ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Rapilysin 10 U powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 10 U* reteplase ** in 0.56 g powder
1 prefilled syringe contains 10 ml water for injections.

The reconstituted solution contains 1 U reteplase per ml.

For the full list of excipients, see section 6.1.

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

** Recombinant plasminogen activator produced in Escherichia coli by recombinant DNA technology.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White powder and clear colourless liquid (water for injections).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rapilysin is indicated for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 12 hours after the onset of acute myocardial infarction AMI symptoms.

4.2 Posology and method of administration

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

Rapilysin should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor its use.

Posology

Dosage of Rapilysin

Rapilysin is administered as a 10 U bolus dose followed by a second 10 U bolus dose 30 minutes later (double bolus).
Each bolus is administered as a slow intravenous injection within 2 minutes. Ensure that the injection is not mistakenly given paravenously.
Heparin and acetylsalicylic acid should be administered before and following the administration of Rapilysin to reduce the risk of re-thrombosis.

Dosage of Heparin

The recommended dose of heparin 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

Medicinal product no longer authorised

be administered for at least 24 hours, preferably for 48 – 72 hours, aiming to keep aPTT values 1.5 to 2 times normal.

Dosage of Acetylsalicylic Acid

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.

Paediatric population

No data are available.

Method of administration

Reteplase is supplied as a freeze-dried substance in vials. The lyophilisate is reconstituted with the contents of the accompanying syringe. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Rapilysin should be injected preferably through an intravenous line whose sole purpose is the injection of Rapilysin. No other medicines should be injected through the line reserved for Rapilysin, neither at the same time, nor prior to, nor following Rapilysin injection. This applies to all products including heparin, and acetylsalicylic acid, which should be administered before and following the administration of reteplase to reduce the risk of re-thrombosis.

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 % glucose solution prior to and following the Rapilysin injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

- 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
- recent (< 10 days) prolonged and vigorous external heart massage
- severe uncontrolled hypertension
- active peptic ulceration
- portal hypertension (oesophageal varices)
- severe liver or renal dysfunction
- acute pancreatitis, pericarditis, bacterial endocarditis

Medicinal product no longer authorised

- 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 non-compressible vessels.

4.4 Special warnings and precautions for use

Each patient being considered for therapy with reteplase should be carefully evaluated.
For information on product incompatibilities see section 6.2.

Bleeding

The most common complication encountered during reteplase therapy is bleeding. 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 mmHg
- 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
- age over 75 years
- any other condition in which bleeding constitutes a significant hazard or would be particularly difficult because of its location

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, cut down 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.

Caution should be employed when used with other medicinal products affecting haemostasis such as heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants and antiplatelet agents other than acetylsalicylic acid, such as dipyridamole, ticlopidine, clopidogrel or glycoprotein IIb/IIIa receptor antagonists.

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 the 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.

At present, insufficient data in patients with a diastolic blood pressure > 100 mmHg prior to thrombolytic therapy are available for reteplase.

Medicinal product no longer authorised

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.

Readministration

Since at present there is no experience with readministration of reteplase, the readministration is not recommended. However, no antibody formation to the reteplase molecule has been observed.
If an anaphylactoid reaction occurs, the injection should be discontinued immediately and appropriate therapy should be initiated.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Retrospective analyses of clinical studies did not reveal any clinically relevant interactions with medicinal product used concomitantly with reteplase in patients with acute myocardial infarction. Heparin, vitamin K antagonists and medicinal product 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).

For information on product incompatibilities see section 4.2.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of reteplase in pregnant women. The only relevant available animal data refer to studies performed in rabbits, which showed vaginal bleedings associated with abortions (see section 5.3). The potential risk for humans is unknown.
Except in life-threatening situations, Rapilysin should not be used in pregnant women.

Breast-feeding
It is not known whether reteplase is excreted into breast milk. Breast milk should be discarded within the first 24 hours after thrombolytic therapy.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reaction associated with reteplase treatment is haemorrhage, predominantly at the injection site. Local reactions at injection site can also occur.

As with other thrombolytic agents, recurrent ischaemia/angina, hypotension and heart failure/pulmonary oedema have been reported frequently as sequelae of myocardial infarction and/or thrombolytic administration.

Haemorrhage

The most frequent adverse drug reaction associated with reteplase treatment is haemorrhage.

