Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Urokinase medac 10,000 IU, powder for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White powder for solution for infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Urokinase is indicated for the treatment of acute vascular occlusions caused by thrombosis or embolism such as:
- acute occlusive peripheral arterial disease with limb-threatening ischaemia,
- severe pulmonary embolism,
- haemodialysis shunts blocked by fibrin clots.

4.2 Posology and method of administration

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.

<u>Posology</u>
Dose and duration of administration depend on the respective indication. They may be adjusted individually depending on the clinical condition. The following dose regimens should be used as a guideline.

Acute occlusive peripheral arterial disease with limb threatening ischaemia
Various regimens have been described in the literature, but none has been proven to be superior. However, catheter-directed local lysis is the preferred method of administration.

4,000 IU/min (240,000 IU/h) is infused through an intra-arterial catheter for the first 2 – 4 hours or until restoration of antegrade flow and 1,000 – 2,000 IU/min thereafter. Infusion should be stopped when lysis is complete, arteriography shows no further progress or 48 hours have passed.

Severe pulmonary embolism
The initial dose is 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.

Haemodialysis shunts blocked by fibrin clots
Urokinase solution with a concentration of 5,000 - 25,000 IU/ml (dissolved in 2 – 3 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection) is instilled into both tube sets in the shunt. If necessary, the application can be repeated every 30 – 45 minutes up to a maximum of 2 hours.

Elderly
Available data are limited in elderly patients and it is not known whether they respond differently from younger subjects. Urokinase should be used with caution in elderly patients.

Paediatric population
The safety and efficacy of urokinase in children have not been established.

Renal or hepatic impairment
A dose reduction may be required in patients with moderately impaired renal and/or hepatic function. In these cases, the fibrinogen level should not fall below 100 mg/dl. Urokinase is contraindicated in patients with severe renal or hepatic impairment.

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.

Therapeutic monitoring
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 reclotting, treatment with heparin and oral anticoagulants should be initiated following the treatment with urokinase, in the usual dose and with monitoring of the usual parameters.

Precautions to be taken before handling or administering the medicinal product
For instructions on reconstitution and further dilution of the medicinal product before administration, see section 6.6. After reconstitution, the solution should be clear and colourless.

4.3 Contraindications

Urokinase must not be used in the following conditions:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- active clinically relevant bleeding,
- decreased blood coagulation (in particular spontaneous fibrinolysis, haemorrhagic diathesis, concomitant therapy with anticoagulants) and severe thrombocytopenia,
- severe uncontrolled arterial hypertension (systolic > 200 mmHg, diastolic > 100 mmHg; grade III or IV hypertensive retinopathy),
- aneurysm and arteriovenous malformation,
- acute cerebrovascular events (e.g. cerebral insult, transient ischaemic attack), in particular intracranial haemorrhage,
- intracranial neoplasms,
- recent major surgery until primary wound healing, recent organ biopsy, lumbar puncture, translumbal aortography (e.g. within 10 days),
- recent trauma including cardiopulmonary resuscitation, thoracic surgery or neurosurgery (e.g. within 2 months),
- acute pancreatitis, pericarditis, bacterial endocarditis, sepsis,
- gastrointestinal disorders such as malignant tumours, gastric or duodenal ulcers, acute ulcerative colitis, recent gastrointestinal bleeding, oesophageal varices,
- pulmonary disorders such as cavitary tuberculosis or bronchiectasis,
- severe hepatic disorders, such as cirrhosis of the liver, and oesophageal varices,
- severe renal disorders,
- recent delivery, abortion, imminent abortion, suspected placenta praevia.

In patients with high-risk pulmonary embolism presenting with cardiogenic shock and/or persistent arterial hypotension, the treating physician should decide on the treatment on an individual basis, taking into regard the mortality rate of the underlying disease and the risk of the treatment.

4.4 Special warnings and precautions for use

In older patients (especially age > 75 years) efficacy of thrombolysis has to be weighed against the increased risk of bleeding in the brain.
In patients with atrial fibrillation or other conditions in which there is possible risk of cerebral embolism, urokinase therapy may be hazardous because of the risk of bleeding into the infarcted area.

The overall clinical status and history of the patient including previous or concomitant medicinal products must be assessed carefully before initiation of urokinase therapy.

Urokinase should be used with caution with antiplatelet or anticoagulant medicinal products due to the risk of synergistic interactions with urokinase.

Intramuscular injections and the use of stiff catheters should be avoided during therapy with urokinase.

Urokinase should be used with caution in patients with
- moderate coagulation defects (including due to severe hepatic or renal disease, abnormal low thromboplastin time/partial thrombin time/bleeding time),
- moderate arterial hypertension,
- moderate thrombocytopenia,
- recent surgery other than thoracic or neurosurgery (see section 4.3),
- suspected thrombus of left ventricle (e.g. mitral stenosis with atrial fibrillation).

When bleeding occurs in patients receiving urokinase, it may be difficult to control. Although this medicinal product 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 punctures, cuts, 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.
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. 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. Invasive venous procedures should be performed carefully and as infrequently as possible. 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.
If serious spontaneous bleeding occurs, urokinase infusions should be terminated immediately. 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 e-aminocaproic acid may be considered (see section 4.9).

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.

Paediatric population
The safety and efficacy of urokinase in children have not been established.

4.5 Interaction with other medicinal products and other forms of interactions

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

Medicinal products 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, abciximab, allopurinol, clofibric acid derivatives, clopidogrel, cytostatic agents, dextrans, dipyridamole, ticlopidine, tetracycline, valproic acid, thiouracils, sulfonamides) should be avoided.

