. Long-term studies in
490 animals have not been performed to evaluate the carcinogenic potential or effects on
491 fertility in male or female animals.
492
493 **Pregnancy Category C-** Animal reproduction studies have not been conducted with
494 Abciximab. It is also not known whether Abciximab can cause fetal harm when
495 administered to a pregnant woman or can affect reproduction capacity. Abciximab
496 should be given to a pregnant woman only if clearly needed.
497
498 **Nursing Mothers-** It is not known whether this drug is excreted in human milk or
499 absorbed systemically after ingestion. Because many drugs are excreted in human milk,
500 caution should be exercised when Abciximab is administered to a nursing woman.
501
502 **Pediatric Use-** Safety and effectiveness in pediatric patients have not been studied.
503
504 **Geriatric Use-** Of the total number of 7860 patients in the four Phase 3 trials, 2933
505 (37%) were 65 and over, while 653 (8%) were 75 and over. No overall differences in
506 safety or efficacy were observed between patients of age 65 to less than 75 as compared
507 to younger patients. The clinical experience is not adequate to determine whether
508 patients of age 75 or greater respond differently than younger patients.
509
510 **ADVERSE REACTIONS:**

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511 **Bleeding-** Abciximab has the potential to increase the risk of bleeding, particularly in the
512 presence of anticoagulation, e.g., from heparin, other anticoagulants or thrombolytics.
513 Bleeding in the Phase 3 trials was classified as major, minor or insignificant by the
514 criteria of the Thrombolysis in Myocardial Infarction study group (16). Major bleeding
515 events were defined as either an intracranial hemorrhage or a decrease in hemoglobin
516 greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria,
517 spontaneous hematemesis, observed blood loss with a hemoglobin decrease of more than
518 3 g/dL, or a decrease in hemoglobin of at least 4 g/dL without an identified bleeding site.
519 Insignificant bleeding events were defined as a decrease in hemoglobin of less than 3
520 g/dL or a decrease in hemoglobin between 3-4 g/dL without observed bleeding. In
521 patients who received transfusions, the number of units of blood lost was estimated
522 through an adaptation of the method of Landefeld, et al. (17).
523

524 In the EPIC trial, in which a non-weight-adjusted, longer-duration heparin dose regimen
525 was used, the most common complication during Abciximab therapy was bleeding during
526 the first 36 hours. The incidences of major bleeding, minor bleeding and transfusion of
527 blood products were significantly increased. Major bleeding occurred in 10.6% of
528 patients in the Abciximab bolus plus infusion arm compared with 3.3% of patients in the
529 placebo arm. Minor bleeding was seen in 16.8% of Abciximab bolus plus infusion
530 patients and 9.2% of placebo patients (7). Approximately 70% of Abciximab-treated
531 patients with major bleeding had bleeding at the arterial access site in the groin.
532 Abciximab-treated patients also had a higher incidence of major bleeding events from
533 gastrointestinal, genitourinary, retroperitoneal, and other sites.
534

535 Bleeding rates were reduced in the CAPTURE trial, and further reduced in the EPILOG
536 and EPISTENT trials by use of modified dosing regimens and specific patient
537 management techniques. In EPILOG and EPISTENT, using the heparin and Abciximab
538 dosing, sheath removal and arterial access site guidelines described under
539 PRECAUTIONS, the incidence of major bleeding in patients treated with Abciximab and
540 low-dose, weight-adjusted heparin was not significantly different from that in patients
541 receiving placebo.
542

543 Subgroup analyses in the EPIC and CAPTURE trials showed that non-CABG major
544 bleeding was more common in Abciximab patients weighing ≤ 75 kg. In the EPILOG
545 and EPISTENT trials, which used weight-adjusted heparin dosing, the non-CABG major
546 bleeding rates for Abciximab-treated patients did not differ substantially by weight
547 subgroup.
548

549 Although data are limited, Abciximab treatment was not associated with excess major
550 bleeding in patients who underwent CABG surgery. (The range among all treatment
551 arms was 3-5% in EPIC, and 1-2% in the CAPTURE, EPILOG, and EPISTENT trials.)
552 Some patients with prolonged bleeding times received platelet transfusions to correct the
553 bleeding time prior to surgery. (*see PRECAUTIONS: Restoration of Platelet Function*.)
554

