

RAPILYSIN® Actavis

Reteplase

COMPOSITION

Vial containing dried substance

Active ingredient: reteplase (rNN)

Excipients: sucrose, phosphoric acid, dipotassium hydrogen phosphate, tranexamic acid, polysorbate 80.

Prefilled syringe containing solvent
10 ml water for injections.

PHARMACEUTICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

Dried substance and solvent for the preparation of a solution for injection.

Vial containing 10 U.

The strength of reteplase is expressed in units (U) based on a reference standard specific to reteplase which are not comparable with the units used for other thrombolytic agents.

INDICATIONS AND POTENTIAL USES

Thrombolytic treatment in acute myocardial infarction (within 12 h following the onset of symptoms).

DOSAGE AND ADMINISTRATION

Normal dosage

The reteplase therapy should be administered as soon as possible after the onset of the symptoms of acute myocardial infarction.

Reteplase is administered as two bolus injections (10 U + 10 U).

Each bolus is administered as a slow intravenous injection (within 2 min). The second bolus injection is administered 30 min after the first.

The boluses are injected via an intravenous access. Inadvertent paravenous injection must be avoided.

The reteplase supplied in the vial is in a dried form. The lyophilizate is dissolved using the contents of the accompanying prefilled syringe.

The reconstituted solution must be used immediately. After reconstitution, the solution must be visually checked.

The solution should only be used if it is clear and colourless. If the solution is not clear and colourless, it must be discarded.

Concomitant treatment with heparin and acetylsalicylic acid:

Concomitant treatment with heparin and acetylsalicylic acid should be carried out before and after reteplase therapy, in order to avoid the risk of rethrombosis.

The recommended dose of heparin is 5000 IU as a bolus injection, followed by an infusion of 1000 IU per h after the second reteplase bolus. Heparin should be administered for at least 24 h, the target aPTT values being around 1.5 to 2 times the upper limit of the normal range.

Acetylsalicylic acid should be administered from the start of the thrombolytic therapy and be continued at least until the patient's discharge from hospital. The initial dosage is 250-500 mg; the dosage is then reduced to 75-150 mg per day (see "Interactions").

Heparin and Rapilysin are incompatible if combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution (see below and the "Incompatibilities" section). Rapilysin should preferably be injected via an intravenous access reserved for this medicinal product. No other products should be injected via the access reserved for Rapilysin, before, during, or after the injection of Rapilysin. This applies to all products, including heparin and acetylsalicylic acid.

In patients who have only one intravenous access for all medicines, this access (including the Y-connector) must be flushed thoroughly with 0.9% saline or 5% glucose solution before and after injection of Rapilysin.

Special dosage instructions

Patients with hepatic or renal impairment:

There are no empirical clinical data available on the use of reteplase in patients with severe disturbances of liver or kidney function.

Children:

There are no empirical data available on the use of reteplase in children.

Readministration

There are no empirical data available concerning readministration of reteplase. No anaphylactic reactions have so far been observed during treatment with reteplase. This accords with the observation that reteplase does not induce antibody formation. If an anaphylactoid reaction occurs, the injection should be stopped immediately and appropriate therapy initiated.

CONTRAINDICATIONS

Hypersensitivity to any of the constituents.

Since thrombolysis therapy increases the risk of bleeding, reteplase must not be used in the following circumstances:

- within 3 months of severe bleeding, severe trauma, or major surgery, e.g. coronary bypass, obstetric delivery, organ biopsy, and previous puncture of non-compressible vessels
- history of cerebrovascular events
- recent intracranial or intraspinal surgery or trauma (within the last 3 months)
- intracranial neoplasia, arteriovenous malformations or aneurysms
- known hemorrhagic diathesis
- severe, uncontrolled hypertension
- active peptic ulcers
- portal hypertension (esophageal varices)
- other known contraindications to fibrinolytic therapy, e.g. acute pancreatitis, acute pericarditis, bacterial endocarditis, hemorrhagic retinopathy, e.g. in diabetes mellitus, or patients simultaneously receiving oral anticoagulants, e.g. phenprocoumon.

