
New Perspectives In Cardiac Care
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PC Version
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Fragmin®

dalteparin sodium injection

Pharmacia & Upjohn

For *Subcutaneous* Use Only

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (also see WARNINGS, Hemorrhage and PRECAUTIONS, Drug Interactions).

DESCRIPTION

FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes and a multiple-dose vial. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains 2500 (16 mg dalteparin sodium) or 5000 (32 mg dalteparin sodium) anti-Factor Xa international units (IU) in 0.2 mL. Each 9.5 mL vial contains 10,000 (64 mg dalteparin sodium) anti-Factor Xa IU per 1 mL, for a total of 95,000 anti-Factor Xa IU per vial.

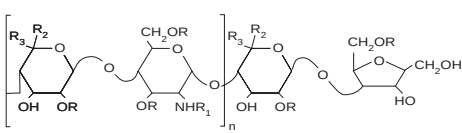
Each prefilled syringe also contains Water for Injection and sodium chloride, when required, to maintain physiologic ionic strength. The prefilled syringes are preservative free. Each multiple-dose vial also contains Water for Injection and 14 mg of benzyl alcohol per mL as a preservative. The pH of both formulations is 5.0 to 7.5.

Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and about 90% of the material within the range 2000-9000. The molecular weight distribution is:

< 3000 daltons	3.0-15.0%
3000 to 8000 daltons	65.0-78.0%
> 8000 daltons	14.0-26.0%

420-559

Structural Formula



Fragmin

brand of dalteparin sodium injection

CLINICAL PHARMACOLOGY

Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In man, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting clotting time, e.g., activated partial thromboplastin time (APTT).

Pharmacodynamics:

Doses of FRAGMIN Injection of up to 10,000 anti-Factor Xa IU administered subcutaneously as a single dose or two 5000 IU doses 12 hours apart to healthy subjects do not produce a significant change in platelet aggregation, fibrinolysis, or global clotting tests such as prothrombin time (PT), thrombin time (TT) or APTT. Subcutaneous administration of doses of 5000 IU bid of FRAGMIN for seven consecutive days to patients undergoing abdominal surgery did not markedly affect APTT, Platelet Factor 4 (PF4), or lipoprotein lipase.

Pharmacokinetics:

Mean peak levels of plasma anti-Factor Xa activity following single subcutaneous (s.c.) doses of 2500, 5000 and 10,000 IU were 0.19 ± 0.04, 0.41 ± 0.07 and 0.82 ± 0.10 IU/mL, respectively, and were attained in about 4 hours in most subjects. Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was 87 ± 6%. Increasing the dose from 2500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was greater than proportional by about one-third.

Peak anti-Factor Xa activity increased more or less linearly with dose over the same dose range. There appeared to be no appreciable accumulation of anti-Factor Xa activity with twice-daily dosing of 100 IU/kg s.c. for up to 7 days.

The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60 mL/kg. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 mL/hr/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hr.

Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hrs, respectively. Longer apparent terminal half-lives (3 to 5 hrs) are observed following s.c. dosing, possibly due to delayed absorption. In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single intravenous dose of 5000 IU FRAGMIN was 5.7 ± 2.0 hrs, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

CLINICAL TRIALS

Abdominal Surgery:

FRAGMIN Injection, administered once daily beginning prior to surgery and continuing for 5 to 10 days after surgery, has been shown to prevent deep vein thrombosis (DVT) in patients at risk for thromboembolic complications (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION). Data from two double-blind randomized controlled clinical trials performed in patients undergoing major abdominal surgery, summarized in the following tables, show that FRAGMIN 2500 IU was superior to placebo and similar to heparin in preventing DVT (see Tables 1 and 2).

Table 1
Efficacy of FRAGMIN in Abdominal Surgery

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	**Placebo** qd s.c.
All Treated Abdominal Surgery Patients	102	102
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	4/91 (4.4%)[1]	16/91 (17.6%)
Proximal DVT	0	5/91 (5.5%)
Distal DVT	4/91 (4.4%)	11/91 (12.1%)
PE	0	2/91 (2.2%)[2]

[1] p-value versus placebo = 0.008
[2] Both patients also had DVT, 1 proximal and 1 distal

Table 2
Efficacy of FRAGMIN in Abdominal Surgery

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	**Heparin** 5000 U bid s.c.
All Treated Abdominal Surgery Patients	195	196
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	7/178 (3.9%)[1]	7/174 (4.0%)
Proximal DVT	3/178 (1.7%)	4/174 (2.3%)
Distal DVT	3/178 (1.7%)	3/174 (1.7%)
PE	1/178 (0.6%)	0

[1] p-value versus heparin = 0.74

Data from a double-blind randomized controlled trial show that FRAGMIN 5000 IU once daily is more effective than FRAGMIN 2500 IU once daily in preventing DVT in patients undergoing abdominal surgery with malignancy (see Table 3).

Table 3
Efficacy of FRAGMIN in Abdominal Surgery Patients with Malignancy

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	**FRAGMIN** 5000 IU qd s.c.
All Treated Abdominal Surgery Patients	696	679
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	99/656 (15.1%)[1]	60/645 (9.3%)
Proximal DVT	18/657 (2.7%)	14/646 (2.2%)
Distal DVT	80/657 (12.2%)	41/646 (6.3%)
PE		
Fatal	1/674 (0.1%)	1/669 (0.1%)
Non-fatal	2	4

[1] p-value = 0.001

Hip Replacement Surgery:
In an open-label randomized study, FRAGMIN 5000 IU administered once daily subcutaneously (s.c.) was compared to warfarin sodium, administered orally, in patients undergoing hip replacement surgery. Treatment with FRAGMIN was initiated with a 2500 IU dose s.c. within 2 hours before surgery, followed by a 2500 IU s.c. dose the evening of the day of surgery. Then, a dosing regimen of FRAGMIN 5000 IU s.c. once daily was initiated on the first postoperative day. The first dose of warfarin sodium was given the evening before surgery, then continued daily at a dose adjusted for INR 2.0 to 3.0. Treatment in both groups was then continued for 5 to 9 days postoperatively. The incidence of total DVT, as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared to patients treated with warfarin sodium (28/192 vs 49/190; p=0.006) [see Table 4].

Table 4
Efficacy of FRAGMIN in Hip Replacement Surgery

Indication	Dosing Regimen	
	FRAGMIN 5000 IU qd[1] s.c.	**Warfarin Sodium** qd[2] oral
All Treated Hip Replacement Surgery Patients	271	279
Treatment Failures in Evaluable Patients		
DVT, Total	28/192 (14.6%)[3]	49/190 (25.8%)
Proximal DVT	10/192 (5.2%)[4]	16/190 (8.4%)
PE	2/271 (0.7%)	2/279 (0.7%)

[1] The daily dose on the day of surgery was divided: 2500 IU was given two hours before surgery and again in the evening of the day of surgery.

[2] Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.

[3] p-value = 0.006

[4] p-value = 0.185

In a second study (single-center, double-blind) of 136 patients undergoing hip replacement surgery, FRAGMIN 5000 IU once daily s.c. starting the evening before surgery, was compared to heparin 5000 U s.c. tid, starting the morning of surgery. Treatment in both groups was continued for up to 9 days postoperatively. In the intent-to-treat analysis, the incidence of proximal DVT was significantly lower for patients treated with FRAGMIN compared to patients treated with heparin (6/67 vs 18/69; p=0.01). Further, the incidence of pulmonary embolism detected by lung scan was also significantly lower in the group treated with FRAGMIN (9/67 vs 19/69; p=0.032).

INDICATIONS AND USAGE
FRAGMIN Injection is indicated for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism:

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications. Patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes, or who have additional risk factors such as malignancy, or a history of deep venous thrombosis or pulmonary embolism.

