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UROKINASE MEDAC 10,000 I.U, 50,000 I.U, 100,000 I.U, 250,000 I.U, 500,000 I.U

Information for Health Professionals

1. Name of the medicinal product

Urokinase medac 10,000 I.U.
Urokinase medac 50,000 I.U.
Urokinase medac 100,000 I.U.
Urokinase medac 250,000 I.U.
Urokinase medac 500,000 I.U.
Powder for solution for injection or infusion

2. Qualitative and quantitative composition

1 vial of Urokinase medac 10,000 I.U. with 24 mg of powder for solution for injection or infusion contains 10,000 IU of urokinase.
1 vial of Urokinase medac 50,000 I.U. with 38 mg of powder for solution for injection or infusion contains 50,000 IU of urokinase.
1 vial of Urokinase medac 100,000 I.U. with 39 mg of powder for solution for injection or infusion contains 100,000 IU of urokinase.
1 vial of Urokinase medac 250,000 I.U. with 63 mg of powder for solution for injection or infusion contains 250,000 IU of urokinase.
1 vial of Urokinase medac 500,000 I.U. with 125 mg of powder for solution for injection or infusion contains 500,000 IU of urokinase.

For a complete list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection/infusion

4. Clinical particulars

4.1 Therapeutic indications

- Peripheral arterial thrombosis
- Acute and subacute deep vein thrombosis
- Acute diagnostically confirmed pulmonary embolism, in particular when associated with unstable haemodynamic status
- Thrombosed arteriovenous shunt

4.2 Posology and method of administration

Dosage:
Dosages are determined in accordance with the respective indication.

Peripheral arterial thrombosis
Systemic lysis:
For the treatment of arterial occlusion, the recommended initial dose of urokinase is 250,000 - 600,000 IU given intravenously over 10 - 20 minutes, with 80,000 - 150,000 IU urokinase/h as a maintenance dose.

Simultaneous administration of heparin is generally required to ensure adequate protection against recurrent thrombosis. The start time and duration of the heparin infusion will depend on the aPTT, which should be extended to 1.5 to 2.5 times the normal aPTT. A dose of 500 - 1,000 IU of unfractionated heparin/h i.v. is generally sufficient.

Local lysis:
The thrombus is first infiltrated with urokinase solution. The dose should not exceed 100,000 - 120,000 IU/hour for a patient weighing 70 kg. Local lysis is performed until a successful outcome has been achieved (up to a maximum of 48 hours).

Deep vein thrombosis
The initial dose of urokinase is 250,000 - 600,000 IU urokinase given intravenously over 10 - 20 minutes. The maintenance dose is 40,000 - 100,000 IU/h.

Simultaneous administration of heparin is generally required to ensure adequate protection against recurrent thrombosis. The start time and duration of the heparin infusion will depend on the aPTT, which should be extended to 1.5 to 2.5 times the normal aPTT. A dose of 500 - 1,000 IU of unfractionated heparin/h i.v. is generally sufficient.

Pulmonary embolism
The initial dose is 2,000 or 4,400 IU of urokinase/kg body weight given intravenously over 10 - 20 minutes. The maintenance dose is 2,000 IU of urokinase/kg body weight/h over 24 hours with simultaneous administration of heparin, or 4,400 IU of urokinase/kg of body weight/h over 12 hours without heparin. The start time and duration of the heparin infusion will depend on the aPTT.

Subsequent administration of heparin is generally required to ensure adequate protection against recurrent thrombosis. The start and duration of the heparin infusion will depend on the aPTT, which should be extended to 1.5 to 2.5 times the normal aPTT. A dose of 500 - 1,000 IU of unfractionated heparin/h i.v. is generally sufficient.

Thrombosed arteriovenous shunt
Urokinase solution with a concentration of 5,000 - 25,000 IU/ml is instilled into both tube sets in the shunt.

Method of administration
For injection, infusion and local instillation after dissolution as instructed.

The contents of one vial of Urokinase medac 10,000 I.U. are dissolved in 2 ml of water for injections.
The contents of one vial of Urokinase medac 50,000 I.U. are dissolved in 2 ml of water for injections.
The contents of one vial of Urokinase medac 100,000 I.U. are dissolved in 2 ml of water for injections.
The contents of one vial of Urokinase medac 250,000 I.U. are dissolved in 5 ml of water for injections.
The contents of one vial of Urokinase medac 500,000 I.U. are dissolved in 10 ml of water for injections.

