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Package leaflet: Information for the user

Urokinase medac 10,000 IU,
powder for solution for infusion
Urokinase medac 50,000 IU,
powder for solution for infusion
Urokinase medac 100,000 IU,
powder for solution for infusion
Urokinase medac 250,000 IU,
powder for solution for infusion
Urokinase medac 500,000 IU,
powder for solution for infusion

Urokinase

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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

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

1. What Urokinase is and what it is used for

Urokinase medac contains human urokinase extracted from human urine. Urokinase is an antithrombotic agent and is indicated for the treatment of acute occlusions of blood vessels caused by blood clots such as peripheral vascular occlusion, i.e. blood clots blocking the blood vessel system of the extremities, and severe pulmonary embolism, i.e. blood clots in lungs. In addition, urokinase can be used to dissolve blood clots that develop in shunts of dialysis patients.

Urokinase is a powder for intravenous infusion (administration into the veins). Strength of urokinase is given in international units (IU). Urokinase contains 10,000, 50,000, 100,000, 250,000 or 500,000 IU per vial.

2. What you need to know before you use Urokinase

Urokinase is used by doctors in hospitals who have experience in the treatment of thrombosis disorders. Your general state of health and medical history, including previously or currently used medicines, will be carefully assessed before the treatment with this medicine is commenced.

Your doctor will not give you Urokinase if you
- are allergic to urokinase or any of the other ingredients of this medicine (listed in section 6).
- are suffering from severe bleeding.
- have reduced blood coagulation (spontaneous dissolving of blood clots, tendency to bleed, or take medicine to prevent blood coagulation and severe decrease in blood platelet (clotting cells) count).
- have severe, uncontrolled high blood pressure.
- have dilation of a blood vessel in the brain (intracranial aneurysm) or any form of vein abnormality.
- have acute blood vessel problems in the brain (e.g. cerebral haemorrhages, cerebral infarction, transient disturbances of blood supply to the brain that leave few/no residual symptoms (TIA))
- have a tumour in the brain.
- had a recent operation until the wound has healed, an examination of tissue that has been taken from an organ (organ biopsy), a lumbar puncture (medical procedure in which cerebrospinal fluid is removed from the spinal canal for diagnostic testing or treatment), an injection into the muscles (intramuscular injection), or an examination of the aorta (in the last 10 days).
- had recent injury including cardiopulmonary resuscitation, operation with opening of the chest cavity or on the head or spine (within 2 months).
- have acute inflammation of the pancreas or heart or pericardium (the sac surrounding the heart) or a severe systemic infection.
- have gastrointestinal disorders, e.g.
  - o tumour
  - o ulcer of the stomach and/or duodenum
  - o acute inflammatory bowel disease (ulcerative colitis)
  - o recent bleeding of the stomach and/or the bowel
  - o enlarged oesophageal (gullet) veins.
- have disorders of the lung (e.g. tuberculosis).
- have severe disorders of the liver (e.g. liver cirrhosis).
- have severe renal (kidney) impairment.
- had recent delivery of a child, an abortion, a threatening abortion, or abnormal position of the placenta.

Warnings and precautions
Talk to your doctor before you are given urokinase if you
- suffer from mild blood coagulation disturbances.
- suffer from slightly raised blood pressure.
- have a slight reduction in the number of blood platelets.
- have recently had an operation other than opening of the chest cavity or have undergone an operation on the head or spine.
- have suspected blood clots in the left ventricle of the heart (e.g. mitral stenosis with atrial fibrillation).

In patients with atrial fibrillation or other conditions in which there is possible risk of cerebral embolism (blood clot in the brain), urokinase therapy may be hazardous because of the risk of bleeding into the affected area of the brain.
The use of this medicine is not recommended in patients with low-risk pulmonary embolism (blood clot in the lungs), as the bleeding risks may outweigh the potential benefits.

Patients over 65 years
In older patients, particularly over 75 years, the benefit of dissolving blood clots must be weighed against the increased risk of bleeding in the brain.

Children and adolescents
Safety and efficacy of urokinase in children and adolescents have not been established.

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

The possibility of bleeding can be increased by medicines that counteract the clotting of blood, such as
- heparin and coumarin derivates (prevent the formation of blood clots),
- acetylsalicylic acid (aspirin), non-steroidal anti-inflammatory drugs, abciximab (prevents blood clot formation after surgery of blood vessels around the heart), allopurinol, clofibric acid derivates, clopidogrel, cytostatic medicines (anticancer medicines), dextrans, dipyridamole, ticlopidine, tetracycline, valproic acid, thiouracils and sulfonamides.

The following medicines decrease the effect of urokinase:
- p-aminobenzoic acid, epsilon aminocaproic acid, tranexamic acid (substances that inhibit the dissolution of blood clots),
- contrast media (used to enhance visibility of body structures in medical imaging).

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

Pregnancy
There is too little experience with the use of this medicine in pregnant women to enable an assessment of the harmful effect. Urokinase should not be used during pregnancy or immediately after giving birth unless clearly necessary.

Breast-feeding
It is unknown whether urokinase is excreted in human milk. Urokinase should not be used during breast-feeding unless clearly necessary.

Fertility
There are no data available regarding the influence of urokinase treatment on fertility.

Driving and using machines
Driving and using machines is not recommended during treatment with this medicine.

Important information about Urokinase
Urokinase is a highly purified enzyme produced from human urine. 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.