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Reports of intracranial bleeding, many of which are fatal, are of particular concern.

Systolic blood pressure over 160 mmHg before thrombolysis with reteplase was associated with greater risk for cerebral bleeding. The risk of intracranial bleeding and fatal intracranial bleeding increases with increasing age. Blood transfusions were rarely required. Death and permanent disability are not uncommonly reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

Tabulated list of adverse reactions

The frequency of adverse reactions reported is listed in the following table. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions seen with reteplase
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. allergic reactions)[1]
	Very rare	Serious anaphylaxis/anaphylactoid reactions[1]
Nervous system disorders	Uncommon	Cerebral haemorrhage[2]
	Very rare	Events related to the nervous system (e.g. epileptic seizure, convulsion, aphasia, speech disorder, delirium, acute brain syndrome, agitation, confusion, depression, psychosis)
Cardiac disorders[3]	Very common	Recurrent ischaemia/angina, hypotension and heart failure/pulmonary oedema
	Common	Arrhythmias (e.g. AV block, atrial fibrillation/flutter, ventricular tachycardia/fibrillation, electromechanical dissociation (EMD)), cardiac arrest, cardiogenic shock and reinfarction
	Uncommon	Mitral regurgitation, pulmonary embolism, other systemic embolism/cerebral embolism and ventricular septal defect
Vascular disorders	Common	Gastrointestinal haemorrhage (haematemesis, melena), gingival or genitourinary bleeding
	Uncommon	Haemopericardium, retroperitoneal bleeding, cerebral haemorrhage, epistaxis, haemoptysis, eye haemorrhage and ecchymosis
General disorders and administration site conditions	Very common	Haemorrhage at the injection site (e.g. haematoma), a local reaction at injection site, for example a burning sensation

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Injury, poisoning and procedural complications	Not known	Fat embolism, which may lead to corresponding consequences in the organs concerned[4]

1. Available evidence on reteplase does not indicate an antibody-mediated origin of these hypersensitivity reactions.
2. Ischaemic or haemorrhagic cerebrovascular events may be contributing or underlying conditions.
3. As with other thrombolytic agents these cardiovascular events have been reported as sequelae of myocardial infarction and/or thrombolytic administration. These events can be life-threatening and may lead to death.
4. This event has been reported for the therapeutic class of thrombolytic agents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

For further information see section 4.4, section bleeding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agent, ATC Code: B01AD07

Mechanism of action
Reteplase is a recombinant plasminogen activator that catalyzes the cleavage of endogenous plasminogen to generate plasmin. This plasminogenolysis occurs preferentially in the presence of fibrin. Plasmin in turn degrades fibrin, which is the main component of the matrix of thrombi, thereby exerting its thrombolytic action.

Reteplase (10+10 U) dose-dependently reduces plasma fibrinogen levels by about 60 to 80 %. 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.

Reductions of plasma levels of plasminogen and α2-antiplasmin normalise within 1 to 3 days. Coagulation factor V, clotting factor VIII, α2-macroglobulin, and C1-esterase inhibitor are only slightly reduced and normalise within 1 to 2 days. Plasminogen activator inhibitor 1 (PAI-1) activity can be reduced to around zero, but rapidly normalises within two hours showing a rebound phenomenon. Prothrombin activation fragment 1 levels and thrombin-antithrombin III-complexes increase during thrombolysis indicating thrombin production of which the clinical relevance is unknown.

Clinical efficacy and safety
A large comparative mortality trial (INJECT) in approx. 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. In two clinical trials aiming primarily at coronary artery patency (RAPID I and II) reteplase was associated with higher early patency rates (primary efficacy criterion), as well as with a

Medicinal product no longer authorised

lower incidence of heart failure (secondary efficacy criterion) than alteplase (3 hour and "accelerated" dosage regimens). A clinical trial in approximately 15 000 patients comparing reteplase with the accelerated dose regimen of alteplase (GUSTO III) (2:1 randomisation reteplase: alteplase) did not show statistically different results for the primary endpoint of 30-day mortality (reteplase: 7.47 %, alteplase 7.23 %, p = 0.61) or for the combined endpoint of 30-day mortality and non-fatal disabling stroke (reteplase: 7.89 %, alteplase 7.88 %, p = 0.99). Overall stroke rates were 1.64 % in the reteplase and 1.79 % in the alteplase group. In the reteplase group, 49.4 % of these strokes were fatal and 27.1 % were disabling. In the alteplase group 33.0 % were fatal and 39.8 % were disabling.