WARNINGS AND PRECAUTIONS**Bleeding**

The most common complication encountered during reteplase therapy is bleeding. Concomitant heparin therapy can increase the risk of bleeding. Because of the fibrinolytic effects of reteplase, bleeding from puncture sites can occur. Therefore, in patients receiving thrombolytic therapy, it is important to keep an eye on possible bleeding sites

(e.g. catheters, arterial or venous puncture sites, other cutdown and puncture sites). The use of rigid catheters should be avoided for 3 days in patients receiving reteplase therapy, as should intramuscular injections and non-essential procedures. The risk of bleeding is increased for up to 3 days. In the event of severe bleeding (which cannot be controlled by the application of local pressure) any concomitant heparin therapy must be discontinued immediately. Furthermore, if the first bolus injection of reteplase is followed by severe bleeding, the second bolus injection should not be administered. (For emergency measures, see the "Overdosage" section).

Any patient being considered for reteplase therapy should be carefully investigated.

In the following cases reteplase therapy can carry increased risks, so a careful evaluation of the risks and benefits is required:

- cerebrovascular diseases
- recent gastrointestinal or urogenital bleeding (within the last 10 days)
- intensive (traumatic) cardiac massage
- hypertension: systolic BP \geq 180 mm Hg and/or diastolic BP \geq 110 mm Hg
- high probability of a left-heart thrombus, e.g. in mitral stenosis with atrial fibrillation
- hemostatic disturbances due to severe liver or kidney disease
- neoplasia with increased risk of bleeding
- pregnancy
- septic thrombophlebitis or occluded, infected arteriovenous fistula
- advanced age (over 75 years)
- any other circumstances in which bleeding represents a serious danger or in which the source of bleeding is difficult to reach.

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These reperfusion arrhythmias do not differ from those that can occur in the course of acute myocardial infarction. They can be controlled with the usual antiarrhythmic measures. Antiarrhythmic intervention facilities should therefore be available when reteplase is administered.

Seizures

As with other thrombolytic agents, there have been isolated reports of convulsions. Ischemic or hemorrhagic cerebrovascular events may be contributory or underlying factors.

INTERACTIONS

There have been no systematic studies of the interactions of reteplase and other drugs commonly administered to patients with myocardial infarction.

Retrospective analyses of clinical studies in which reteplase was administered alongside other medicines did not find any clinically relevant interactions in patients with acute myocardial infarction.

Heparin, vitamin K antagonists, medicines that interfere with platelet function (e.g. acetylsalicylic acid, dipyridamole), and combinations of heparin and acetylsalicylic acid can increase the risk of bleeding if used before, during, or after reteplase therapy.

PREGNANCY AND LACTATION

There are no empirical data available on the use of reteplase during human pregnancy. Reteplase should not be used during pregnancy unless it is strictly necessary.

In animal studies, dose-dependent apathy and bleeding occurred after higher doses in the parent animals, and bleeding of the genital tract resulted in abortions in pregnant rabbits given higher doses.

UNDESIRABLE EFFECTS

Frequencies:

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Blood and lymph system

Very common: bleeding, particularly from puncture sites [7.9% (0.9%)*].

Uncommon: gastrointestinal [2.9% (0.4%)*], urogenital [2.1% (0.1%)*], or gingival bleeding [1.8%*], retroperitoneal bleeding [0.2% (0.2%)*] or epistaxis [1.0%*], cerebral hemorrhage / hemorrhagic stroke [0.76%*].

Very rare: ocular bleeding and ecchymosis.

* These frequencies (crude rates) were observed in 3288 patients treated with 10U + 10U reteplase.

The figures in parentheses () represent the frequency of bleeding necessitating transfusion.

Nervous system

Very rare: convulsions, aphasia, speech disturbances, delirium, acute brain syndrome, agitation, confusion, depression, psychosis.