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555 The rates of major bleeding, minor bleeding and bleeding events requiring transfusions in
556 the CAPTURE, EPILOG, and EPISTENT trials are shown in Table 4. The rates of
557 insignificant bleeding events are not included in Table 4.
558
559 Cases of fatal bleeding have been reported rarely during post-marketing use of
560 Abciximab (*see WARNINGS: Bleeding Events*).
561
562 Pulmonary alveolar hemorrhage has been rarely reported during use of Abciximab. This
563 can present with any or all of the following in close association with ReoPro
564 administration: hypoxemia, alveolar infiltrates on chest x-ray, hemoptysis, or an
565 unexplained drop in hemoglobin.
566
567

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Table 4
NON-CABG BLEEDING IN TRIALS OF PERCUTANEOUS CORONARY INTERVENTION (EPILOG, EPISTENT and CAPTURE)
Number of Patients with Bleeds (%)

EPILOG and EPISTENT:

	Placebo[c] (n = 1748)	Abciximab + Low-dose Heparin[d] (n=2525)	Abciximab + Standard-dose Heparin[e] (n=918)
Major[a]	18 (1.0)	21 (0.8)	17 (1.9)
Minor	46 (2.6)	82 (3.2)	70 (7.6)
Requiring transfusion[b]	15 (0.9)	13 (0.5)	7 (0.8)

CAPTURE:

	Placebo[f] (n=635)	Abciximab[f] (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)

[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] Patients with major non-CABG bleeding who received packed red blood cells or whole blood transfusion.
[c] Standard-dose heparin with or without stent (EPILOG and EPISTENT)
[d] Low-dose heparin with or without stent (EPILOG and EPISTENT)
[e] Standard-dose heparin (EPILOG)
[f] Standard-dose heparin (CAPTURE)

568
569 **Intracranial Hemorrhage and Stroke-** The total incidence of intracranial hemorrhage
570 and non-hemorrhagic stroke across all four trials was not significantly different, 9/3023
571 for placebo patients and 15/4680 for Abciximab-treated patients. The incidence of
572 intracranial hemorrhage was 3/3023 for placebo patients and 7/4680 for Abciximab
573 patients.
574
575 **Thrombocytopenia-** In the clinical trials, patients treated with Abciximab were more
576 likely than patients treated with placebo to experience decreases in platelet counts.
577

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Among patients in the EPILOG and EPISTENT trials who were treated with Abciximab plus low-dose heparin, the proportion of patients with any thrombocytopenia (platelets less than 100,000 cells/µL) ranged from 2.5 to 3.0%. The incidence of severe thrombocytopenia (platelets less than 50,000 cells/µL) ranged from 0.4 to 1.0% and platelet transfusions were required in 0.9 to 1.1%, respectively. Modestly lower rates were observed among patients treated with placebo plus standard-dose heparin. Overall higher rates were observed among patients in the EPIC and CAPTURE trials treated with Abciximab plus longer duration heparin: 2.6 to 5.2% were found to have any thrombocytopenia, 0.9 to 1.7% had severe thrombocytopenia, and 2.1 to 5.5% required platelet transfusion, respectively.

In a readministration registry study of patients receiving a second or subsequent exposure to Abciximab (*see 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 Abciximab 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 Abciximab, 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.

Allergic Reactions- There have been rare reports of allergic reactions, some of which were anaphylaxis (*see WARNINGS: Allergic Reactions*).

Other Adverse Reactions- Table 5 shows adverse events other than bleeding and thrombocytopenia from the combined EPIC, EPILOG and CAPTURE trials which occurred in patients in the bolus plus infusion arm at an incidence of more than 0.5% higher than in those treated with placebo.