5.2 Pharmacokinetic properties

Elimination
Following intravenous bolus injection of 10 + 10 U in patients with acute myocardial infarction reteplase antigen is distributed in plasma with a dominant half-life (t1/2α) of 18±5 min and eliminated with a terminal half-life (t1/2ß) 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 (t1/2α) of 14.6±6.7 min and a terminal half-life (t1/2ß) of 1.6 hours±39 min. Only minor amounts of reteplase were immunologically detected in the urine. Exact data on the main elimination routes for reteplase in humans are not available and the consequences of hepatic or renal insufficiency are not known. Experiments in rats indicate that the liver and the kidneys are the main organs of active uptake and lysosomal degradation.
Additional studies in human plasma samples *in vitro* suggest that complexation with C1-inactivator, α2-antiplasmin and α2-antitrypsin contributes to the inactivation of reteplase in plasma. The relative contribution of the inhibitors to inactivation of reteplase decreases as follows: C1-inactivator > α2-antiplasmin > α2-antitrypsin.

The half-life of reteplase was increased in patients with AMI as compared to healthy volunteers. An additional increase of half-life of activity in patients with myocardial infarction and severely impaired liver and renal function cannot be excluded, but no clinical data of pharmacokinetics of reteplase in these patients are available. Animal data show that in case of severely impaired renal function with a pronounced increase in serum creatinine and serum urea an increase in half-life of reteplase has to be expected. Mild impairment of renal function did not significantly affect the pharmacokinetic properties of reteplase.

5.3 Preclinical safety data

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

Subacute toxicity studies did not reveal any unexpected adverse events. In dogs repeated dosing of the human peptide reteplase led to immunologic-allergic reactions. Genotoxicity of reteplase was excluded by a complete battery of tests at different genetic end points in vitro and in vivo.

Reproductive toxicity studies were performed in rats (fertility and embryo-foetotoxicity study including a littering phase) and in rabbits (embryo-foetotoxicity study, dose-range finding only). In rats, a species insensitive to the pharmacological effects of reteplase, there were no adverse effects on fertility, embryo-foetal development and offspring. In rabbits, vaginal bleedings and abortions possibly associated to prolonged haemostasis, but no foetal abnormalities were noted. A pre- and postnatal toxicity study was not performed with reteplase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medicinal product no longer authorised

Powder:
Tranexamic acid
di potassium-hydrogen phosphate
phosphoric acid
sucrose
Polysorbate 80

Solvent:
Water for injections

6.2 Incompatibilities

This medicinal product should not be mixed with Heparin and/or acetylsalicylic acid.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

6.3 Shelf life

Shelf-life as package for sale:
3 years.

Reconstituted product:
Chemical and physical in-use stability has been demonstrated for 8 hours between 2° and 30 °C after dissolving with water for injection.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25 °C.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack contains:

2 colourless glass vials (type I) with a rubber (butyl) closure and an aluminium flip-off cap, containing 0.56 mg of powder.
2 pre-filled glass syringes (borosilicate, type I) for single use, with a bromobutyl plunger stopper and a bromobutyl rubber tip cap, containing 10 ml of solvent.
2 reconstitution spikes
2 needles 19 G1

6.6 Special precautions for disposal and other handling

Incompatibility of some prefilled glass syringes (including Rapilysin) with certain needle free connectors has been reported. Therefore, the compatibility of the glass syringe and intravenous access should be ensured before use. In case of incompatibility an adaptor can be used and removed together with the glass syringe immediately after administration

Use aseptic technique throughout.

Medicinal product no longer authorised

1. Remove the protective flip-cap from the vial of Rapilysin 10 U and clean the rubber closure with an alcohol wipe.

2. Open the package containing the reconstitution spike, remove both protective caps from the reconstitution spike.

3. Insert the spike through the rubber closure into the vial of Rapilysin 10 U.

4. Take the 10 ml syringe out of the package. Remove the tip cap from the syringe. Connect the syringe to the reconstitution spike and transfer the 10 ml of solvent into the vial of Rapilysin 10 U.