CONTRAINDICATIONS
FRAGMIN Injection is contraindicated in patients with known hypersensitivity to the drug, active major bleeding, or thrombocytopenia associated with positive *in vitro* tests for anti-platelet antibody in the presence of FRAGMIN.

Patients with known hypersensitivity to heparin or pork products should not be treated with FRAGMIN.

WARNINGS

FRAGMIN Injection is not intended for intramuscular administration.

FRAGMIN cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins.

FRAGMIN should be used with extreme caution in patients with history of heparin-induced thrombocytopenia.

Hemorrhage:

FRAGMIN, like other anticoagulants, should be used with extreme caution in patients who have an increased risk of hemorrhage, such as those with severe uncontrolled hypertension, bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke or shortly after brain, spinal or ophthalmological surgery.

Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture, which can result in long-term or permanent paralysis. The risk of these events is higher with the use of indwelling epidural catheters or concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING and ADVERSE REACTIONS, Ongoing Safety Surveillance).

As with other anticoagulants, bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:

In clinical trials, thrombocytopenia with platelet counts of < 50,000 / mm^3 and <100,000 / mm^3 occurred in <1% and <1%, respectively, of patients undergoing abdominal surgery or hip replacement surgery. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.

Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. The incidence of this complication is unknown at present.

Miscellaneous:

The multiple-dose vial of FRAGMIN contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see PRECAUTIONS, Pregnancy Category B., Nonteratogenic Effects).

PRECAUTIONS

General:

FRAGMIN Injection should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing.

FRAGMIN should be used with caution in patients with bleeding diathesis, thrombocytopenia or platelet defects; severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding.

If a thromboembolic event should occur despite dalteparin prophylaxis, FRAGMIN should be discontinued and appropriate therapy initiated.

Drug Interactions:

FRAGMIN should be used with care in patients receiving oral anticoagulants and / or platelet inhibitors because of increased risk of bleeding.

Laboratory Tests:

Periodic routine complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. No special monitoring of blood clotting times (e.g., APTT) is needed.

When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are relatively insensitive measures of FRAGMIN activity and, therefore, unsuitable for monitoring.

Drug / Laboratory Test Interactions:

Elevations of Serum Transaminases:

Asymptomatic increases in transaminase levels (SGOT / AST and SGPT / ALT) greater than three times the upper limit of normal of the laboratory reference range have been reported in 1.7 and 4.3%, respectively, of patients during treatment with FRAGMIN. Similar significant increases in transaminase levels have also been observed in patients treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since transaminase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, elevations that might be caused by drugs like FRAGMIN should be interpreted with caution.

Carcinogenicity, Mutagenesis, Impairment of Fertility:

Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the *in vitro* Ames Test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the *in vivo* mouse micronucleus test. Dalteparin sodium at subcutaneous doses up to 1200 IU / kg (7080 IU / m^2) did not affect the fertility or reproductive performance of male and female rats.

Pregnancy: Pregnancy Category B.

Teratogenic Effects:

Reproduction studies with dalteparin sodium at intravenous doses up to 2400 IU / kg (14,160 IU / m^2) in pregnant rats and 4800 IU / kg (40,800 IU / m^2) in pregnant rabbits did not produce any evidence of impaired fertility or harm to the fetuses. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects:

Cases of "Gasping Syndrome" have occurred when large amounts of benzyl alcohol have been administered (99 - 404 mg / kg / day). The 9.5 mL multi-dose vial of FRAGMIN contains 14 mg / mL of benzyl alcohol.

Nursing Mothers:

It is not known whether dalteparin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hemorrhage:

The incidence of hemorrhagic complications during treatment with FRAGMIN Injection has been low. The most commonly reported side effect is hematoma at the injection site. The incidence of bleeding may increase with higher doses; however, in abdominal surgery patients with malignancy, no significant increase in bleeding was observed when comparing FRAGMIN 5000 IU to either FRAGMIN 2500 IU or low dose heparin.

In a study comparing FRAGMIN 5000 IU once daily to FRAGMIN 2500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding events was 4.6% and 3.6%, respectively (n.s.). In a study comparing FRAGMIN 5000 IU once daily to heparin 5000 IU twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (n.s.) in the malignancy subgroup.

Abdominal Surgery:
Table 5 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 5
Bleeding Events in Abdominal Surgery

Indication	FRAGMIN vs Heparin				FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen				Dosing Regimen		Dosing Regimen	
Abdominal Surgery	FRAGMIN 2500 IU qd s.c.	Heparin 5000 U bid s.c.	FRAGMIN 5000 IU qd s.c.	Heparin 5000 U bid s.c.	FRAGMIN 2500 IU qd s.c.	Placebo qd s.c.	FRAGMIN 2500 IU qd s.c.	FRAGMIN 5000 IU qd s.c.
Postoperative Transfusions	26/459 (5.7%)	36/454 (7.9%)	81/508 (15.9%)	63/498 (12.7%)	14/182 (7.7%)	13/182 (7.1%)	89/1025 (8.7%)	125/1033 (12.1%)
Wound Hematoma	16/467 (3.4%)	18/467 (3.9%)	12/508 (2.4%)	6/498 (1.2%)	2/79 (2.5%)	2/77 (2.6%)	1/1030 (0.1%)	4/1039 (0.4%)
Reoperation Due to Bleeding	2/392 (0.5%)	3/392 (0.8%)	4/508 (0.8%)	2/498 (0.4%)	1/79 (1.3%)	1/78 (1.3%)	2/1030 (0.2%)	13/1038 (1.3%)
Injection Site Hematoma	1/466 (0.2%)	5/464 (1.1%)	36/506 (7.1%)	47/493 (9.5%)	8/172 (4.7%)	2/174 (1.1%)	36/1026 (3.5%)	57/1035 (5.5%)

Hip Replacement Surgery:
Table 6 summarizes: 1) all major bleeding events and, 2) other bleeding events possibly or probably related to treatment with FRAGMIN, warfarin, or heparin in clinical trials of hip replacement surgery.

Table 6
Bleeding Events in Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	FRAGMIN 5000 IU qd s.c. (n = 274[2])	Warfarin Sodium[1] oral (n = 279)	FRAGMIN 5000 IU qd s.c. (n = 69[4])	Heparin 5000 U tid s.c. (n = 69)
Major Bleeding Events[3]	7/274 (2.6%)	1/279 (0.4%)	0	3/69 (4.3%)
Other Bleeding Events[5]				
Hematuria	8/274 (2.9%)	5/279 (1.8%)	0	0
Wound Hematoma	6/274 (2.2%)	0	0	0
Injection Site Hematoma	3/274 (1.1%)	NA	2/69 (2.9%)	7/69 (10.1%)

[1] Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.

[2] Includes three treated patients who did not undergo a surgical procedure.

[3] A bleeding event was considered major if: 1) hemorrhage caused a significant clinical event, 2) it was associated with a hemoglobin decrease of ≥2 g/dL or transfusion of 2 or more units of blood products, 3) it resulted in reoperation due to bleeding, or 4) it involved retroperitoneal or intracranial hemorrhage.

[4] Includes two treated patients who did not undergo a surgical procedure.

[5] Occurred at a rate of at least 2% in the group treated with FRAGMIN 5000 IU once daily.

Six of the patients treated with FRAGMIN experienced seven major bleeding events. Two of the events were wound hematoma (one requiring reoperation), three were bleeding from the operative site, one was intraoperative bleeding due to vessel damage, and one was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial hemorrhage nor died of bleeding complications.

Thrombocytopenia: See WARNINGS: Thrombocytopenia.