Ischemic or hemorrhagic cerebrovascular events may be contributory or underlying factors.

Cardiovascular system

As with other thrombolytic agents, the following undesirable effects have been reported as sequelae of myocardial infarction and/or thrombolytic therapy:

Common: recurrent ischemia / angina pectoris, hypotension and heart failure / pulmonary edema, *Uncommon:* disturbances of cardiac rhythm (e.g. AV block, atrial fibrillation /? utter, ventricular tachycardia / fibrillation, electromechanical dissociation (EMD)), cardiac arrest, cardiogenic shock, and reinfarction, *Rare:* mitral insufficiency, pulmonary embolism, other systemic embolisms / cerebral embolisms and ventricular septal defect.

These cardiovascular side effects can be life threatening and prove fatal.

General disturbances, and reactions at the administration site

Rare: hypersensitivity reactions (e.g. allergic reactions).

Very rare: serious anaphylactic / anaphylactoid reactions.

In the case of reteplase there is no evidence that the hypersensitivity reactions are antibody-mediated. They are much more likely to be due to the fact that plasminogen activators can trigger non-specific activation of bradykinin and the complement cascade.

OVERDOSAGE

After an overdosage there is likely to be a drop in fibrinogen levels and an increase in the consumption of other hemostasiological parameters (e.g. coagulation factor V) and, subsequently, an increased risk of hemorrhage. Any concomitant heparin therapy should be stopped. In the event of substantial blood loss, it is recommended that fresh plasma or fresh blood be administered.

Anti fibrinolytics (e.g. tranexamic acid, aprotinin) may be administered if required.

PROPERTIES/EFFECTS**ATC code:** B01AD07**Action mechanism/Pharmacodynamics**

Retepase is a recombinant plasminogen activator which catalyses the formation of plasmin through cleavage of endogenous plasminogen. This plasminogenolysis occurs chiefly through interaction with fibrin, which is mediated via the kringle 2 domain of reteplase. Plasmin in turn breaks down the fibrin network of the thrombus, thereby exerting its thrombolytic action.

Retepase (10U + 10U) dose-dependently lowers plasma fibrinogen levels by about 60 to 80%. The fibrinogen levels return to normal within 2 days. As with other plasminogen activators, this is followed by a rebound phenomenon, during which fibrinogen levels reach a maximum within 9 days and remain elevated for up to 18 days.

Decreased plasma levels of hemostasiological parameters (e.g. plasminogen, α 2-antiplasmin, α 2-macroglobulin) normalize within 1 to 3 days.

Co-administration of acetylsalicylic acid and reteplase can lead to inhibition of platelet aggregation. This effect should therefore be taken into account if plasma fibrinogen levels are low.

In vitro studies of human-plasma clots showed concentration-dependent lysis of the clots with reteplase. Animal studies found a dose-dependent thrombolytic effect.

Clinical studies in patients with acute myocardial infarction showed earlier patency and higher patency rates after reteplase than after other registered thrombolytics.

A large phase III comparative study showed that reteplase lowers the incidence of heart failure and acute myocardial infarction-associated mortality (primary end point).

There is no evidence that reteplase has an antigenic effect.

PHARMACOKINETICS**Distribution**

After intravenous bolus injection of 10U + 10U in patients with acute myocardial infarction, reteplase

antigen is distributed in plasma with a dominant half-life ($t_{1/2}$) of 19 min and eliminated with a terminal half-life ($t_{1/2}$) of 5.5 h.

The plasma clearance rate of reteplase antigen is 121 ml/min; the volume of distribution (VD) is 35l.

Metabolism

Only small amounts of reteplase were immunologically detectable in the urine. Experiments in rats indicate that active uptake and lysosomal degradation take place mainly in the liver and the kidneys.