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612

Table 5
ADVERSE EVENTS AMONG TREATED PATIENTS IN THE EPIC, EPILOG, AND CAPTURE TRIALS

Event	Placebo (n=2226)	Bolus + Infusion (n=3111)
	Number of Patients (%)	
Cardiovascular system		
Hypotension	230 (10.3)	447 (14.4)
Bradycardia	79 (3.5)	140 (4.5)
Gastrointestinal system		
Nausea	255 (11.5)	423 (13.6)
Vomiting	152 (6.8)	226 (7.3)
Abdominal pain	49 (2.2)	97 (3.1)
Miscellaneous		
Back pain	304 (13.7)	546 (17.6)
Chest pain	208 (9.3)	356 (11.4)
Headache	122 (5.5)	200 (6.4)
Puncture site pain	58 (2.6)	113 (3.6)
Peripheral edema	25 (1.1)	49 (1.6)

613
614
615 The following additional adverse events from the EPIC, EPILOG and CAPTURE trials
616 were reported by investigators for patients treated with a bolus plus infusion of
617 Abciximab at incidences which were less than 0.5% higher than for patients in the
618 placebo arm.
619
620 Cardiovascular System: ventricular tachycardia (1.4%), pseudoaneurysm (0.8%),
621 palpitation (0.5%), arteriovenous fistula (0.4%), incomplete AV block (0.3%), nodal
622 arrhythmia (0.2%), complete AV block (0.1%), embolism (limb)(0.1%);
623 thrombophlebitis (0.1%);
624
625 Gastrointestinal System: dyspepsia (2.1%), diarrhea (1.1%), ileus (0.1%),
626 gastroesophogeal reflux (0.1%);
627
628 Hemic and Lymphatic System: anemia (1.3%), leukocytosis (0.5%), petechiae (0.2%);
629
630 Nervous System: dizziness (2.9%), anxiety (1.7%), abnormal thinking (1.3%), agitation
631 (0.7%), hypesthesia (0.6%), confusion (0.5%) muscle contractions (0.4%), coma (0.2%),
632 hypertonia (0.2%), diplopia (0.1%);
633

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634 Respiratory System: pneumonia (0.4%), rales (0.4%), pleural effusion (0.3%), bronchitis
635 (0.3%) bronchospasm (0.3%), pleurisy (0.2%), pulmonary embolism (0.2%), rhonchi
636 (0.1%);
637
638 Musculoskeletal System: myalgia (0.2%);
639
640 Urogenital System: urinary retention (0.7%), dysuria (0.4%), abnormal renal function
641 (0.4%), frequent micturition (0.1%), cystalgia (0.1%), urinary incontinence (0.1%),
642 prostatitis (0.1%);
643
644 Miscellaneous: pain (5.4%), sweating increased (1.0%), asthenia (0.7%), incisional pain
645 (0.6%), pruritus (0.5%), abnormal vision (0.3%), edema (0.3%), wound (0.2%), abscess
646 (0.2%), cellulitis (0.2%), peripheral coldness (0.2%), injection site pain (0.1%), dry
647 mouth (0.1%), pallor (0.1%), diabetes mellitus (0.1%), hyperkalemia (0.1%), enlarged
648 abdomen (0.1%), bullous eruption (0.1%), inflammation (0.1%), drug toxicity (0.1%).
649
650 **Immunogenicity**
651
652 As with all therapeutic proteins, there is a potential for immunogenicity. In the EPIC,
653 EPILOG, and CAPTURE trials, positive HACA responses occurred in approximately
654 5.8% of these patients receiving a first exposure to Abciximab. No increase in
655 hypersensitivity or allergic reactions was observed with Abciximab treatment (*see*
656 *WARNINGS: Allergic Reactions*).
657
658 In a study of readministration of Abciximab to patients (*see PRECAUTIONS:*
659 *Readministration*) the overall rate of HACA positivity prior to the readministration was
660 6% and increased post-readministration to 27%. Among the 36 subjects receiving a
661 fourth or greater Abciximab exposure, HACA positive assays were observed post-
662 readministration in 16 subjects (44%). There were no reports of serious allergic reactions
663 or anaphylaxis (*see WARNINGS: Allergic Reactions*). HACA positive status was
664 associated with an increased risk of thrombocytopenia (*see PRECAUTIONS:*
665 *Thrombocytopenia*).
666
667 The data reflect the percentage of patients whose test results were considered positive for
668 antibodies to Abciximab using an ELISA assay, and are highly dependent on the
669 sensitivity and specificity of the assay. Additionally, the observed incidence of antibody
670 positivity in an assay may be influenced by several factors including sample handling,
671 timing of sample collection, concomitant medications, and underlying disease. For these
672 reasons, comparison of the incidence of antibodies to Abciximab with the incidence of
673 antibodies to other products may be misleading.
674
675 **OVERDOSAGE:**
676 There has been no experience of overdosage in human clinical trials.
677
678 **DOSAGE AND ADMINISTRATION:**

