

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Urokinase medac 10,000 I.U.

Powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10,000 I.U. of human urokinase extracted from human urine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravascular lysis of blood clots in the following conditions:

- extensive acute proximal deep vein thrombosis
- acute massive pulmonary embolism
- acute occlusive peripheral arterial disease with limb threatening ischemia
- thrombosed arteriovenous haemodialysis shunts
- thrombosed central venous catheters

4.2 Posology and method of administration

Urokinase medac should only be used by physicians experienced in the management of thrombotic diseases in hospitals where adequate diagnostic and monitoring techniques are available.

Depending on the indication, the route of administration of Urokinase medac is by systemic intravenous infusion, by local intra-arterial catheter-directed infusion during arteriography, or by local instillation.

It must not be given by subcutaneous or intramuscular injection.

For instructions regarding reconstitution and further dilution, see section 6.6.

Adults

The dosage may be adjusted individually depending on the clinical condition. The following dose regimens should be used as a guideline.

Deep vein thrombosis

Urokinase medac should be administered by intravenous infusion into a peripheral vein using an initial dose of 4,400 I.U./kg bodyweight infused over 10 – 20 min, followed by a maintenance dose of 100,000 I.U. per hour for 2 – 3 days.

Pulmonary embolism

Urokinase medac should be administered by intravenous infusion into a peripheral vein using an initial dose of 4,400 I.U./kg bodyweight infused over 10 – 20 min, followed by a maintenance dose of 4,400 I.U./kg bodyweight per hour for 12 hours.

Occlusive peripheral arterial disease

Urokinase medac should be administered by local intra-arterial catheter-directed graded infusion using an initial dose of 4,000 I.U./min (i.e. 240,000 I.U. per hour) for 2 – 4 hours or until restoration of antegrade flow, followed by a dose of 1,000 – 2,000 I.U./min until complete lysis or a maximum of 48 hours.

Thrombosed arteriovenous haemodialysis shunts

Urokinase medac should be administered by local forced periodic infusion (pulse spray) into both branches of the shunt at a concentration of 5,000 to 25,000 I.U./ml up to a total dose of 250,000 I.U. If necessary, the application can be repeated every 30 – 45 minutes up to a maximum of 2 hours.

Thrombosed central venous catheters

Urokinase medac should be dissolved in physiological saline at a concentration of 5,000 I.U./ml. A volume sufficient to completely fill the lumen of the occluded catheter should be instilled and either locked for a duration of 20 to 60 minutes or pushed with aliquots of saline before the lysate is aspirated. The procedure may be repeated if necessary.

Special populations

- Elderly patients: Available data are limited in patients over 65 years and it is not known whether they respond differently from younger subjects. Urokinase medac should be used with caution in elderly patients (see section 4.4).
- Patients with renal or hepatic impairment: A dose reduction may be required in patients with impaired renal and/or hepatic function. In these cases, the fibrinogen level should not fall below 100 mg/dl.

Paediatric patients

There is very limited experience with urokinase in children with thromboembolic occlusive vascular disease and urokinase should not be used in this indication.

Urokinase medac may be used in children of all ages for the treatment of thrombosed central venous catheters using the same lock procedure as in adults.

Therapeutic monitoring

Before starting thrombolytic therapy, haemostasis tests should be performed including haematocrit, platelet count, thrombin time (TT) and activated partial thromboplastin time (aPTT).

If heparin has been given, it should be discontinued and the aPTT should be less than twice the normal control value before urokinase therapy is initiated.

For systemic administration, a 3 to 5 fold prolongation of the TT measured 4 hours after initiation of therapy is generally considered sufficient. However, results of coagulation tests and fibrinolytic activity do not reliably predict either efficacy or risk of bleeding.

Follow-up treatment

In order to prevent recurrent thrombosis subsequent administration of anticoagulants should be instituted provided the aPTT is less than twice the normal control value.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Active clinically relevant bleeding
- Aneurysm and arteriovenous malformation
- Intracranial neoplasm or other neoplasm with risk of haemorrhage
- Decreased blood coagulation (haemorrhagic diathesis, concomitant therapy with anticoagulants, spontaneous fibrinolysis) and severe thrombocytopenia
- Severe uncontrolled arterial hypertension (systolic > 200 mmHg, diastolic > 100 mmHg; grade III or IV hypertensive retinopathy)
- Acute pancreatitis, pericarditis, bacterial endocarditis, sepsis
- Recent cerebrovascular accident (e.g. within 2 months)
- Recent trauma including cardiopulmonary resuscitation, thoracic surgery or neurosurgery (e.g. within 2 months)
- Recent major surgery until primary wound healing, recent organ biopsy, lumbar puncture, translumbal aortography (e.g. within 10 days)