Other:

Allergic Reactions:

Allergic reactions (i.e., pruritus, rash, fever, injection site reaction, bulleous eruption) and skin necrosis have occurred rarely. A few cases of anaphylactoid reactions have been reported.

Local Reactions:

Pain at the injection site, the only non-bleeding event determined to be possibly or probably related to treatment with FRAGMIN and reported at a rate of at least 2% in the group treated with FRAGMIN, was reported in 4.5% of patients treated with FRAGMIN 5000 IU qd vs 11.8% of patients treated with heparin 5000 U bid in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with FRAGMIN 5000 IU qd vs 13% of patients treated with heparin 5000 U tid.

Ongoing Safety Surveillance:

Since first international market introduction in 1985, there have been five reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. No cases have been reported in the United States since approval in 1994. Four of the five patients had post-operative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis in four of the cases (one complete, three partial paralyses). The fifth patient experienced temporary paraplegia but made a full recovery. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

OVERDOSAGE

Symptoms/Treatment:

An excessive dosage of FRAGMIN Injection may lead to hemorrhagic complications. These may generally be stopped by the slow intravenous injection of protamine sulfate (1% solution), at a dose of 1 mg protamine for every 100 anti-Xa IU of FRAGMIN given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. Even with these additional doses of protamine, the APTT may remain more prolonged than would usually be found following administration of conventional heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60 to 75%).

Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information, consult the labeling of Protamine Sulfate Injection, USP, products. A single subcutaneous dose of 100,000 IU/kg of FRAGMIN to mice caused a mortality of 8% (1/12) whereas 50,000 IU/kg was a non-lethal dose. The observed sign was hematoma at the site of injection.

DOSAGE AND ADMINISTRATION

Abdominal Surgery:

In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of FRAGMIN Injection is 2500 IU administered by subcutaneous (s.c.) injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily for 5 to 10 days postoperatively (see INDICATIONS AND USAGE).

In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of FRAGMIN is 5000 IU s.c. the evening before surgery, then once daily for 5 to 10 days postoperatively. Alternatively, in patients with malignancy, 2500 IU of FRAGMIN can be administered s.c. 1 to 2 hours before surgery followed by 2500 IU s.c. 12 hours later, and then 5000 IU once daily for 5 to 10 days postoperatively.

Fragmin

brand of dalteparin sodium injection

Hip Replacement Surgery:
In patients undergoing hip replacement surgery, the recommended first dose of FRAGMIN is 2500 IU administered by s.c. injection within 2 hours before surgery and the second dose of 2500 IU s.c. in the evening of the day of surgery (at least 6 hours after the first dose). If surgery is performed in the evening, omit the second dose on the day of surgery. Starting on the first postoperative day, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. Alternatively, 5000 IU of FRAGMIN can be administered the evening before surgery, followed by 5000 IU once daily, starting in the evening of the day of surgery. Up to 14 days of treatment was well tolerated in controlled clinical trials, where the average duration of treatment was 5 to 10 days postoperatively.

Dosage adjustment and routine monitoring of coagulation parameters are not required if the dosage and administration recommendations specified above are followed.

Administration:
FRAGMIN is administered by subcutaneous injection. It must not be administered by intramuscular injection.

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep subcutaneous injection. FRAGMIN may be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site should be varied daily. When the area around the navel or the thigh is used, using the thumb and forefinger, you **must** lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45 to 90 degree angle.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED
FRAGMIN Injection is available in the following strengths and package sizes:

0.2 mL single-dose prefilled syringe, affixed with a 27-gauge x 1/2 inch needle. Package of 10:

2500 anti-Factor Xa IU	NDC 0013-2406-91
5000 anti-Factor Xa IU	NDC 0013-2426-91

9.5 mL multiple-dose vial:

10,000 anti-Factor Xa IU / mL (95,000 anti-Factor Xa IU / vial)	NDC 0013-2436-06

Storage
Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

℞ only

U.S. Patent 4,303,651

Manufactured for: Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

By: Vetter Pharma-Fertigung
Ravensburg, Germany
(prefilled syringes)

Pharmacia & Upjohn AB
Stockholm, Sweden
(multiple-dose vial)

132010399 Revised March 1999

420-559

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 ($\alpha_{IIb}\beta_3$) 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 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 (2,3), 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, 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.

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 three Phase 3 clinical trials, all of which evaluated the effect of Abciximab in patients undergoing percutaneous coronary intervention: in patients at high risk for abrupt closure of the treated coronary vessel (EPIC), in a broader group of patients (EPILOG), and in unstable angina patients not responding to conventional medical therapy (CAPTURE). 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 (4). 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) an Abciximab bolus (0.25 mg/kg) followed by an Abciximab infusion (10 μg/min) for 12

hours (bolus plus infusion group); 2) an Abciximab 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 percutaneous coronary intervention were defined as those with unstable angina or non-Q wave myocardial infarction (n=489), those with an acute Q-wave myocardial infarction within 12 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 percutaneous coronary intervention. 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 percutaneous coronary intervention. Heparin infusion was continued for 12 hours to maintain a therapeutic elevation of activated partial thromboplastin time (APTT, 1.5-2.5 times normal).

The primary endpoint was the occurrence of any of the following events within 30 days of percutaneous coronary intervention: death, myocardial infarction (MI), or the need for urgent intervention for recurrent ischemia [i.e., urgent percutaneous transluminal coronary angioplasty, urgent coronary artery bypass graft (CABG) surgery, a coronary stent, or an intra-aortic balloon pump]. The 30-day (Kaplan-Meier) primary endpoint event rates for each treatment group by intention-to-treat analysis of all randomized patients are shown in Table 1. The 4.5% lower incidence of the primary endpoint rates in the bolus plus infusion treatment group, compared with the placebo group, was statistically significant, whereas the 1.3% lower incidence in the bolus treatment group was not. A lower incidence of the primary endpoint was observed in the bolus plus infusion treatment arm for all three high-risk subgroups: patients with unstable angina, patients presenting within 12 hours of the onset of symptoms of an acute myocardial infarction, and patients with other high-risk clinical and/or morphologic characteristics (4). The treatment effect was largest in the first two subgroups and smallest in the third subgroup.

Table 1
PRIMARY ENDPOINT EVENT RATE AT 30 DAYS - EPIC TRIAL

	Placebo (n=696)	Abciximab Bolus (n=695)	Abciximab Bolus + Infusion (n=708)
		Number of Patients (%)	
Death, MI, or urgent intervention[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 event rates 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(4), six months(5) and three years(6). At the six- month 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). Median long-term follow up was 3.1 years (99% of patients had follow up between 2.5 and 3.5 years). Using Kaplan-Meier estimates, at 3 years the absolute reduction in events was maintained with an event rate of 19.6% in the bolus plus infusion arm and 24.4% in the placebo arm (p=0.027 vs. placebo).

EPILOG was a randomized, double-blind, multicenter, placebo-controlled trial which evaluated Abciximab in a broad population of patients undergoing percutaneous coronary intervention (excluding patients with myocardial infarction and unstable angina meeting the EPIC high risk criteria)(7). EPILOG tested the hypothesis that use of a low-dose, weight-adjusted heparin regimen, early femoral arterial sheath removal, improved access site management and weight-adjustment of the Abciximab infusion dose could significantly lower the bleeding rate yet maintain the efficacy seen in the EPIC trial. EPILOG was a three treatment-arm trial: Abciximab plus standard dose, weight-adjusted heparin[1]; Abciximab plus low dose, weight-adjusted heparin[2]; and placebo plus standard dose, weight-adjusted heparin. The Abciximab bolus dose was the same as that used in the EPIC trial (0.25 mg/kg), but the continuous infusion dose was weight adjusted in patients up to 80 kg[3] (0.125 μg/kg/min). Specific patient and access site management procedures as well as a strong recommendation for early sheath removal were also incorporated into the trial as described in PRECAUTIONS. The EPILOG trial achieved the objective of lowering the bleeding rate while maintaining efficacy: in the Abciximab treatment arms major bleeding was not significantly different from that in the placebo arm (see ADVERSE REACTIONS: Bleeding).