Additional *in vitro* studies performed using a human-plasma medium suggest that inhibition due to complexation contributes to the inactivation of reteplase in plasma. The clearance rate for the functionally active reteplase molecule is 283 ml/min, which thus exceeds the clearance rate for reteplase antigen.

Elimination

At therapeutic doses the effective half-life of reteplase activity is 13-16 min.

It is not known whether reteplase is excreted in breast milk.

Pharmacokinetics in special patient populations

Pharmacokinetic behaviour in cases of hepatic and renal impairment has not yet been investigated.

PRECLINICAL DATA

Acute toxicity studies were carried out in rats, rabbits, and monkeys. Subacute toxicity studies were performed in rats, dogs, and monkeys. The main acute symptom after administration of single high doses of reteplase to rats and rabbits was transient apathy immediately after the injection. In cynomolgus monkeys, the sedative effect ranged from slight apathy to unconsciousness, caused by a reversible dose-dependent drop in blood pressure. There was increased local hemorrhage at the injection site.

Subacute toxicity studies did not reveal any unexpected side effects. In dogs, repeated administration of the human peptide reteplase led to immunological allergic reactions. Genotoxicity of reteplase was excluded by a comprehensive battery of tests with various genetic end points, both *in vitro* and *in vivo*.

Reproductive toxicity studies were performed in rats (fertility and embryofetotoxicity studies including a

littering phase) and in rabbits (embryofetotoxicity study, dose-range finding only). In rats, a species which is insensitive to the pharmacological effects of reteplase, there were no detectable adverse effects on fertility, embryofetal development, or the newborn offspring. In rabbits vaginal bleeding and abortions – possibly connected with prolonged hemostasis – were observed, but no fetal abnormalities. No pre- and postnatal toxicity studies of reteplase were performed.

SPECIAL REMARKS

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

No other products should be injected via the access reserved for Rapilysin, before, during, or after the injection of Rapilysin. This applies to all products, including heparin and acetylsalicylic acid, which should be injected before and after administration of reteplase, to avoid the risk of rethrombosis.

In patients who have only one intravenous access for all medicines, this access (including the Y-connector) must be flushed thoroughly with 0.9% saline or 5% glucose solution before and after injection of Rapilysin.

Shelf life

The product must be used before the date indicated by EXP on the pack.

Special precautions for storage

Vial containing dried substance:

Do not store above 30°C. Keep the container in the original pack in order to protect the contents from light.

Instructions for use and handling

- a) Correctly prepared, the solution is physically and chemically stable for 8 h at 2-8°C. For microbiological reasons, the reconstituted product must be used immediately.
- b) Special instructions regarding the mode of use
 1. Work under aseptic conditions.
 2. Remove the plastic cap from the reteplase vial and disinfect the rubber closure with an alcohol wipe.

3. Take the reconstitution device out of the pack and remove the protective cap from the Luer attachment of the reconstitution device.
4. Take the 10 ml prefilled syringe with the Luer tip out of the pack. Remove the protective cap from the syringe.
5. Remove the protective cap from the spike of the reconstitution device. Insert the spike through the rubber closure into the vial of reteplase. Connect the syringe to the Luer attachment of the reconstitution device and inject the solvent (10 ml) into the reteplase vial.
6. With the spike of the reconstitution device (and the syringe) still attached to the vial, swirl the vial gently until the reteplase powder has completely dissolved. Do not shake. The prepared solution should be clear and colourless.
7. The reconstituted product is a clear, colourless solution. If the solution is not clear and colourless, it must be discarded.
8. Draw 10 ml of the reteplase solution into the syringe. The quantity left over in the vial is due to overage. Remove the syringe from the reconstitution device. The solution can now be administered.
9. Heparin and Rapilysin are incompatible if combined in solution. Other incompatibilities may also exist. No other medication should be added to the injection solution.

PACKS

- 1 pack contains:
 - 2 vials with powder for solution for injection
 - 2 syringes with solvent
 - 2 reconstitution devices and 2 needles 19 G 1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

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Marketing Authorization Holder:

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