# RAPILYSIN®

Reteplase: Recombinant Plasminogen Activator (r-PA)

## DESCRIPTION

RAPILYSIN® is a sterile, purified, stable recombinant plasminogen activator (r-PA), (reteplase), concentrate produced from genetically engineered E Coli cells containing a cloned human gene for part of the plasminogen activator protein structure.

RAPILYSIN® is a highly purified single chain protein with a molecular weight of 39 kD. Reteplase is obtained by genetic engineering technology, and is a variant of plasminogen activator comprising only the kringle 2 and protease domains. RAPILYSIN is a lyophilised powder for reconstitution prior to injection. RAPILYSIN® is reconstituted with sterile Water for injections.

Potency is expressed in units (U) using a reference standard which is specific for reteplase, and is not comparable for units used for other thrombolytic agents. 10 units of reteplase correspond to 17.4 mg of reteplase protein mass.

### Composition

Each single use vial of lyophilisate powder for injection contains the active ingredient reteplase (plasminogen activator) 10U (rDNA) nominal activity. Each vial also contains the excipients potassium phosphate dibasic, phosphoric acid, tranexamic acid, sucrose and polysorbate 80.

Each single use pre-filled syringe with solvent for reconstitution contains sterile Water for injections 10mL.

RAPILYSIN contains no preservatives.

## PHARMACOLOGY

### Pharmacodynamics

Reteplase is recombinant plasminogen activator which catalyses the cleavage of endogenous plasminogen to generate plasmin. Plasmin in turn degrades fibrinogen and fibrin, which is a component of the matrix of the thrombi, thereby exerting its thrombolytic effect.

Reteplase (10 + 10 U) dose dependently reduces plasma fibrinogen levels by about 75 to 90%. The fibrinogen level normalises within 2 days. As with other plasminogen activators a rebound phenomenon then occurs during which fibrinogen levels reach a maximum within 9 days and remain elevated for up to 18 days.

### Pharmacokinetics

#### *Intravenous administration*

Following intravenous bolus injection (10 + 10 U) in AMI patients, reteplase antigen is distributed in plasma with a dominant half-life ($t_{1/2}\alpha$) of 18 ± 5 min. and eliminated with a terminal half-life ($t_{1/2}\beta$) of 5.5

hours ± 12.5 min. at a clearance rate of 121 ± 25 mL/min. Reteplase activity is cleared from the plasma at a rate of 283 ± 101 mL/min. resulting in a dominant half-life ($t_{1/2}\alpha$) of 14.6 ± 6.7 min. and a terminal half-life ($t_{1/2}\beta$) of 1.6 hours ± 39 min. Only minor amounts of reteplase were immunologically detected in urine. Exact details of the main elimination route in humans are not available and the consequences of hepatic or renal insufficiency are not known. Animal experiments (rats) indicate the liver and kidney to be the main organs of active uptake and lysosomal degradation.

Additional studies in human plasma samples in vitro suggest that complexation with C1-inactivator, $\alpha_2$-antiplasmin and $\alpha_1$-antitrypsin contribute to the inactivation of reteplase in plasma. The relative contribution of the inhibitors to inactivation of reteplase decreases as follows: C1-inactivator > $\alpha_2$-antiplasmin > $\alpha_1$-antitrypsin.

The half-life of reteplase was increased in patients with AMI as compared to healthy volunteers. An additional increase of half-life activity in patients with myocardial infarction and severely impaired liver and kidney function cannot be excluded, but no clinical data relating to the pharmacokinetics of reteplase in these patients is available. Animal data show that in cases of severe impairment of renal function with pronounced concomitant elevation of serum creatine and serum urea, an increase in half-life of reteplase has to be expected.

## CLINICAL TRIALS

Reductions of plasma levels of plasminogen and $\alpha$-2 antiplasmin normalise within 1-3 days. Coagulation factor V, $\alpha$-2-macroglobulin, C1-esterase inhibitor are only slightly reduced and normalised within 1 to 2 days. Prothrombin degradation product (F1 +2) levels and thrombin-antithrombin III complexes increase during thrombolysis indicating thrombin production of which the clinical relevance is unknown.