For drip infusions, the contents of one vial can be dissolved in water for injections and then diluted to a final volume of 50 ml in e.g. a 5% or 10% glucose solution or physiological saline.

Duration of administration:
The duration of administration depends on the respective indication.
Peripheral arterial thrombosis
The duration of treatment with urokinase depends on the clinical findings and on the results of diagnostic procedures. The average duration of treatment is 4 - 5 days.

Deep vein thrombosis
The duration of treatment, which depends on an objectively confirmed successful therapeutic outcome, is generally 7 - 14 days.

Pulmonary embolism
The treatment duration is 24 hours when following the low-dose urokinase/heparin dosing regimen and 12 hours when following the high-dose urokinase regimen.

Thrombosed arteriovenous shunt
The application of urokinase can if necessary be repeated every 30 minutes. However, the duration of treatment should not exceed 2 hours.

4.3 Contraindications

Urokinase medac must not be used:
- in the event of hypersensitivity (allergy) to the active substance urokinase or to any of the excipients of Urokinase medac,
- in the event of any form of reduced blood coagulation, in particular spontaneous fibrinolysis, haemorrhagic diathesis and during concomitant treatment with oral anticoagulants,
- in the event of acute cerebrovascular events (e.g. cerebral insult, TIA), in particular intracranial haemorrhage,
- in the event of intracranial neoplasms, aneurysms or arteriovenous malformation of the cerebral arteries,
- in the event of dissecting aneurysms,
- in the event of manifest, clinically relevant bleeding,
- in the event of increased susceptibility to bleeding as a result of:
  - gastrointestinal disorders, such as malignant tumours, gastric or duodenal ulcers, acute ulcerative colitis,
  - genitourinary tract disorders, such as malignant tumours, urolithiasis,
  - pulmonary disorders such as cavitary tuberculosis or bronchiectasis,
  - severe hepatic disorders, such as cirrhosis of the liver, oesophageal varices,
  - severe renal disorders;
- within three months of severe bleeding (such as gastrointestinal or intracranial haemorrhage), after severe trauma or a major surgical intervention (such as coronary bypass surgery, intracranial or intraspinal surgeries or traumas),
- in the first four weeks after giving birth,
- in the event of abortion,
- in the event of imminent abortion,
- in the event of suspected placenta praevia,
- following the puncture of a non-compressible vessel,
- within 10 days of an organ biopsy, lumbar puncture, external cardiac massage over an extended period or recent intramuscular injection,
- in the event of severe arterial hypertension refractory to treatment (systolic pressure over 200 mmHg, diastolic over 100 mmHg, grade III and IV hypertensive retinopathy),
- in the event of haemorrhagic retinopathy or other diseases of the eye involving susceptibility to bleeding,
- in the event of acute pancreatitis, pericarditis, bacterial endocarditis,
- in the event of sepsis.

4.4 Special warnings and special precautions for use

Urokinase may only be used with extreme caution:
- in cerebrovascular diseases other than those mentioned in section 4.3 or where there is a known history of cerebrovascular events in the more distant past,
- in arterial hypertension,
- in the event of thrombi in the left heart (e.g. accompanying mitral valve stenosis with atrial fibrillation),
- in the event of septic thrombophlebitis or an infected arteriovenous fistula with thrombotic occlusion,
- in any circumstances in which a possible source of bleeding is difficult to access,
- in the event of a reduced platelet count and/or changes in laboratory parameters indicative of impaired haemostasis (such as prolonged thrombin time, aPTT, Quick etc.).

Intramuscular injections and the use of rigid catheters are to be avoided during treatment with urokinase.

After cardiac massage administered during cardiopulmonary resuscitation there is an increased risk of complications associated with bleeding.

If bleeding occurs, the procedures described in section 4.9 should be followed.

When using medicinal products made from human proteins, the transmission of infectious diseases - including those of a previously unknown nature - cannot be ruled out entirely. However, due to the required inactivation procedure (heating in solution for 10 hours at + 60 °C), this risk is extremely small.

Patients on a high dosage are monitored, as under any fibrinolytic therapy, by determining their fibrinogen and aPTT, and thrombin time if applicable.

By contrast, at dosages below 40,000 IU/hour, there is generally hardly any change in laboratory parameters; fibrinolytic activity is shown in this case by a reduced euglobulin lysis time and an increase in fibrin degradation products.