The primary endpoint of the EPILOG trial was the composite of death or MI occurring within 30 days of percutaneous coronary intervention. The composite of death, MI, or urgent intervention was an important secondary endpoint. As seen in the EPIC trial, the endpoint events in the Abciximab treatment group were reduced mostly in the first 48 hours and this benefit was sustained through blinded evaluations at 30 days and six months. The (Kaplan-Meier) endpoint event rates at 30 days are shown in Table 2 for each treatment group by intention-to-treat analysis of all 2792 randomized patients. 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 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.

[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 Abciximab 10 to 60 minutes before percutaneous coronary intervention immediately followed by a 0.125 μg/kg/min infusion (maximum 10 μg/min) for 12 hours

Table 2
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).

CAPTURE was a randomized, double-blind, multicenter, placebo-controlled trial of the use of Abciximab in unstable angina patients not responding to conventional medical therapy for whom percutaneous coronary intervention was planned, but not immediately performed (8). In contrast to the EPIC and EPILOG trials, the CAPTURE trial involved the administration of placebo or Abciximab starting 18 to 24 hours prior to percutaneous coronary intervention and continuing until one hour after completion of the intervention.

Patients were assessed as having unstable angina not responding to conventional medical therapy if they had at least one episode of myocardial ischemia despite bed rest and at least two hours of therapy with intravenous heparin and oral or intravenous nitrates. These patients were enrolled into the CAPTURE trial, if during a screening angiogram, they were determined to have a coronary lesion amenable to percutaneous coronary intervention. Patients received a bolus dose and intravenous infusion of placebo or Abciximab for 18 to 24 hours. At the end of the infusion period, the intervention was performed. The Abciximab or placebo infusion was discontinued one hour following the intervention. Patients were treated with intravenous heparin and oral or intravenous nitrates throughout the 18 to 24-hour Abciximab infusion period prior to the percutaneous coronary intervention.

The Abciximab dose was a 0.25 mg/kg bolus followed by a continuous infusion at a rate of 10 μg/min. The CAPTURE trial incorporated weight adjustment of the standard heparin dose only during the performance of the intervention, but did not investigate the effect of a lower heparin dose, and arterial sheaths were left in place for approximately 40 hours. The primary endpoint of the CAPTURE trial was the occurrence of any of the following events within 30 days of percutaneous coronary intervention: death, MI, or urgent intervention. The 30-day (Kaplan-Meier) primary endpoint event rates for each treatment group by intention-to-treat analysis of all 1265 randomized patients are shown in Table 3.

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 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 percutaneous coronary intervention 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).

The 30-day results are consistent with EPIC results, with the greatest effects on the myocardial infarction and urgent intervention components of the composite endpoint. As secondary endpoints, the components of the composite endpoint were analyzed separately for the period prior to the percutaneous coronary intervention and the period from the beginning of the intervention through Day 30. The greatest difference in MI occurred in the post-intervention period: the rates of MI were lower in the Abciximab group compared with placebo (Abciximab 3.6%, placebo 6.1%). There was also a reduction in MI occurring prior to the percutaneous coronary intervention (Abciximab 0.6%, placebo 2.0%). An Abciximab-associated 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 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 three trials, EPIC, EPILOG and CAPTURE. Similar mortality rates were observed in all arms within each trial. In all three trials, the rates of acute MI were significantly lower in the groups treated with Abciximab. Urgent intervention rates were also lower in Abciximab-treated groups in these trials.

Anticoagulation: Due to the incidence of bleeding seen in the EPIC trial, the dosing regimens of concomitant heparin and the target levels for anticoagulation were successively varied in the CAPTURE and EPILOG trials. These modified dosing regimens combined with other measures for patient management were associated with reduced bleeding rates (see ADVERSE REACTIONS: Bleeding)

EPILOG trial: Heparin was weight adjusted in all treatment arms. A baseline ACT was determined prior to percutaneous coronary intervention. In the low-dose heparin arm of the trial, heparin was administered as follows:

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 trial. 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.

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 percutaneous coronary intervention. Following the intervention, heparin management was as outlined above for the EPILOG trial.

INDICATIONS AND USAGE:

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

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

Abciximab is intended for use with aspirin and heparin and has been studied only in that setting, as described in CLINICAL STUDIES.

CONTRAINDICATIONS:

Because Abciximab may increase the risk of bleeding, Abciximab is contraindicated in the following clinical situations:

- Active internal bleeding
- Recent (within six weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance.
- History of cerebrovascular accident (CVA) within two years, or CVA with a significant residual neurological deficit
- Bleeding diathesis
- Administration of oral anticoagulants within seven days unless prothrombin time is ≤ 1.2 times control
- Thrombocytopenia (< 100,000 cells/μL)

- Recent (within six weeks) major surgery or trauma
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Severe uncontrolled hypertension
- Presumed or documented history of vasculitis
- Use of intravenous dextran before percutaneous coronary intervention, or intent to use it during an intervention

Abciximab is also contraindicated in patients with known hypersensitivity to any component of this product or to murine proteins.

WARNINGS:

Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g., from heparin, other anticoagulants, or thrombolytics (see ADVERSE REACTIONS: Bleeding).

The risk of major bleeds due to Abciximab therapy may be 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 Abciximab and any concomitant heparin should be stopped.

PRECAUTIONS:

Bleeding Precautions

Results of the EPILOG trial show that bleeding can be reduced by the use of low-dose, weight-adjusted heparin regimens, adherence to stricter anticoagulation guidelines, early femoral arterial sheath removal, careful patient and access site management and weight-adjustment of the Abciximab infusion dose.

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

Arterial and venous punctures, intramuscular injections, and use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs should be minimized. 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.

Femoral artery access site:

Arterial access site care is important to prevent bleeding**.** Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Femoral vein sheath placement should be avoided unless needed. While the vascular sheath is in place, patients should be maintained on complete bed rest with the head of the bed ≤30° and the affected limb restrained in a straight position. Patients may be medicated for back/groin pain as necessary.

Discontinuation of heparin immediately upon completion of the procedure and removal of the arterial sheath within six hours is strongly recommended if APTT ≤ 50 sec or ACT ≤ 175 sec (See PRECAUTIONS: Laboratory Tests). In all circumstances, heparin should be discontinued at least two hours prior to arterial sheath removal.

Following sheath removal, pressure should be applied to the femoral artery for at least 30 minutes using either manual compression or a mechanical device for hemostasis. A pressure dressing should be applied following hemostasis. The patient should be maintained on bed rest for six to eight hours following sheath removal or discontinuation of Abciximab, or four hours following discontinuation of heparin, whichever is later. The pressure dressing should be removed prior to ambulation. The sheath insertion site and distal pulses of affected leg(s) should be frequently checked while the femoral artery sheath is in place and for six hours after femoral artery sheath removal. Any hematoma should be measured and monitored for enlargement.

The following conditions have been associated with an increased risk of bleeding and may be additive with the effect of Abciximab in the angioplasty setting: percutaneous coronary intervention within 12 hours of the onset of symptoms for acute myocardial infarction, prolonged percutaneous coronary intervention (lasting more than 70 minutes) and failed percutaneous coronary intervention.

Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents

In the EPIC, EPILOG and CAPTURE trials, Abciximab was used concomitantly with heparin and aspirin. For details of the anticoagulation algorithms used in these clinical trials, see CLINICAL STUDIES: Anticoagulation. Because Abciximab inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, dipyridamole, and ticlopidine.