A large comparative mortality trial (INJECT) in approximately 6000 patients showed that reteplase reduced the incidence of heart failure (secondary efficacy criterion) in a significant manner and was at least equally effective in terms of reducing mortality (primary efficacy criterion) when compared to streptokinase. Patients received 5000 IU intravenous heparin bolus injection prior to administration of the first reteplase bolus.

## INDICATIONS

Thrombolytic therapy of acute myocardial infarction (AMI) (within 6 hours after the onset of AMI symptoms).

## CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, reteplase is contra-indicated in the following situations:

- recent (<10 days), prolonged and vigorous external heart massage
- known haemorrhagic diathesis
- patients with current concomitant therapy with oral anticoagulants (e.g. warfarin sodium)

- intracranial neoplasm, arteriovenous malformation or aneurysm
- neoplasm with increased bleeding risk
- history of cerebrovascular accident
- severe uncontrolled hypertension
- active peptic ulceration
- portal hypertension (oesophageal varices)
- severe liver or renal dysfunction
- acute pancreatitis, pericarditis, bacterial endocarditis
- diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- within 3 months of severe bleeding, major trauma or major surgery (e.g. coronary artery bypass graft, intracranial or intraspinal surgery or trauma), obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels.

## PRECAUTIONS

Current data generally do not support the use of thrombolytic therapy in patients when the ECG shows only ST depression (with the exception of those patients with a "true posterior" infarct, as indicated by tall R waves and marked ST depression in leads V1- V3).

One anaphylactoid/anaphylactic reaction has been observed in the course of a clinical trial.

Reteplase should be used by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

Each patient being considered for therapy with reteplase should be carefully evaluated.

### Bleeding

The most common complication encountered during reteplase therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during reteplase therapy,

bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites). The use of rigid catheter as well as intramuscular injections and nonessential handling of the patient should be avoided during treatment with reteplase.

Should serious bleeding, in particular cerebral haemorrhage, occur, any concomitant heparin should be terminated immediately. In addition, the second bolus of reteplase should not be given if the serious bleeding occurs before it is administered. In general, however, it is not necessary to replace the coagulation factors because of the relatively short half-life of reteplase. Most patients who have bleeding can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement and manual pressure applied to an incompetent vessel. Protamine should be considered if heparin has been administered within 4 hours of the onset of bleeding. In patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusions of cryoprecipitate, fibrinogen, fresh frozen plasma and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/L is desirable with cryoprecipitate or fibrinogen infusion.

In the following conditions the risks of reteplase therapy may be increased and should be weighed against the anticipated benefits:

- cerebrovascular disease
- systolic blood pressure at entry > 160 mm Hg
- recent gastrointestinal or genitourinary bleeding (within 10 days)
- high likelihood of left heart thrombus, e.g. mitral stenosis with atrial fibrillation
- septic thrombophlebitis or occluded arteriovenous cannula at seriously infected site
- advanced age, i.e. over 75 years old
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult because of its location

At present, no sufficient data in patients with a diastolic blood pressure >100 mm Hg prior to thrombolytic therapy are available for reteplase.

## Cholesterol Embolisation

Cholesterol embolisation 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 catheterisation, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticulans, "purple toe" syndrome,

acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal chord infarction, retinal artery occlusion, bowel infarction and rhabdomyolysis.

### Arrhythmias
Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is strongly recommended that antiarrhythmic therapy for bradycardia and/or ventricular tachyarrhythmias (e.g. ventricular tachycardia or fibrillation) be available when reteplase is administered.

### Seizure
As with other thrombolytics, convulsions have been observed in isolated cases, and are most likely caused by transient cerebral ischaemia or embolisation (see **ADVERSE REACTIONS**, **Post-Marketing**).

### Readministration
Since at present there is no experience with readministration of reteplase, readministration is not recommended.

### Use in Hepatic or Renal Insufficiency
There is no clinical experience with use of reteplase in patients with severely impaired hepatic or renal function.