4.4 Special warnings and precautions for use

In the following conditions, the risk of bleeding may be increased and should be weighed against the anticipated benefits:

- Recent severe gastrointestinal bleeding
- Recent surgery other than thoracic or neurosurgery, recent obstetrical delivery, puncture of non-compressible vessels
- Moderate coagulation defects including those due to severe hepatic or renal diseases
- Cavernous pulmonary diseases
- Genitourinary tract diseases with existing or potential sources of bleeding (e.g. implanted bladder catheter)

- High likelihood of a left heart thrombus (e.g. mitral stenosis with atrial fibrillation) with possible risk of cerebral embolism
- Known septic thrombotic disease
- Severe cerebrovascular disease
- Elderly patients (especially those over 75 years)

Concomitant administration of urokinase with other thrombolytic agents, anticoagulants, or agents inhibiting platelet function may further increase the risk of serious bleeding (see section 4.5).

When bleeding occurs in patients receiving urokinase, it may be difficult to control. Although urokinase is intended to produce sufficient amounts of plasmin to lyse intravascular deposits of fibrin, other fibrin deposits including those which provide haemostasis (at sites of needle puncture, catheter insertion, cut, etc.) are also subject to lysis, and bleeding from such sites may result. Oozing of blood from sites of percutaneous trauma occurs frequently.

The possibility of bruising or haematoma formation, especially after intramuscular injections, is high during urokinase therapy. Intramuscular injections and unnecessary handling of the patient should be avoided. Venipunctures and invasive venous procedures should be performed as infrequently as possible and with care to minimize bleeding. If bleeding from an invasive site is not serious, urokinase therapy may be continued while closely observing the patient; local measures such as application of pressure should be initiated immediately.

Arterial invasive procedures must be avoided before and during urokinase treatment to minimise bleeding. If an arterial puncture is absolutely essential, it should be performed by a physician experienced in the procedure, using a radial or brachial rather than a femoral artery. Direct pressure should be applied at the puncture site for at least 30 minutes, a pressure dressing applied, and the site checked frequently for evidence of bleeding.

If severe bleeding occurs following systemic treatment with urokinase, infusion should be stopped immediately and measures to manage the bleeding implemented. Plasma volume expanders other than dextrans may be used to replace blood volume deficits; if blood loss has been extensive, administration of packed red blood cells is preferred to whole blood. If very rapid reversal of the fibrinolytic state is required, administration of an antifibrinolytic agent such as epsilon-aminocaproic acid may be considered (see section 4.9).

Urokinase medac is a highly purified enzyme produced from human urine. It also contains human serum albumin. Products manufactured from human source materials have the potential to transmit infectious agents. Procedures to control such risks strongly reduce but cannot completely eliminate the risk of transmitting infectious agents.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants

Oral anticoagulants or heparin may increase the risk of haemorrhage and should not be used concomitantly with urokinase.

Active substances affecting platelet function

Due to increased risk of haemorrhage, concomitant use of urokinase and active substances that affect platelet function (e.g., acetylsalicylic acid, other non-steroidal anti-inflammatory agents, dipyridamole, dextrans) should be avoided.

Contrast agents

Contrast agents may delay fibrinolysis.

4.6 Pregnancy and lactation

There are no adequate data from the use of urokinase in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/fetal development, parturition or postnatal development. The potential risk for humans is unknown. However, low-molecular urokinase fragments and active plasmin cross the placenta.

Urokinase should not be used during pregnancy or in the immediate post-partum period unless clearly necessary.

It is unknown whether urokinase is excreted into human breast milk. Breast-feeding should be avoided during treatment with urokinase.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Haemorrhage

The most frequent and severe adverse effect of urokinase therapy is haemorrhage. The haemostatic status of the patient may be more profoundly altered with urokinase therapy than with heparin or coumarin-derivative anticoagulant therapy.

Severe spontaneous bleeding, including fatalities resulting from cerebral haemorrhage, has occurred during urokinase therapy. Less severe spontaneous bleeding has occurred approximately twice as frequently as that occurring during heparin therapy. Patients with pre-existing haemostatic defects have the greatest risk of spontaneous bleeding.

Moderate decreases in haematocrit not accompanied by clinically detectable bleeding have been reported in approximately 20 % of patients receiving urokinase.