In the EPIC trial, there was limited experience with the administration of Abciximab with low molecular weight dextran. Low molecular weight dextran was usually given for the deployment of a coronary stent, for which oral anticoagulants were also given. In the 11 patients who received low molecular weight dextran with Abciximab, five had major bleeding events and four had minor bleeding events. None of the five placebo patients treated with low molecular weight dextran had a major or minor bleeding event (see CONTRAINDICATIONS).

There are limited data on the use of Abciximab in patients receiving thrombolytic agents. Because of concern about synergistic effects on bleeding, systemic thrombolytic therapy should be used judiciously.

Thrombocytopenia

Platelet counts should be monitored prior to treatment, two to four hours following the bolus dose of Abciximab 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 pre-treatment value), additional platelet counts should be determined. These platelet counts should be drawn in three separate tubes containing ethylenediaminetetraacetic acid (EDTA), citrate and heparin, respectively, to exclude pseudothrombocytopenia due to *in vitro* anticoagulant interaction. If true thrombocytopenia is verified, Abciximab should be immediately discontinued and the condition appropriately monitored and treated. For patients with thrombocytopenia in the clinical trials, a daily platelet count was obtained until it returned to normal. If a patient's platelet count dropped to 60,000 cells/μL, heparin and aspirin were discontinued. If a patient's platelet count dropped below 50,000 cells/μL, platelets were transfused. Most cases of severe thrombocytopenia (<50,000 cells/μL) occurred within the first 24 hours of Abciximab administration.

Restoration of Platelet Function

In the event of serious uncontrolled bleeding or the need for emergency surgery, Abciximab should be discontinued. If platelet function does not return to normal, it may be restored, at least in part, with platelet transfusions.

Laboratory Tests

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

Based on an integrated analysis of data from all studies, the following guidelines may be utilized to minimize the risk for bleeding:

When Abciximab is initiated 18 to 24 hours before percutaneous coronary intervention, the APTT should be maintained between 60 and 85 seconds during the Abciximab and heparin infusion period.

During percutaneous coronary intervention the ACT should be maintained between 200 and 300 seconds.

If anticoagulation is continued in these patients following percutaneous coronary intervention, the APTT should be maintained between 60 and 85 seconds.

The APTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless APTT $\leq$ 50 seconds or ACT $\leq$ 175 seconds.

Readministration

Administration of Abciximab may result in human anti-chimeric antibody (HACA) formation that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis), thrombocytopenia or diminished benefit upon readministration of Abciximab. In the EPIC, EPILOG, and CAPTURE trials, positive HACA responses occurred in approximately 5.8% of the Abciximab-treated patients. There was no excess of hypersensitivity or allergic reactions related to Abciximab treatment.

Readministration of Abciximab to 29 healthy volunteers who had not developed a HACA response after first administration has not led to any change in Abciximab pharmacokinetics or to any reduction in antiplatelet potency. However, results in this small group of patients suggest that the incidence of HACA response may be increased after readministration. Readministration to patients who have developed a positive HACA response after initial administration has not been evaluated in clinical trials.

Allergic Reactions

Anaphylaxis has not been reported for Abciximab-treated patients in any of the Phase 3 clinical trials. However, anaphylaxis may occur. If it does, administration of Abciximab should be immediately stopped and standard appropriate resuscitative measures should be initiated.

Drug Interactions

Although drug interactions with Abciximab have not been studied systematically, Abciximab 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 aspirin. Heparin, other anticoagulants, thrombolytics, and

antiplatelet agents may be associated with an increase in bleeding. Patients with HACA titers may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In vitro and *in vivo* mutagenicity studies have not demonstrated any mutagenic effect. Long-term studies in animals have not been performed to evaluate the carcinogenic potential or effects on fertility in male or female animals.

Pregnancy Category C

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

Nursing Mothers

It is not known whether this drug is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Abciximab is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been studied.

ADVERSE REACTIONS:

Bleeding

Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g. from heparin, other anticoagulants or thrombolytics. Bleeding in the Phase 3 trials was classified as major, minor or insignificant by the criteria of the Thrombolysis in Myocardial Infarction study group(9). Major bleeding events were defined as either an intracranial hemorrhage or a decrease in hemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, observed blood loss with a hemoglobin decrease of more than 3 g/dL, or a decrease in hemoglobin of at least 4 g/dL without an identified bleeding site. Insignificant bleeding events were defined as a decrease in hemoglobin of less than 3 g/dL or a decrease in hemoglobin between 3-4 g/dL without observed bleeding. In patients who received transfusions, the number of units of blood lost was estimated through an adaptation of the method of Landefeld, et al.(10).

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

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

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

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

The rates of major bleeding, minor bleeding and bleeding events requiring transfusions in the EPIC, CAPTURE and EPILOG trials are shown in Table 4. The rates of insignificant bleeding events are not included in Table 4.

Table 4
NON-CABG BLEEDING IN THE EPIC, EPILOG AND CAPTURE TRIALS
Number of Patients with Bleeds (%)

EPIC:

	Placebo (n = 696)	Abciximab (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)	Abciximab (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 (n = 939)	Abciximab + Standard-dose Heparin (n = 918)	Abciximab + 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

Intracranial Hemorrhage and Stroke

The total incidence of intracranial hemorrhage and non-hemorrhagic stroke across all three trials was not significantly different, 7/2225 for placebo patients and 10/3112 for Abciximab treated patients**.** The incidence of intracranial hemorrhage was 3/2225 for placebo patients and 6/3112 for Abciximab patients.

Thrombocytopenia

In the clinical trials, patients treated with Abciximab were more likely than patients treated with placebo to experience decreases in platelet counts. The rates of thrombocytopenia and transfusions were lower in the subsequent CAPTURE and EPILOG trials (Table 5).

Table 5
THROMBOCYTOPENIA AND PLATELET TRANSFUSIONS[a]

	Placebo + Standard-dose Heparin	Abciximab + Standard-dose Heparin	Abciximab + Low-dose Heparin
	Total number of patients enrolled		
EPIC	n = 696	n = 708	--
CAPTURE	n = 635	n = 630	--
EPILOG	n = 939	n = 918	n = 935
Patients with decrease of platelets to <50,000 cells/μL[a]	% of patients with events		
EPIC	0.7	1.6	--
CAPTURE	0.3	1.7	--
EPILOG	0.4	0.9	0.4
Patients with decrease of platelets to <100,000 cells/μL[a]			
EPIC	3.4	5.2	--
CAPTURE	1.3	5.6	--
EPILOG	1.5	2.6	2.5
Patients who received platelet transfusions[b]			
EPIC	2.6	5.5	--
CAPTURE	0.3	2.1	--
EPILOG	1.1	1.6	0.9

[a]Patients with a platelet count of <50,000 cells/μL are also included in the category of patients with a platelet count of <100,000 cells/μL.
[b]Includes patients receiving platelet transfusions for thrombocytopenia or any other reason.

Other Adverse Reactions

Table 6 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.

Table 6
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)

The following additional adverse events from the EPIC, EPILOG and CAPTURE trials were reported by investigators for patients treated with a bolus plus infusion of Abciximab at incidences which were less than 0.5% higher than for patients in the placebo arm.