3. How to use Urokinase

Urokinase is administered into a vein.
The required dose differs in individual persons and is dependent on state of health. Your doctor will take this into account when determining the amount that you need, and will use the guidelines below for this:

Blood clots that block the blood vessel system in the limbs
Initially you will probably be given 4,000 IU per minute for 2 to 4 hours, and then 1,000 to 2,000 IU per minute. Administration is stopped when the blood clot has dissolved, or after 48 hours.

Severe pulmonary embolism
Initially you will be given 4,400 IU of urokinase/kg body weight given intravenously over 10 – 20 minutes.
The maintenance dose is 4,400 IU of urokinase/kg of body weight/h over 12 hours without heparin.

Shunts for haemodialysis that are blocked by blood clots
For the dissolution of blood clots that block shunts for haemodialysis urokinase is dissolved in 2 to 3 ml sodium chloride 9 mg/ml (0.9 %) solution for injection to an end concentration of 5,000 to 25,000 IU per ml. The solution is poured into both branches of the shunts for haemodialysis. If necessary, the treatment may be repeated after 30 – 45 minutes. Administration must be limited to 2 hours.

In order to prevent new clot formation after treatment with this medicine, your doctor will start treatment with heparin and oral anticoagulants (medicines that reduce the coagulation capacity of the blood) in the usual dose with the usual controls.

If you use more Urokinase than you should
Using more urokinase than prescribed could result in bleeding; your doctor can take countermeasures to stop these bleeds. As this medicine is administered by your doctor this is not likely to occur. However, if you are worried contact your doctor.

If you forget to use Urokinase
This medicine is administered by your doctor therefore it should not be forgotten, but if you are worried contact your doctor.

4. Possible side effects

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

Bleeding
The most frequent and severe side effect of urokinase therapy is bleeding. When bleeding occurs during administration of urokinase, it may be difficult to control. If bleeding is not serious, urokinase therapy may be continued while closely observing your state of health; local measures such as application of pressure should be initiated immediately. If serious spontaneous bleeding occurs, administration must be stopped immediately and countermeasures initiated.

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

Other side effects
Circulating blood clots after breakdown of blood clots were reported uncommonly. Approximately 20% of patients using urokinase show a moderate decrease in the percentage of red blood cells in the blood without an increase in bleeding. Other adverse effects reported with urokinase therapy include shortness of breath, bluish discolouration of the skin due to lack of oxygen, low blood oxygen, increased acidity of the blood, back pain, sickness and/or vomiting.

Side effects may include:

Very common (may affect more than 1 in 10 people):
- Bleeding at injection sites or from wounds, bruising
- Nose bleed, bleeding gums
- Small amounts of blood in the urine
- Transient elevated liver enzymes
- Drop in haematocrit (percentage of red blood cells in blood)

Common (may affect up to 1 in 10 people):
- Bleeding of retroperitoneum, peritoneum, stomach, bowel, of organs of the urinary or reproduction system, or inside the head
- Blood clots in the blood vessels
- Fever, chills

Uncommon (may affect up to 1 in 100 people):
- Life-threatening bleeding complications of retroperitoneum, peritoneum, stomach, bowel, of organs of the urinary or reproduction system, inside the head or liver
- Bleeding in muscle or organs other than those referred to

Rare (may affect up to 1 in 1,000 people):
- Allergic reaction with skin reactions (flush, urticaria), shortness of breath, chest tightness and low blood pressure

Very rare (may affect up to 1 in 10,000 people):
- Life-threatening allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Urokinase

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

Do not use this medicine after the expiry date stated on the label after EXP.

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

Use reconstituted medicine immediately. Do not keep reconstituted material for later use.

Do not use urokinase if you notice that the contents of the vial are discoloured.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Urokinase contains

- The active substance is urokinase, an enzyme isolated and purified from human urine.
- The other excipients are disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.

What Urokinase looks like and contents of the pack
Each vial contains white powder for solution for infusion.

Urokinase medac is available in the following packs each containing one vial:
Urokinase medac 10,000 IU
Urokinase medac 50,000 IU
Urokinase medac 100,000 IU
Urokinase medac 250,000 IU
Urokinase medac 500,000 IU

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

medac Gesellschaft für klinische
Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

This leaflet was last revised in September 2018.

The following information is intended for healthcare professionals only:

The contents of one vial are diluted with water for injections. The resultant solution should be clear and colourless and then further reconstituted with saline or glucose. The solution for infusion should be used immediately.

Urokinase should only be used by physicians experienced in the management of thromboembolic diseases in hospitals where adequate diagnostic and monitoring techniques are available.
Before starting thrombolytic therapy with urokinase, 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.

Method of administration
Depending on the indication, the route of administration of urokinase 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.

Incompatibilities
No information is available regarding loss of activity in PVC containers or plastic bags/syringes.
This medicinal product must not be mixed with other medicinal products except those mentioned in the next paragraph.

Special precautions for disposal and other handling
The powder for solution for infusion may be dissolved in 2 ml water for injections (10,000 IU, 50,000 IU, 100,000 IU), 5 ml water for injections (250,000 IU) or 10 ml (500,000 IU), respectively. The solution should be clear and colourless.
This is further diluted with 0.9 % sodium chloride solution or glucose 5 % or glucose 10 % solution.

After reconstitution and further dilution in sodium chloride 9 mg/ml (0.9 %) solution for injection to as low as 1,000 IU, chemical and physical stability has been demonstrated for 72 hours at temperatures of 20 – 25°C and 2 – 8°C when stored in polyethylene infusion sets or bags.

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 unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

After reconstitution and further dilution in glucose 5 % or glucose 10 % solution, the solution should be used immediately due to loss in activity of urokinase.

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

Special precautions for storage
Do not store above 25°C. Keep the vial in the outer container to protect from light.