### Use in Children
Safety and efficacy of reteplase in children has not been established.

### Mutagenesis, Carcinogenesis and Impairment of Fertility
Reteplase was not genotoxic in a battery of tests for gene mutations and chromosomal damage. Long-term studies in animals have not been done to evaluate the carcinogenic potential of reteplase. No adverse effects on fertility were seen in male and female rats when reteplase was administered at intravenous doses up to 4.3 U/kg/day.

### Use in Pregnancy: *Category C*
No experience in pregnant women is available for reteplase. Animal studies showed no evidence of embryotoxicity, fetotoxicity or teratogenicity in pregnant rats when reteplase was administered intravenously during organogenesis at doses up to 4.3 U/kg/day. In a preliminary study in rabbits, however, IV dosing at 0.9 U/kg/day caused abortion associated with haemorrhage in the genital tract. Potential embryotoxicity and teratogenicity have not been adequately assessed in rabbits, and perinatal effects have not been investigated. A potential risk of haemorrhage and abortion can be expected in pregnant women, and the use of reteplase in pregnancy is contraindicated except in life-saving situations.

### Use in Lactation
It is not known whether reteplase is excreted into breast milk, and there are no animal data on effects on post natal development. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

### Drug Interactions
Heparin, vitamin K antagonists and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole and abciximab) may increase the risk of bleeding if administered prior to, during or after reteplase therapy. Attention should be paid to this effect especially during periods of low plasma fibrinogen (up to about 2 days after fibrinolytic therapy of AMI).

The combination of full-dose reteplase and abciximab should be avoided due to an increased risk of bleeding. If a patient who has recently received abciximab requires treatment with reteplase, the doses of reteplase and heparin should be reduced.

## ADVERSE REACTIONS

***Haemorrhage***

Very common (> 10%)

injection site

Common (1%-10%)

gastrointestinal

gingival

genitourinary

Uncommon (<1%)

haemopericardium

retroperitoneal bleeding

cerebral haemorrhage

epistaxis

Systolic blood pressure >160 mm Hg before thrombolysis with reteplase was associated with greater risk for cerebral bleeding. Blood transfusions were required rarely.

Death and permanent disability are not uncommonly reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

The risk of intracranial bleeding and fatal intracranial bleeding increase with increasing age.

***Cardiovascular***

Very common (>10%)

Hypotension

Common (1%-10%)

Arrhythmias (e.g. complete AV-block, ventricular tachycardia and fibrillation)

These cardiovascular events can be life-threatening and may lead to death.

### *Hypersensitivity*

Hypersensitivity reactions (e.g.allergic reactions) have rarely been reported. Serious anaphylaxis / anaphylactoid reactions have been observed in isolated cases.

Regarding reteplase, available evidence does not indicate an antibody-mediated origin of these hypersensitivity reactions.

### *Other Adverse Reactions*

Patients administered reteplase as treatment for myocardial infarction have experienced many events which are frequent sequelae of myocardial infarction and may or may not be attributable to reteplase therapy. These events include cardiogenic shock, arrhthymias (eg sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarisations, supraventricular tachycardia, atrial fibrillation/flutter), AV block, pulmonary oedema, heart failure, cardiac arrest, recurrent ischaemia/angina, reinfarction, mitral regurgitation, pericardial effusion, pericarditis, venous thrombosis and embolism, pulmonary embolism, cerebral embolism, ventricular septal defect 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, and fever.

## Post-Marketing

### *Haemorrhage*

Rare: Eye haemorrhage and ecchymosis (see also **PRECAUTIONS** for more information regarding bleeding).

Haematoma, haematemesis, melaena and haemoptysis.

### *Nervous System*

Rare: Events related to the nervous system (e.g. convulsion, aphasia, speech disorder, delirium, acute brain syndrome, agitation, confusion, depression, psychosis) have been reported. Ischaemic or haemorrhagic cerebrovascular events may be contributing or underlying conditions (see also **PRECAUTIONS** for information regarding seizures).

### *Application site*

A local reaction at injection site for example a burning sensation can occur.

# DOSAGE AND ADMINISTRATION

Treatment with RAPILYSIN® should be initiated as soon as possible after the onset of AMI symptoms.