Cardiovascular System—ventricular tachycardia (1.4%), pseudoaneurysm (0.8%), palpitation (0.5%), arteriovenous fistula (0.4%), incomplete AV block (0.3%), nodal arrhythmia (0.2%), complete AV block (0.1%), embolism (limb)(0.1%); thrombophlebitis (0.1%);

Gastrointestinal System—dyspepsia (2.1%), diarrhea (1.1%), ileus (0.1%), gastroesophogeal reflux (0.1%);

Hemic and Lymphatic System—anemia (1.3%), leukocytosis (0.5%), petechiae (0.2%);

Nervous System—dizziness (2.9%), anxiety (1.7%), abnormal thinking (1.3%), agitation (0.7%), hypesthesia (0.6%), confusion (0.5%) muscle contractions (0.4%), coma (0.2%), hypertonia (0.2%), diplopia (0.1%);

Respiratory System—pneumonia (0.4%), rales (0.4%), pleural effusion (0.3%), bronchitis (0.3%) bronchospasm (0.3%), pleurisy (0.2%), pulmonary embolism (0.2%), rhonchi (0.1%);

Musculoskeletal System—myalgia (0.2%);

Urogenital System—urinary retention (0.7%), dysuria (0.4%), abnormal renal function (0.4%), frequent micturition (0.1%), cystalgia (0.1%), urinary incontinence (0.1%), prostatitis (0.1%);

Miscellaneous—pain (5.4%), sweating increased (1.0%), asthenia (0.7%), incisional pain (0.6%), pruritus (0.5%), abnormal vision (0.3%), edema (0.3%), wound (0.2%), abscess (0.2%), cellulitis (0.2%), peripheral coldness (0.2%), injection site pain (0.1%), dry mouth (0.1%), pallor (0.1%), diabetes mellitus (0.1%), hyperkalemia (0.1%), enlarged abdomen (0.1%), bullous eruption (0.1%), inflammation (0.1%), drug toxicity (0.1%).

OVERDOSAGE:

There has been no experience of overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION:

The safety and efficacy of Abciximab have only been investigated with concomitant administration of heparin and aspirin as described in CLINICAL STUDIES.

In patients with failed percutaneous coronary interventions, the continuous infusion of Abciximab should be stopped because there is no evidence for Abciximab efficacy in that setting.

In the event of serious bleeding that cannot be controlled by compression, Abciximab and heparin should be discontinued immediately.

The recommended dosage of Abciximab in adults is a 0.25 mg/kg intravenous bolus administered 10-60 minutes before the start of percutaneous coronary intervention, followed by a continuous intravenous infusion of 0.125 μg/kg/min (to a maximum of 10 μg/min) for 12 hours.

Patients with unstable angina not responding to conventional medical therapy and who are planned to undergo percutaneous coronary intervention within 24 hours may be treated with an Abciximab 0.25 mg/kg intravenous bolus followed by an 18 to 24-hour intravenous infusion of 10 μg/min, concluding one hour after the percutaneous coronary intervention.

Instructions for Administration

1. Parenteral drug products should be inspected visually for particulate matter prior to administration. Preparations of Abciximab containing visibly opaque particles should NOT be used.

2. Hypersensitivity reactions should be anticipated whenever protein solutions such as Abciximab 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 Abciximab.

4. Withdraw the necessary amount of Abciximab 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 Abciximab 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). Discard the unused portion at the end of the infusion.

6. No incompatibilities have been shown with intravenous infusion fluids or commonly used cardiovascular drugs. Nevertheless, Abciximab should be administered in a separate intravenous line whenever possible and not mixed with other medications.

7. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets.

HOW SUPPLIED:

Abciximab (ReoPro®) 2 mg/mL is supplied in 5 mL vials containing 10 mg (NDC 0002-7140-01).

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.

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RETAVASE®
Reteplase recombinant

DESCRIPTION

Retavase® (Reteplase) is a non-glycosylated deletion mutein of tissue plasminogen activator (tPA), containing the kringle 2 and the protease domains of human tPA. Retavase® contains 355 of the 527 amino acids of native tPA (amino acids 1-3 and 176-527). Retavase® is produced by recombinant DNA technology in E. coli. The protein is isolated as inactive inclusion bodies from E. coli, converted into its active form by an in vitro folding process and purified by chromatographic separation. The molecular weight of Reteplase is 39,571 daltons.

Potency is expressed in units (U) using a reference standard which is specific for Retavase® and is not comparable with units used for other thrombolytic agents.

Retavase® is a sterile, white, lyophilized powder for intravenous bolus injection after reconstitution with Sterile Water for Injection, USP (without preservatives) provided as part of a kit. Following reconstitution, the pH is 6.0 ± 0.3. Retavase® is supplied as a 10.4 U vial to ensure sufficient drug for administration of each 10 U dose. Each single-use vial contains:

10.4 U (18.1 mg) Vial

Reteplase	18.1 mg
Tranexamic Acid	8.32 mg
Dipotassium Hydrogen Phosphate	136.24 mg
Phosphoric Acid	51.27 mg
Sucrose	364.0 mg
Polysorbate 80	5.20 mg

CLINICAL PHARMACOLOGY

General

Retavase® is a recombinant plasminogen activator which catalyzes the cleavage of endogenous plasminogen to generate plasmin. Plasmin in turn degrades the fibrin matrix of the thrombus, thereby exerting its thrombolytic action.[1,2] In a controlled trial, 36 of 56 patients treated for an acute myocardial infarction (AMI) had a decrease in fibrinogen levels to below 100 mg/dL by 2 hours following the administration of Retavase® as a double-bolus intravenous injection (10 + 10 U) in which 10 U (17.4 mg) was followed 30 minutes later by a second bolus of 10 U (17.4 mg).[3] The mean fibrinogen level returned to the baseline value by 48 hours.

Pharmacokinetics

Based on the measurement of thrombolytic activity, Retavase® is cleared from plasma at a rate of 250-450 mL/min, with an effective half-life of 13-16 minutes. Retavase® is cleared primarily by the liver and kidney.

Clinical Studies

The safety and efficacy of Retavase® were evaluated in three controlled clinical trials in which Retavase® was compared to other thrombolytic agents. The INJECT study was designed to assess the relative effects of Retavase® or the Streptase® brand of Streptokinase upon mortality rates at 35 days following an AMI. The other studies (RAPID 1 and RAPID 2) were arteriographic studies which compared the effect on coronary patency of Retavase® to two regimens of Alteplase (a tissue plasminogen activator; Activase® in the USA and Actilyse® in Europe) in patients with an AMI. In all three studies, patients were treated with aspirin (initial doses of 160 mg to 350 mg and subsequent doses of 75 mg to 350 mg) and heparin (a 5,000 U IV bolus prior to the administration of Retavase®, followed by a 1000 U/hour continuous IV infusion for at least 24 hours).[3,4,5] The safety and efficacy of Retavase® have not been evaluated using antithrombotic or antiplatelet regimens other than those described above.

Retavase® (10 + 10 U) was compared to Streptokinase (1.5 million units over 60 minutes) in a double-blind, randomized, European study (INJECT), which studied 6,010 patients treated within 12 hours of the onset of symptoms of AMI. To be eligible for enrollment, patients had to have chest pain consistent with coronary ischemia and ST segment elevation, or a bundle branch block pattern on the EKG. Patients with known cerebrovascular or other bleeding risks or those with a systolic blood pressure >200 mm Hg or a diastolic blood pressure >100 mm Hg were excluded from enrollment. The results of the primary endpoint (mortality at 35 days), six month mortality and selected other 35 day endpoints are shown in Table 1 for patients receiving study medications.

Table 1
INJECT TRIAL
Incidence of Selected Outcomes

Endpoint	Retavase® n = 2,965	Streptokinase n = 2,971	Retavase®-Streptokinase difference (95% CI)	p Value
35 Day mortality	8.9%	9.4%	-0.5 (-2.0, 0.9)	0.49*
6 Month mortality†	11.0%	12.1%	-1.1 (-2.7, 0.6)	0.22
Combined outcome of 35 day mortality or nonfatal stroke within 35 days	9.6%	10.2%	-0.6 (-2.1, 1.0)	0.47
Heart failure	24.8%	28.1%	-3.3 (-5.6, -1.1)	0.004
Cardiogenic shock	4.6%	5.8%	-1.2 (-2.4, -0.1)	0.03
Any stroke	1.4%	1.1%	0.3 (-0.3, 0.8)	0.34
Intracranial hemorrhage	0.8%	0.4%	0.4 (0.0, 0.8)	0.04

*p value for the exploratory analysis comparing Retavase® versus Streptokinase.
†Kaplan-Meier estimates.