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679 The safety and efficacy of Abciximab have only been investigated with concomitant
680 administration of heparin and aspirin as described in CLINICAL STUDIES.
681
682 In patients with failed PCIs, the continuous infusion of Abciximab should be stopped
683 because there is no evidence for Abciximab efficacy in that setting.
684
685 In the event of serious bleeding that cannot be controlled by compression, Abciximab and
686 heparin should be discontinued immediately.
687
688 The recommended dosage of Abciximab in adults is a 0.25 mg/kg intravenous bolus
689 administered 10-60 minutes before the start of PCI, followed by a continuous intravenous
690 infusion of 0.125 μg/kg/min (to a maximum of 10 μg/min) for 12 hours.
691
692 Patients with unstable angina not responding to conventional medical therapy and who
693 are planned to undergo PCI within 24 hours may be treated with an Abciximab
694 0.25 mg/kg intravenous bolus followed by an 18- to 24-hour intravenous infusion of 10
695 μg/min, concluding one hour after the PCI.
696
697 **Instructions for Administration**
698 1. Parenteral drug products should be inspected visually for particulate matter prior
699 to administration. Preparations of Abciximab containing visibly opaque particles should
700 NOT be used.
701
702 2. Hypersensitivity reactions should be anticipated whenever protein solutions such
703 as Abciximab are administered. Epinephrine, dopamine, theophylline, antihistamines and
704 corticosteroids should be available for immediate use. If symptoms of an allergic
705 reaction or anaphylaxis appear, the infusion should be stopped and appropriate treatment
706 given (*see WARNINGS: Allergic Reactions*).
707
708 3. As with all parenteral drug products, aseptic procedures should be used during the
709 administration of Abciximab.
710
711 4. Withdraw the necessary amount of Abciximab for bolus injection into a syringe.
712 Filter the bolus injection using a sterile, non-pyrogenic, low protein-binding 0.2 or 5 μm
713 syringe filter (Millipore SLGV025LS or SLSV025LS or equivalent).
714
715 5. Withdraw the necessary amount of Abciximab for the continuous infusion into a
716 syringe. Inject into an appropriate container of sterile 0.9% saline or 5% dextrose and
717 infuse at the calculated rate via a continuous infusion pump. The continuous infusion
718 should be filtered either upon admixture using a sterile, non-pyrogenic, low
719 protein-binding 0.2 or 5 μm syringe filter (Millipore SLGV025LS or SLSV025LS or
720 equivalent) or upon administration using an in-line, sterile, non-pyrogenic, low
721 protein-binding 0.2 or 0.22 μm filter (Abbott #4524 or equivalent). Discard the unused
722 portion at the end of the infusion.
723

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724 6. No incompatibilities have been shown with intravenous infusion fluids or commonly
725 used cardiovascular drugs. Nevertheless, Abciximab should be administered in a
726 separate intravenous line whenever possible and not mixed with other medications.
727
728 7. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags
729 and administration sets.
730
731 **HOW SUPPLIED:**
732 Abciximab (ReoPro®) 2 mg/mL is supplied in 5 mL vials containing 10 mg
733 (NDC 0002-7140-01).
734
735 Vials should be stored at 2 to 8 °C (36 to 46 °F). Do not freeze. Do not shake. Do not
736 use beyond the expiration date. Discard any unused portion left in the vial.
737
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