5. With the reconstitution spike and syringe still attached to the vial, swirl the vial gently to dissolve the Rapilysin 10 U powder. DO NOT SHAKE.

6. The reconstituted preparation results in a clear, colourless solution. If the solution is not clear and colourless it should be discarded.

7. Withdraw 10 ml of Rapilysin 10 U 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. The dose is now ready for intravenous administration

9. The reconstituted solution must be used immediately. Visual inspection of the solution is necessary after reconstitution. Only clear, colourless solutions should be injected. If the solution is not clear and colourless it should be discarded.

10. No other medicines should be injected through the line reserved for Rapilysin either at the same time, or prior to, or following Rapilysin injection. This applies to all products including heparin and acetylsalicylic acid, which should be administered before and following the administration of reteplase to reduce the risk of re-thrombosis

11. In those patients where the same line has to be used, this line (including Y-line) must be flushed thoroughly with a 0.9 % sodium chloride or 5 % glucose solution prior to and following the Rapilysin injection (see section 4.2 Posology and method of administration).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Dalshraun 1
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/018/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 1996

Medicinal product no longer authorised

Date of last renewal: 29 August 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Medicinal product no longer authorised

Medicinal product no longer authorised

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Wacker Biotech GmbH
Heinrich-Damerow-Str. 4
06120 Halle
Germany

Name and address of the manufacturers responsible for batch release

Actavis Italy S.p.A.
Nerviano Plant
Via Pasteur 10
20014 Nerviano (Milan)
Italy

Cenexi
52, Rue Marcel et Jacques Gaucher
94120 Fontenay-Sous-Bois
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent published on the European medicines web-portal.

Not applicable

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rapilysin 10 U powder and solvent for solution for injection
Water for injections for Rapilysin 10 U solution for intravenous use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Reteplase 10 U (recombinant plasminogen activator, thrombolytic agent)

3. LIST OF EXCIPIENTS

Powder:
Tranexamic acid
di potassium-hydrogen phosphate
phosphoric acid
sucrose
Polysorbate 80

Solvent:
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for injection (contains 2x [0.56 g of powder in a vial and 10 ml solvent in a pre-filled syringe with reconstitution spike and needle])

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use the solution immediately after reconstitution

8. EXPIRY DATE

EXP

Medicinal product no longer authorised

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Dalshraun 1
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/018/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL OF THE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rapilysin 10 U powder and solvent for solution for injection
Reteplase Intravenous use

2. METHOD OF ADMINISTRATION

Use the solution immediately after reconstitution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 U reteplase

6. OTHER

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL OF THE SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: Information for the user

Rapilysin 10 U powder and solvent for solution for injection
reteplase

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rapilysin is and what it is used for
2. What you need to know before Rapilysin is given to you
3. How to use Rapilysin
4. Possible side effects
5. How to store Rapilysin
6. Contents of the pack and other information

1. What Rapilysin is and what it is used for

Rapilysin contains the active substance reteplase(a recombinant plasminogen activator). It is a thrombolytic medicine used to dissolve blood clots that have formed in certain blood vessels and to restore the blood flow in these blocked vessels (=thrombolysis).

Rapilysin is used after an acute myocardial infarction (heart attack) in order to dissolve the blood clot causing the heart attack. It is given within 12 hours after the onset of symptoms.

2. What you need to know before Rapilysin is given to you

The doctor will ask you questions before giving you Rapilysin, to find out if you have an increased risk of bleeding.

Do not use Rapilysin
- if you are allergic to reteplase or any of the other ingredients of this medicine (listed in section 6).
- if you have a bleeding disorder.
- if you are taking medicine to thin your blood (oral anticoagulants, e.g. warfarin).
- if you have a brain tumour or a malformed blood vessel or a vessel wall dilatation (aneurysm) in the brain.
- if you have other tumours associated with an increased risk of bleeding.
- if you have had a stroke.
- if you have had external heart massage within the past 10 days.
- if you have severe uncontrolled high blood pressure (hypertension).
- if you have an ulcer in the stomach or small intestine.
- if you have enlarged blood vessels in the gullet (oesophagus) (frequently caused by liver disease).
- if you have severe liver or kidney disease.
- if you have acute inflammation of the pancreas or pericardium (the sac surrounding the heart), or an infection of the heart muscle (bacterial endocarditis).
- if you have in the past 3 months had severe bleeding, a major injury or major surgery (e.g. coronary artery bypass graft, or surgery or injury to the head or spine), given birth, or had an organ biopsy or other medical / surgical procedure.