For mortality, stroke and the combined outcome of mortality or stroke, the 95% confidence intervals in Table 1 reflect the range within which the true difference in outcomes probably lies and includes the possibility of no difference. The incidences of congestive heart failure and of cardiogenic shock were significantly lower among patients treated with Retavase®.

The total incidence of stroke was similar between the groups. However, more patients treated with Retavase® experienced hemorrhagic strokes than patients treated with Streptokinase. An exploratory analysis indicated that the incidence of intracranial hemorrhage was higher among older patients or those with elevated blood pressure. The incidence of intracranial hemorrhage among the 698 patients treated with Retavase® who were older than 70 years was 2.2%. Intracranial hemorrhage occurred in 8 of the 332 (2.4%) patients treated with Retavase® who had an initial systolic blood pressure >160 mm Hg and in 15 of the 2,629 (0.6%) Retavase® patients who had an initial systolic blood pressure <160 mm Hg.

Two arteriographic studies (RAPID 1 and RAPID 2) were performed utilizing open-label administration of the study agents and a blinded review of the arteriograms. In RAPID 1, patients were treated within 6 hours of the onset of symptoms, and in RAPID 2, patients were treated within 12 hours of the onset of symptoms. Both studies evaluated coronary artery perfusion through the infarct-related artery 90 minutes after the initiation of therapy as the primary endpoint. Some patients in each study also had perfusion through the infarct-related artery evaluated at 60 minutes after the initiation of therapy. In RAPID 1, Retavase® (in doses of 10 + 10 U, 15 U, or 10 + 5 U) was compared to a 3 hour regimen of Alteplase (100 mg administered over 3 hrs). In RAPID 2, Retavase® (10 + 10 U) was compared to an accelerated regimen of Alteplase (100 mg administered over 1.5 hrs). The percentages of patients with partial or complete flow (TIMI grades 2 or 3) and complete flow (TIMI grade 3), are shown along with ventricular function assessments in Table 2. The follow-up arteriogram was performed at a median of 8 (RAPID 1) and 5 (RAPID 2) days following the administration of the thrombolytics. In RAPID 1 the best patency results were obtained with the 10 + 10 U dose. In RAPID 2, the percentage of patients with partial or complete flow and the percentage of patients with complete flow was significantly higher with Retavase® than with Alteplase at 90 minutes after the initiation of therapy. In both clinical trials the reocclusion rates were similar for Retavase® and Alteplase. The relationship between coronary artery patency and clinical efficacy has not been established.

Table 2
RAPID 1 and RAPID 2 TRIALS
Arteriographic Results

Outcome	RAPID 2			RAPID 1*		
	Retavase® (10 +10 U)	Alteplase (Accelerated regimen)	p	Retavase® (10 +10 U)	Alteplase (Standard regimen)	p
90 minute patency rates	n = 157	n = 146		n = 142	n = 145	
TIMI 2 or 3	83%	73%	0.03	85%	77%	0.08
TIMI 3	60%	45%	0.01	63%	49%	0.02
Follow-up patency rates	n = 128	n = 113		n = 123	n = 123	
TIMI 2 or 3	89%	90%	0.76	95%	88%	0.04
TIMI 3	75%	77%	0.72	88%	71%	0.001
Follow-up ejection fraction	n = 89	n = 77		n = 91	n = 84	
mean %	52%	54%	0.25	53%	49%	0.03
Follow-up regional wall motion	n = 87	n = 72		n = 84	n = 80	
Standard deviation from mean normal value	-2.3	-2.3	0.96	-2.2	-2.6	0.02

*p values represent one of multiple dose comparisons.

Approximately 70% (RAPID 1) and 78% (RAPID 2) of the patients in the arteriographic studies underwent optional arteriography at 60 minutes following the administration of the study agents. In both trials the percentage of patients with complete flow at 60 minutes was significantly higher with Retavase® than with Alteplase. Neither RAPID clinical trial was designed nor powered to compare the efficacy or safety of Retavase® and Alteplase with respect to the outcomes of mortality and stroke.

INDICATIONS AND USAGE

Retavase® (Reteplase) is indicated for use in the management of acute myocardial infarction (AMI) in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see **CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, Retavase® is contraindicated in the following situations:

- **Active internal bleeding**
- **History of cerebrovascular accident**
- **Recent intracranial or intraspinal surgery or trauma (see WARNINGS)**
- **Intracranial neoplasm, arteriovenous malformation, or aneurysm**
- **Known bleeding diathesis**
- **Severe uncontrolled hypertension**

WARNINGS

Bleeding

The most common complication encountered during Retavase® therapy is bleeding. The sites of bleeding include both internal bleeding sites (intracranial, retroperitoneal, gastrointestinal, genitourinary, or respiratory) and superficial bleeding sites (venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to bleeding. In clinical trials some of the hemorrhage episodes occurred one or more days after the effects of Retavase® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during Retavase® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from noncompressible sites.

Should an arterial puncture be necessary during the administration of Retavase®, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with Retavase®. Venipunctures should be performed carefully and only as required.

Should serious bleeding (not controllable by local pressure) occur, concomitant anticoagulant therapy should be terminated immediately. In addition, the second bolus of Retavase® should not be given if serious bleeding occurs before it is administered.

Each patient being considered for therapy with Retavase® should be carefully evaluated and anticipated benefits weighed against the potential risks associated with therapy. In the following conditions, the risks of Retavase® therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy
- Previous puncture of noncompressible vessels
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Hypertension: systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Severe hepatic or renal dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at a seriously infected site
- Advanced age
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Cholesterol Embolization

Cholesterol embolism has been reported rarely in patients treated with thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and should be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when Retavase® is administered.

RETAVASE®
Reteplase recombinant

PRECAUTIONS

General

Standard management of myocardial infarction should be implemented concomitantly with Retavase® treatment. Arterial and venous punctures should be minimized (see **WARNINGS**). In addition, the second bolus of Retavase® should not be given if the serious bleeding occurs before it is administered. In the event of serious bleeding, any concomitant heparin should be terminated immediately. Heparin effects can be reversed by protamine.

Readministration

There is no experience with patients receiving repeat courses of therapy with Retavase®. Retavase® did not induce the formation of Retavase® specific antibodies in any of the approximately 2,400 patients who were tested for antibody formation in clinical trials. If an anaphylactoid reaction occurs, the second bolus of Retavase® should not be given, and appropriate therapy should be initiated.

Drug Interactions

The interaction of Retavase® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin, dipyridamole, and abciximab) may increase the risk of bleeding if administered prior to or after Retavase® therapy.

Drug/Laboratory Test Interactions

Administration of Retavase® may cause decreases in plasminogen and fibrinogen. During Retavase® therapy, if coagulation tests and/or measurements of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent in vitro artifacts. Retavase® is an enzyme that when present in blood in pharmacologic concentrations remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of PPACK (chloromethylketone) at 2 µM concentrations was used in clinical trials to prevent in vitro fibrinolytic artifacts.[6]

Use of Antithrombotics

Heparin and aspirin have been administered concomitantly with and following the administration of Retavase® in the management of acute myocardial infarction. Because heparin, aspirin, or Retavase® may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Retavase®. Studies to determine mutagenicity, chromosomal aberrations, gene mutations, and micronuclei induction were negative at all concentrations tested. Reproductive toxicity studies in rats revealed no effects on fertility at doses up to 15 times the human dose (4.31 U/kg).