RAPILYSIN® is administered as a 10 + 10 U double bolus injection.

Each bolus should be administered as a slow intravenous injection over not more than 2 minutes. The second bolus is administered 30 minutes after administration of the first bolus injection.

The bolus injection is given via an intravenous line. Ensure that the injection is not mistakenly given paravenously.

**Heparin and RAPILYSIN® are incompatible when combined in solution.** Other incompatibilities may also exist. No other medication should be added to the injection solution.

In those patients where the same line has to be used this line (including Y-line) must be flushed thoroughly with 0.9% sodium chloride or 5% dextrose solution prior to and following the RAPILYSIN® injection.

Heparin and acetylsalicylic acid should be administered before and following the administration of reteplase to reduce the risk of rethrombosis. The recommended heparin dose is 5000 I. U. given as a bolus injection prior to reteplase therapy followed by an infusion of 1000 I. U. per hour starting after the second reteplase bolus. Heparin should be administered for at least 24 hours, preferably for 48 (-72) hours, aiming to keep aPTT values 1.5 to 2 times normal.

The initial dose of acetylsalicylic acid prior to thrombolysis should be at least 250 mg (250-350 mg) followed by 75-150 mg/day at least until discharge.

## Instructions for Use/Handling

1. Use aseptic technique throughout.

2. Remove the protective flip-cap from the vial of reteplase and clean the rubber closure with an alcohol wipe.

3. Open the package containing the reconstitution spike, remove the protective cap from the Luer lock port of the reconstitution spike.

4. Open the package containing the 10 mL syringe with Luer tip. Remove the tip cap from the syringe and connect the syringe to the reconstitution spike.

5. Remove the protective cap from the spike end of the reconstitution spike and insert the spike through the rubber closure into the vial of reteplase. Transfer the 10 mL of solvent into the vial of reteplase.

6. With the reconstitution spike and syringe still attached to the vial, swirl the vial gently to dissolve the reteplase powder. DO NOT SHAKE. The reconstituted preparation results in a clear, colourless solution.

7. Withdraw 10mL of reteplase solution back into the syringe. A small amount of solution may remain in the vial due to overfill.

8. Disconnect the syringe from the reconstitution spike and attach the sterile needle provided. The dose is now ready for intravenous administration.

**Administration**
The injection is prepared by reconstituting the lyophilisate with the content of the accompanying syringe (sterile water for injections).

Do not mix with other drugs or use any solvents other than sterile Water for injections.

Heparin and RAPILYSIN® are incompatible when combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution.

Only solutions which are clear, colourless and practically free of visible particles may be injected. Discard any unused solution.

The reconstituted solution may be held at 2 - 8°C for not more than 4 hours.

## OVERDOSAGE

In the event of overdosage one may expect depletion of fibrinogen and other blood coagulation components (e.g. coagulation factor V) with a consequent risk of bleeding.

Should serious bleeding, in particular cerebral haemorrhage, occur, any concomitant heparin should be terminated immediately. In addition, the second bolus of reteplase should not be given if the serious bleeding occurs before it is administered. In general, however, it is not necessary to replace the coagulation factors because of the relatively short half-life of reteplase. Most patients who have bleeding can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement and manual pressure applied to an incompetent vessel. Protamine should be considered if heparin has been administered within 4 hours of the onset of bleeding. In patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusions of cryoprecipitate, fibrinogen, fresh frozen plasma and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1g/L is desirable with cryoprecipitate or fibrinogen infusion.

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

## PRESENTATION

RAPILYSIN® is presented as vials for reconstitution, and pre-filled syringes containing the solvent (sterile Water for injections).

Packs are presented as:

2 Vials with freeze-dried substance (Reteplase 10 units)

2 Pre-filled syringes containing Water for injections 10mL

2 Reconstitution devices and

2 Needles.

## Pharmaceutical Precautions

RAPILYSIN® must not be used after the expiry date.

Store below 25°C. Do not freeze.

Protect from light.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C to 8 °C for not more than 4 hours.

## SPONSOR

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