Medicinal product no longer authorised

Warnings and precautions

Bleeding
The most common side effect of Rapilysin is bleeding. Therefore Rapilysin must be given only in the presence and under the instructions of an emergency doctor.

Pay careful attention to all possible bleeding sites (e.g. injection sites). Heparin, which is given together with Rapilysin, may also increase bleeding.

The risks of Rapilysin treatment may be increased if you have any of the following conditions:
- diseases of the blood vessels in the brain
- systolic blood pressure higher than 160 mmHg
- bleeding in the gastrointestinal, urinary or genital tract within the past 10 days
- high likelihood of a blood clot in the heart (e.g. as a result of narrowing of a heart valve or atrial fibrillation)
- septic inflammation of a vein with blood clotting (septic thrombophlebitis) or blocked blood vessels at an infected site
- age over 75 years
- any other condition in which bleeding might be especially dangerous or might occur at a site where it would be difficult to control

At present, little data are available on the use of Rapilysin in patients with diastolic blood pressure higher than 100 mmHg.

Abnormal heart beats (arrhythmias)
Thrombolytic treatment may cause the heart to beat irregularly. Therefore tell the medical staff immediately if you

- feel palpitations or an irregular heart beat

Repeated use
At present there is no experience with repeated use of Rapilysin. Therefore, repeated use is not recommended. Antibody formation to the reteplase molecule has not been seen.

Children
Safety and effectiveness of Rapilysin in children have not been established. Treatment of children with Rapilysin is not recommended.

Other medicines and Rapilysin:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Heparin and other medicines that thin the blood (anticoagulants) and acetylsalicylic acid (a substance used in many medicines used to relieve pain and lower fever) may increase the risk of bleeding.

For information on medicines that should not be physically mixed with Rapilysin solution for injection, see section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
There is no experience with Rapilysin in pregnant women. Therefore it should not be used except in life-threatening situations. You must tell your doctor if you are pregnant or think you are pregnant. Your doctor can tell you the risks and benefits of using Rapilysin during pregnancy.

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Breast-feeding
You should not breast-feed your baby during treatment with Rapilysin as it is not known whether Rapilysin is excreted into mother's milk. Mother's milk should be thrown away during the first 24 hours after thrombolytic treatment. Discuss with your doctor when you can take up breast-feeding again.

3. How to use Rapilysin

Rapilysin is usually given in a hospital. The medicine is supplied in vials as a powder for injection. Before use, the powder for injection must be dissolved in the water for injection supplied in the prefilled syringe that is in the package. Do not add any other medicines. The resulting solution must be used immediately. The solution must be examined to ensure that only clear, colourless solution is injected. If the solution is not clear and colourless it should be thrown away.

Treatment with Rapilysin 10 U should be started as soon as possible after the symptoms of heart attack begin.

Heparin and Rapilysin cannot be mixed in the same solution. Other medicines may also not mix well with Rapilysin. No other medicines should be added to the injection solution (see below). Rapilysin should be injected preferably through an intravenous line that is used only for the injection of Rapilysin. No other medicines should be injected through the line reserved for Rapilysin, either at the same time, or before or after Rapilysin injection. This applies to all medicines including heparin and acetylsalicylic acid, which are given before and after Rapilysin to reduce the risk of new blood clots forming.
If the same line has to be used, this line (including Y-line) must be flushed thoroughly with a 0.9 % sodium chloride or 5 % glucose solution before and after the Rapilysin injection.

Dosage of Rapilysin
Rapilysin is given as a 10 U injection followed by a second 10 U injection 30 minutes later (double bolus).

Each injection should be given slowly within 2 minutes. The injection must not be given mistakenly outside the vein. Therefore, be sure to tell the medical staff if you experience pain during the injection.

Heparin and acetylsalicylic acid are given before and after Rapilysin to reduce the risk of new blood clots forming.