Pregnancy Category C

Reteplase has been shown to have an abortifacient effect in rabbits when given in doses 3 times the human dose (0.86 U/kg). Reproduction studies performed in rats at doses up to 15 times the human dose (4.31 U/kg) revealed no evidence of fetal anomalies; however, Reteplase administered to pregnant rabbits resulted in hemorrhaging in the genital tract, leading to abortions in mid-gestation. There are no adequate and well-controlled studies in pregnant women. The most common complication of thrombolytic therapy is bleeding and certain conditions, including pregnancy, can increase this risk. Reteplase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Retavase® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retavase® is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Retavase® in pediatric patients have not been established.

ADVERSE REACTIONS

Bleeding

The most frequent adverse reaction associated with Retavase® is bleeding (see **WARNINGS**). The types of bleeding events associated with thrombolytic therapy may be broadly categorized as either intracranial hemorrhage or other types of hemorrhage.

- Intracranial hemorrhage (see **CLINICAL PHARMACOLOGY**)
  In the INJECT clinical trial the rate of in-hospital, intracranial hemorrhage among all patients treated with Retavase® was 0.8% (23 of 2,965 patients). As seen with Retavase® and other thrombolytic agents, the risk for intracranial hemorrhage is increased in patients with advanced age or with elevated blood pressure.
- Other types of hemorrhage
  The incidence of other types of bleeding events in clinical studies of Retavase® varied depending upon the use of arterial catheterization or other invasive procedures and whether the study was performed in Europe or the USA. The overall incidence of any bleeding event in patients treated with Retavase® in clinical studies (n = 3,805) was 21.1%. The rates for bleeding events, regardless of severity, for the 10 + 10 U Retavase® regimen from controlled clinical studies are summarized in Table 3.

Table 3
Retavase® Hemorrhage Rates

Bleeding Site	INJECT	RAPID 1 and RAPID 2	
	Europe n = 2,965	USA n = 210	Europe n =113
Injection Site*	4.6%	48.6%	19.5%
Gastrointestinal	2.5%	9.0%	1.8%
Genitourinary	1.6%	9.5%	0.9%
Anemia, site unknown	2.6%	1.4%	0.9%

*includes the arterial catheterization site (all patients in the RAPID studies underwent arterial catheterization).

In these studies the severity and sites of bleeding events were comparable for Retavase® and the comparison thrombolytic agents.

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, any concomitant heparin should be terminated immediately. In addition, the second bolus of Retavase® should not be given if the serious bleeding occurs before it is administered. Death and permanent disability are not uncommonly reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during Retavase® therapy. Therefore, Retavase® therapy requires careful attention to potential bleeding sites (e.g., catheter insertion sites, arterial puncture sites).

Allergic Reactions

Among the 2,965 patients receiving Retavase® in the INJECT trial, serious allergic reactions were noted in 3 patients, with one patient experiencing dyspnea and hypotension. No anaphylactoid reactions were observed among the 3,856 patients treated with Retavase® in initial clinical trials. In an ongoing clinical trial two anaphylactoid reactions have been reported among approximately 2,500 patients receiving Retavase®.

Other Adverse Reactions

Patients administered Retavase® as treatment for myocardial infarction have experienced many events which are frequent sequelae of myocardial infarction and may or may not be attributable to Retavase® therapy. These events include cardiogenic shock, arrhythmias (e.g., sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation), AV block, pulmonary edema, heart failure, cardiac arrest, recurrent ischemia, reinfarction, myocardial rupture, mitral regurgitation, pericardial effusion, pericarditis, cardiac tamponade, venous thrombosis and embolism, and electromechanical dissociation. These events can be life-threatening and may lead to death. Other adverse events have been reported, including nausea and/or vomiting, hypotension, and fever.

DOSAGE AND ADMINISTRATION

Retavase® (Reteplase) is for intravenous administration only. Retavase® is administered as a 10 + 10 U double-bolus injection. Each bolus is administered as an intravenous injection over 2 minutes. The second bolus is given 30 minutes after initiation of the first bolus injection. Each bolus injection should be given via an intravenous line in which no other medication is being simultaneously injected or infused. No other medication should be added to the injection solution containing Retavase®. There is no experience with patients receiving repeat courses of therapy with Retavase®.

Heparin and Retavase® are incompatible when combined in solution. Do not administer heparin and Retavase® simultaneously in the same intravenous line. If Retavase® is to be injected through an intravenous line containing heparin, a normal saline or 5% dextrose (D5W) solution should be flushed through the line prior to and following the Retavase® injection.

Although the value of anticoagulants and antiplatelet drugs during and following administration of Retavase® has not been studied, heparin has been administered concomitantly in more than 99% of patients. Aspirin has been given either during and/or following heparin treatment. Studies assessing the safety and efficacy of Retavase® without adjunctive therapy with heparin and aspirin have not been performed.

Reconstitution

Reconstitution should be carried out using the diluent, syringe, needle and dispensing pin provided with Retavase®. It is important that Retavase® be reconstituted only with Sterile Water for Injection, USP (without preservatives). The reconstituted preparation results in a colorless solution containing Retavase® 1 U/mL. Slight foaming upon reconstitution is not unusual; allowing the vial to stand undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

Because Retavase® contains no antibacterial preservatives, it should be reconstituted immediately before use. When reconstituted as directed, the solution may be used within 4 hours when stored at 2-30°C (36-86°F). Prior to administration, the product should be visually inspected for particulate matter and discoloration.

Reconstitution Instructions

Use aseptic technique throughout.

Step 1: Remove the protective flip-cap from one vial of Sterile Water for Injection, USP (SWFI).
Open the package containing the 10 cc syringe with attached needle.
Remove the protective cap from the needle and withdraw 10 mL of SWFI from the vial.

Step 2: Open the package containing the dispensing pin. Remove the needle from the syringe, discard the needle.
Remove the protective cap from the luer lock port of the dispensing pin and connect the syringe to the dispensing pin.
Remove the protective flip-cap from one vial of Retavase®.

Step 3: Remove the protective cap from the spike end of the dispensing pin, and insert the spike into the vial of Retavase® until the security clips lock onto the vial.
Transfer the 10 mL of SWFI through the dispensing pin into the vial of Retavase®.

Step 4: With the dispensing pin and syringe still attached to the vial, swirl the vial gently to dissolve the Retavase®. **DO NOT SHAKE.**

Step 5: Withdraw 10 mL of Retavase® reconstituted solution back into the syringe. A small amount of solution will remain in the vial due to overfill.

Step 6: Detach the syringe from the dispensing pin, and attach the sterile 20 gauge needle provided.

Step 7: The 10 mL bolus dose is now ready for administration.

Safely discard all used reconstitution components and the empty Retavase® vial according to institutional procedures.

HOW SUPPLIED

Retavase®, is supplied as a sterile, preservative-free, lyophilized powder in 10.4 U (18.1 mg) vials without a vacuum, in a kit with components for reconstitution. Each kit contains a package insert, 2 single-use Retavase® vials 10.4 U (18.1 mg), 2 single-use diluent vials for reconstitution (10 mL Sterile Water for Injection, USP), 2 sterile 10 cc syringes with 20 G needle attached, 2 sterile dispensing pins, 2 sterile 20 G needles for dose administration, and 2 alcohol swabs. NDC 57894-040-01.

Storage

Store the kit containing Retavase® at 2-25°C (36-77°F). Kit should remain sealed until use to protect the lyophilisate from exposure to light. Do not use beyond expiration date printed on the kit.

References

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Retavase®,
Reteplase,
recombinant
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For:
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