Antifibrinolytics
Antifibrinolytics such as p-aminobenzoic acid, epsilon aminocaproic acid, and tranexamic acid inhibit the fibrinolytic action of urokinase.

Contrast agents
Contrast agents could impede fibrinolysis

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data from the use of urokinase in pregnant women. Experimental studies in animals provided no evidence of adverse events on reproduction, but were unsatisfactory on account of the low doses tested (see section 5.3).

Due to hazard to the foetus, urokinase is to be used during whole pregnancy only with vital indication under special consideration of the risk.

The occurrence of bleeding and premature labour, as well as passive immunisation of the foetus by maternal antibodies against urokinase can occur (see section 4.3).

Breast-feeding
There is no information on the excretion of urokinase in human 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.

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

4.7 Effects on ability to drive and use machines

During therapy with urokinase the patient should be advised not to drive and not to use machines.

4.8 Undesirable effects

The most frequent and severe adverse event 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.

Tabulated summary of adverse reactions
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)

MedDRA system organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Rare	Allergic reaction with rash, urticaria, bronchospasm,

		dyspnoea and hypotension
	Very rare	Anaphylaxis
Nervous system disorders	Common	Intracranial haemorrhage
	Uncommon	Life-threatening intracranial haemorrhage
Vascular disorders	Common	Embolism
Gastrointestinal disorders	Common	Gastrointestinal haemorrhage, retroperitoneal haemorrhage
	Uncommon	Life-threatening gastrointestinal or retroperitoneal haemorrhage
Hepatobiliary disorders	Very common	Transient rise in transaminase levels
	Uncommon	Life-threatening intrahepatic haemorrhage
Renal and urinary disorders	Very common	Microhaematuria
	Common	Urogenital haemorrhage
	Uncommon	Life-threatening urogenital haemorrhage
General disorders and administration site conditions	Very common	(Oozing) haemorrhage from puncture sites or wounds, appearance or increase in size of haematomas or bruises, epistaxis, gingival bleeding
	Common	Fever, chills
	Uncommon	Life-threatening haemorrhage into parenchymatous organs or muscle
Investigations	Very common	Decrease of haematocrit without clinical signs of bleeding

Description of selected adverse reactions

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, although a definite causal relationship to the medicinal product has not been established. Symptomatic treatment is usually sufficient to

alleviate discomfort caused by urokinase-induced fever; however, acetylsalicylic acid should not be used.

Other adverse events
Uncommonly embolism due to disintegration of thrombi was reported. Moderate decreases in haematocrit not accompanied by clinically detectable bleeding have been reported in approximately 20% of patients receiving urokinase. Other adverse events reported with urokinase therapy include dyspnoea, cyanosis, hypoxaemia, acidosis, back pain, and nausea and/or vomiting; these events have been reported separately or together, and a causal relationship to urokinase therapy has not been established.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdose could result in haemorrhage (see section 4.8).
The urokinase-induced transformation of plasminogen into plasmin can be competitively inhibited with synthetic inhibitors such as e-aminocaproic acid or tranexamic acid. These fibrinolysis inhibitors do not, however, potentiate the anticoagulant effect of fibrinogen/fibrin hydrolysed products in the circulation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-thrombotica, ATC code: B01 AD 04

Urokinase exists in two distinct molecular entities, a high molecular weight form with approximately 54,000 Dalton and a low molecular weight form with approximately 33,000 Dalton. Urokinase contains more than 85 % of the high molecular weight form.
Urokinase is a proteolytic enzyme with the amino acid serine as active centre (syn: serine protease). As a direct plasminogen activator, the enzyme can penetrate the thrombus and there convert plasminogen into plasmin by means of hydrolysis of the arginine-valine bond. Plasmin degradates fibrin, as a result of which the thrombus disintegrates, unlike anticoagulants, which only inhibit the growth of thrombi.

The activity of urokinase leads to a dose-dependent lowering of plasminogen and fibrinogen values and increases the presence of fibrin and fibrinogen degradation products that have an anticoagulant effect and potentiate the effect of heparin.

5.2 Pharmacokinetic properties

Biotransformation
Urokinase is metabolised in the liver. Inactive degradation products are excreted through the bile and urine.

Elimination
The elimination half-life of urokinase is about 10 – 20 minutes. The clinical half-life depends on the duration of action of the activated plasmin. A decrease in plasminogen and fibrinogen levels and increase of fibrin and fibrinogen decomposition products caused by administration of urokinase persists for 12 – 24 hours after end of infusion.

5.3 Preclinical safety data

Pharmacological and toxicological studies in laboratory animals did not indicate a hazard to humans other than those already described in other parts of the SPC. Reproduction studies in rats, rabbits and mice with intravenous doses up to 1.4 times the human dose revealed no evidence for adverse events on reproduction.

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.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.
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.

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

6.4 Special precautions for storage

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

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless, type I glass vial closed with chlorobutyl rubber stoppers and sealed with an aluminium flip-off cap.
The following pack size is available: 1 x 1 vial.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The powder for solution for infusion should be dissolved in water for injection.
The solution should be clear and colourless. This is 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 IU vial use 2 ml of water for injection.

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

7 MARKETING AUTHORISATION HOLDER

Medac Gesellschaft fur Klinische Spezialpraparate mbH
Theaterstrasse 6
22880 Wedel
Germany

8 MARKETING AUTHORISATION NUMBER

PA0623/017/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 April 2016

10 DATE OF REVISION OF THE TEXT

November 2018