Hypersensitivity reactions

In contrast to streptokinase, urokinase is reportedly non-antigenic. However, mild allergic reactions including bronchospasm and rash have been reported rarely. In addition, very rare cases of fatal anaphylaxis have been reported.

Infusion reactions

Fever and chills, including shaking chills (rigors), have been reported occasionally in patients receiving urokinase. Symptomatic treatment is usually sufficient to alleviate discomfort caused by urokinase-induced fever; however, acetylsalicylic acid should not be used.

Other infusion reactions reported with urokinase therapy include dyspnoea, cyanosis, hypoxemia, acidosis, back pain, and nausea and/or vomiting; these reactions generally occurred within one hour of beginning urokinase infusion.

The following frequency convention was used as a basis for the evaluation of undesirable effects:

Very common	$\geq 1/10$
Common:	$\geq 1/100$ to $< 1/10$
Uncommon:	$\geq 1/1,000$ to $< 1/100$
Rare:	$\geq 1/10,000$ to $< 1/1,000$
Very rare	$< 1/10,000$

Immune system disorders

Rare	Hypersensitivity reactions including dyspnoea, hypotension, flushing, urticaria, rash
Very rare	Anaphylactic reactions

Vascular disorders

Very common	Haemorrhage from puncture sites, wounds Haematoma Epistaxis, gingival bleeding Haematuria (microscopic)
Common	Intracranial haemorrhage Gastrointestinal haemorrhage, retroperitoneal haemorrhage Urogenital haemorrhage Muscle haemorrhage Embolism, including cholesterol embolism
Uncommon	Intrahepatic haemorrhage

General disorders and administration site conditions

Common	Fever, chills
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Investigations

Very common	Decrease in haematocrit without clinically detectable haemorrhage Transient increase in transaminases
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4.9 Overdose

Haemorrhage that occurs during treatment with urokinase may be controlled with local pressure and treatment continued. If severe bleeding occurs, treatment with urokinase must be stopped and inhibitors such as aprotinin, epsilon-aminocaproic acid, p-aminoethylbenzoic acid or tranexamic acid can be given. In serious cases, human fibrinogen, factor XII, packed red cells or whole blood should be given as appropriate. For correction of volume deficiency, dextrans should be avoided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: B01A D04, antithrombotic agent.

Urokinase medac is a highly purified form of naturally occurring human urokinase extracted from urine. Urokinase exists in two distinct molecular entities, a high molecular weight (approximately 54,000 daltons) and a low molecular weight (approximately 33,000 daltons). Urokinase medac contains more than 85 % of the HMW form.

Urokinase is a thrombolytic agent which converts plasminogen into plasmin (fibrinolysin) a proteolytic enzyme that degrades fibrin as well as fibrinogen and other plasma proteins. The activity of urokinase leads to a dose-dependent decrease in plasminogen and fibrinogen levels and to increased presence of fibrin and fibrogen degradation products, which have an anticoagulant effect and potentiate the effect of heparin. These effects persist for 12 – 24 hours after the end of urokinase infusion.

5.2 Pharmacokinetic properties

Urokinase is eliminated rapidly from the circulation by the liver with a half-life of 10 to 20 minutes. The inactive degradation products are excreted via the bile and primarily via the kidneys.

Elimination is delayed in patients with liver disease and impaired kidney function.

5.3 Preclinical safety data

There is no preclinical safety data of additional value to the prescribing physician.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.

6.2 Incompatibilities

No information is available regarding loss of activity in PVC containers or plastic bags/syringes.

6.3 Shelf life

26 months

Use reconstituted material immediately.

After reconstitution and dilution, chemical and physical stability has been demonstrated for 72 hours at room temperature. From a microbiological point of view, the product should be used immediately after reconstitution and dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Do not store above 25 °C.

Keep the vial in the outer container to protect from light.

6.5 Nature and contents of container

All presentations are contained in borosilicate clear type 1 glass vials closed with chlorobutyl rubber stoppers and sealed with an aluminium flip-off cap.

6.6 Special precautions for disposal

The powder for solution for infusion should be dissolved in water for injection and further diluted with 0.9 % sodium chloride solution or glucose 5 % or glucose 10 % solution.

The powder is to be reconstituted as follows:

For a 10,000 I.U. vial use 2 ml of water for injection.

After reconstitution the solution must be clear and colourless.

7. MARKETING AUTHORISATION HOLDER

medac

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17/03/2010

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22/09/2010