There is an increased risk of intracranial haemorrhage in elderly patients. Therefore, the risk-benefit ratio should be analysed with extreme care in these patients.

The experience in children is limited.
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.

4.5 Interaction with other medicinal products and other forms of interaction

There is an increased risk of bleeding from the prior or concomitant administration of any of the following:
- anticoagulants such as heparin or coumarin derivatives,
- drugs that affect platelet formation or function, such as:
  - acetylsalicylic acid,
  - allopurinol,
  - clofibric acid derivatives,
  - clopidogrel,
  - indomethazine,
  - dipyridamole,
  - phenylbutazone,
  - ticlopidine,
  - tetracycline,
  - valproic acid,
  - thiouracils,
  - sulfonamides,
  - cytostatic agents,
  - dextrans,
  - non-steroidal anti-inflammatory drugs.

The following substances inhibit the fibrinolytic action of urokinase:
- antifibrinolytics such as aprotinin, p-aminobenzoic acid, epsilon aminocaproic acid and tranexamic acid.

4.6 Pregnancy and lactation

Pregnancy:
To date, there are no adequate data for use of urokinase during pregnancy. Low-molecular urokinase fragments and active plasmin cross the placenta. Although animal studies showed no evidence of reproductive toxicity, maternal exposure was inadequate (see section 5.3). Throughout pregnancy, because of the risk to the foetus, urokinase must only be administered if vitally indicated and following particularly careful consideration of the risk. The occurrence of bleeding and premature labour, as well as passive immunisation of the foetus by maternal antibodies against urokinase, cannot be ruled out.

The use of urokinase is absolutely contraindicated in the first four weeks after giving birth, in the event of abortion or imminent abortion, or if placenta praevia is suspected.

Lactation:
There are no data available regarding the passage of urokinase into breast milk. Urokinase should only be administered during lactation if it is absolutely necessary for the health of the mother. In this case, breast feeding should be interrupted for the duration of the therapy.

4.7 Effects on ability to drive and use machines

Urokinase medac has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

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

Not known (cannot be estimated from the available data)

Blood and lymphatic system

Very common:	Drop in haematocrit without clinically identifiable haemorrhage

Nervous system

Common:	Intracranial haemorrhage
Uncommon:	Life-threatening intracranial haemorrhage

Eyes

Very rare:	Vitreous haemorrhage

Vascular

Common:	Embolism

Gastrointestinal tract

Common:	Gastrointestinal haemorrhage, retroperitoneal haemorrhage
Uncommon:	Life-threatening gastrointestinal haemorrhage, life-threatening retroperitoneal haemorrhage

Hepatobiliary

Very common:	Transient elevated transaminases
Uncommon:	Life-threatening intrahepatic haemorrhage

Kidneys and urinary tract

Very common:	Microscopic haematuria
Common:	Genitourinary haemorrhage
Uncommon:	Life-threatening genitourinary haemorrhage

Skin and allergic reactions

Very rare:	Allergic reactions with flushing, urticaria, dyspnoea and hypotension

General

Very common:	(Oozing) haemorrhage from puncture sites, wounds, appearance or increase in size of haematomas or bruises, nosebleeds and bleeding gums.
Common:	Fever
Uncommon:	Life-threatening haemorrhage into parenchymatous organs or muscle

4.9 Overdose

In the event of bleeding that can be controlled by compression, the therapy can be continued under close monitoring.

In the event of complications due to bleeding which cannot be controlled using the above measures and which require treatment, the urokinase therapy must be stopped and aprotinin or another antifibrinolytic drug must be administered if necessary. The dose of aprotinin is initially 500,000 – 1,000,000 KIU/h i.v., then 50,000 – 100,000 KIU/h until haemostasis is achieved. (Be aware of the possibility of anaphylaxis!)

In the case of severe and life-threatening haemorrhage due to severe hyperfibrinolysis, the urokinase treatment must be discontinued immediately. Antifibrinolytic therapy should be complemented with substitution of fibrinogen concentrate and the appropriate blood products. This treatment should be given in consultation with a specialist in transfusion medicine experienced in haemostaseology.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: fibrinolytic
ATC code: B01AD04

Urokinase is a serine protease that occurs in different molecular forms. A distinction is made between a high-molecular weight and a low-molecular weight form.