Dosage of Heparin
The recommended dose of heparin is 5000 I.U. given as a single injection before Rapilysin, followed by an infusion of 1000 I.U. per hour starting after the second Rapilysin injection. Heparin should be given for at least 24 hours, preferably for 48-72 hours, in order to keep aPTT values 1.5 to 2 times normal.

Dosage of Acetylsalicylic Acid
The dose of acetylsalicylic acid given before Rapilysin should be at least 250 mg-350 mg and should be followed by 75-150 mg/day, at least until discharge from hospital.

If more Rapilysin is used than recommended
In the event of overdosage there may be an increased risk of bleeding.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people)

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- Bleeding at the injection site, e.g. blood blister (haematoma)
- Chest Pain / angina, low blood pressure and heart failure /shortness of breath may reappear
- Burning sensation when Rapilysin is injected

Common side effects (may affect up to 1 in 10 people)
- Bleeding in the digestive tract (e.g. bloody or black vomit, or stools) in the gums or in the urinary or genital tract
- Abnormal heart beats (arrhythmias), cardiac arrest, circulatory collapse or another heart attack may occur

Uncommon side effects (may affect up to 1 in 100 people)
- Bleeding around the heart, in the abdomen, the brain or the eyes, under the skin, from the nose or as coughed up blood
- Damage to the heart or heart valves, or a blood clot in the lung, brain or other part of body mayoccur
- hypersensitivity (e.g. allergic reactions)

Very rare side effects (may affect up to 1 in 10,000 people)
- Events related to the nervous system (e.g. epileptic seizure, convulsion, speech disorder, delirium, agitation, confusion, depression, psychosis)
- severe allergic reaction, causing shock or collapse

Side effects of frequency not known (cannot be estimated from the available data)
- Blockage of blood vessels due to cholesterol (fat)

Cardiovascular events can be life-threatening or cause death.

Patients with systolic blood pressure over 160 mmHg have a greater risk of bleeding in the brain. The risk of intracranial bleeding and fatal intracranial bleeding increases with increasing age. Blood transfusions were rarely required. Death or permanent disability are not uncommon in patients who have a stroke (including bleeding in the brain) or other serious bleeding problem.

Be sure to tell hospital staff immediately if any of these symptoms appear.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rapilysin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Keep the vial in the outer carton in order to protect from light.

After reconstitution (“when dissolved”), the solution must be used immediately.

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6. Contents of the pack and other information

What Rapilysin contains
- The active substance is reteplase 10U/10 ml after reconstitution.
- The other ingredients are:

Powder:
Tranexamic acid
di-potassium-hydrogen phosphate
phosphoric acid
sucrose
polysorbate 80

Solvent:
10 ml Water for injection (prefilled syringe)

What Rapilysin looks like and contents of the pack
Rapilysin is presented as a powder and a solvent for injection (0.56 g powder in a vial and 10 ml solvent in a pre-filled syringe with a reconstitution spike and a needle-pack of 2)

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Instructions for use/handling
Incompatibility of some prefilled glass syringes (including Rapilysin) with certain needle free connectors has been reported. Therefore, the compatibility of the glass syringe and intravenous access should be ensured before use. In case of incompatibility an adaptor can be used and removed together with the glass syringe immediately after administration

Use aseptic technique throughout.

1. Remove the protective flip-cap from the vial of Rapilysin 10 U and clean the rubber closure with an alcohol wipe.

2. Open the package containing the reconstitution spike, remove both protective caps from the reconstitution spike.

3. Insert the spike through the rubber closure into the vial of Rapilysin 10 U.

4. Take the 10 ml syringe out of the package. Remove the tip cap from the syringe. Connect the syringe to the reconstitution spike and transfer the 10 ml of solvent into the vial of Rapilysin 10 U.

5. With the reconstitution spike and syringe still attached to the vial, swirl the vial gently to dissolve the Rapilysin 10 U powder. DO NOT SHAKE.

6. The reconstituted preparation results in a clear, colourless solution. If the solution is not clear and colourless it should be discarded.

7. Withdraw 10 ml of Rapilysin 10 U 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. The dose is now ready for intravenous administration.

9. No other medicines should be injected through the line reserved for Rapilysin either at the same time, or prior to, or following Rapilysin injection. This applies to all products including heparin and acetylsalicylic acid, which should be administered before and following the administration of reteplase to reduce the risk of re-thrombosis.

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

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