



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

Retavase	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.<sup>1,2</sup> 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).<sup>3</sup> 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).<sup>3,4,5</sup> 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 <sup>1</sup>	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.

<sup>1</sup>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.



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.<sup>1</sup>

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 Reteplase® 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.

- 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.
- 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®.
- 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®.
- With the dispensing pin and syringe still attached to the vial, swirl the vial gently to dissolve the Retavase®. **DO NOT SHAKE.**
- Withdraw 10 mL of Retavase® reconstituted solution back into the syringe. A small amount of solution will remain in the vial due to overflow.
- Detach the syringe from the dispensing pin, and attach the sterile 20 gauge needle provided.
- 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**

- Martin U, Sponer G, Strein K. Evaluation of thrombolytic and systemic effects of the novel recombinant plasminogen activator BM 06.022 compared with alteplase, anistreplase, streptokinase and urokinase in a canine model of coronary artery thrombosis. *JACC*. 1992;19:433-440.
- Kohnert U, Rudolph R, Verheijen JH. Biochemical properties of the kringle 2 and protease domains are maintained in the refolded t-PA deletion variant BM 06.022. *Protein Engineering*. 1992;5:93-100.
- Smalling R, Bode C, Kalbfleisch J, et al. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. *Circulation*. 1995;91:2725-2732.
- Bode C, Smalling R, Gunther B, et al. Randomized comparison of coronary thrombolysis achieved with double bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation*. 1996;94:891-898.
- INJECT Study Group. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet*. 1995;346:329-336.
- Martin U, Gärtner D, Markl HJ, et al. D-PHE-PRO-ARGCHLOROMETHYLKETONE prevents in vitro fibrinogen reduction by the novel recombinant plasminogen activator BM 06.022. *Ann Hematol*. 1992; 64(suppl)A47.

Retavase®,  
Reteplase,  
recombinant  
Manufactured by:  
Boehringer Mannheim GmbH  
Nonnenwald 2  
D-82377 Penzberg  
Germany

For:  
Centocor, Inc.  
Malvern, PA 19355  
U.S. License Number 1242