The mean molecular weight of the high-molecular weight form (HUK) is about 54,000 Daltons, that of the low molecular weight form (LUK) is given as approximately 33,000 Daltons.

The enzyme is formed primarily in the kidneys and secreted into the urine. Urokinase can be isolated from human urine or from the supernatants of human kidney cell cultures or produced in recombinant form.

The activity is determined in international units based on the standard preparations established by the WHO.

These units are based on the fibrinolytic activity of urokinase.

Prourokinase (SCUPA) is the zymogen of urokinase. It is converted into urokinase (HUK) by trypsin-type serine proteases such as plasmin or thrombin.

Urokinase has a specific affinity for the plasminogen molecule and converts plasminogen directly into plasmin by hydrolysis of the arginine-valine bond.
Fibrinous thrombi can be broken up by the fibrinolytic effect of the protease plasmin.

The plasmin activity triggered by urokinase results in a dose-dependent drop in the level of plasminogen and fibrinogen and to the increased incidence of fibrin and fibrinogen degradation products (FDP), which in addition to their direct anticoagulant effect potentiate the effect of heparin. Urokinase remains active for up to 12 - 24 hours after the end of the infusion.

The conversion by urokinase of plasminogen into plasmin can be competitively inhibited by epsilon aminocaproic acid, tranexamic acid and p-aminobenzoic acid. However, these fibrinolysis inhibitors do not cancel out the anticoagulant effect of circulating fibrinogen/fibrin degradation products.

Aprotinin (like α_2 antiplasmin in the plasma) has a direct inhibitory effect on plasmin.

Urokinase activity can be inhibited to varying degrees in individual cases by urokinase-inhibiting plasma proteins (e.g. in uraemia).

5.2 Pharmacokinetic properties

Urokinase must be administered parenterally.

Urokinase is removed rapidly from circulating blood after intravenous administration.

The elimination half life of urokinase is approximately 10 – 20 minutes.

Inactivation (enzymatic degradation) probably occurs primarily in the liver. The inactive degradation products are excreted via the bile and primarily via the kidneys.

The clinical efficacy half life depends on the duration of efficacy of the activated plasmin and is therefore longer.

5.3 Preclinical safety data

Chronic toxicity studies in various animal species and studies investigating mutagenic potential do not indicate any particular risks for humans. There are no long-term studies investigating carcinogenic potential.

Embryotoxicity studies in rats, mice and rabbits at doses corresponding at most to 1.4 times the human dose (based on a therapeutic dose in humans of 105,600 IU/kg/day) gave no indication of any teratogenic potential. Neither were the fertility of rats and the perinatal and postnatal development of their offspring impaired at these doses.

6. Pharmaceutical particulars

6.1. List of excipients

disodium phosphate dodecahydrate, sodium dihydrogen phosphate dehydrate, human albumin

6.2 Incompatibilities

None identified to date.

6.3 Shelf life

The Shelf life of Urokinase medac is 3 years.

Shelf life after reconstitution of the preparation ready for use:
Once reconstituted, the solution is to be used immediately.
The solution, made under aseptic conditions, must not be stored for longer than 8 hours at 25^{0}C.
This medicinal product must not be used after the expiry date.

6.4 Special precautions for storage

Do not store above 25^{0}C.

6.5 Nature and contents of container

Urokinase medac 10,000 I.U.:
Original package with 1 vial containing 10,000 IU of urokinase
Urokinase medac 50,000 I.U.:
Original package with 1 vial containing 50,000 IU of urokinase
Urokinase medac 100,000 I.U.:
Original package with 1 vial containing 100,000 IU of urokinase
Urokinase medac 250,000 I.U.:
Original package with 1 vial containing 250,000 IU of urokinase
Urokinase medac 500,000 I.U.:
Original package with 1 vial containing 500,000 IU of urokinase
Original package with 5 x 1 vial containing 500,000 IU of urokinase
Original package with 10 x 1 vial containing 500,000 IU of urokinase

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

None

7. Manufacturer

medac GmbH, Germany.

8. Registration Holder

Tzamal Bio-Pharma, Petah-Tikva.

9. Registration numbers:

Urokinase medac	10,000 I.U: 143-91-33129
Urokinase medac	50,000 I.U: 143-92-33130
Urokinase medac	100,000 I.U: 143-93-33131
Urokinase medac	250,000 I.U: 143-94-33132
Urokinase medac	500,000 I.U: 143-95-33133