Urokinase UKR (10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, 500,000 IU) powder for solution for injection or infusion

(Urokinase)

PL 19364/0023
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UKPAR

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LAY SUMMARY

The MHRA granted UKR Regulatory Affairs Limited a Marketing Authorisation for the medicinal product Urokinase UKR powder for solution for injection or infusion on 17th March 2010. This medicine is subject to restricted medical prescription and is indicated for 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.

Urokinase UKR powder for solution for injection or infusion contains the active ingredient urokinase (extracted from human urine), which is a fibrinolytic enzyme produced by the kidneys and excreted in the urine. Urokinase converts plasminogen to the active enzyme plasmin which can break down blood clots.

This product is available in strengths of 10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, and 5000,000 IU but will be referred to throughout as Urokinase UKR powder for solution for injection or infusion.

A critical review of the pharmaceutical data and non-clinical and clinical literature presented to the MHRA in support of this application demonstrated that Urokinase UKR powder for solution for injection or infusion is effective in the 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. No new safety risks were identified and the safety profile of Urokinase UKR powder for solution for injection or infusion was considered to be acceptable. It was therefore judged that the benefits of using this product outweigh the risks, hence a Marketing Authorisation has been granted.

Urokinase UKR (10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, 500,000 IU) powder for solution for injection or infusion

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to UKR Regulatory Affairs Limited for the medicinal product Urokinase UKR powder for solution for injection or infusion on 17th March 2010. This product is a restricted prescription only medicine.

This application was submitted as an abridged complex national application under Article 10a according to Directive 2001/83/EC, as amended; a well-established use or bibliographic, application.

Urokinase UKR powder for solution for injection or infusion contains urokinase and is indicated for 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.

Urokinase UKR powder for solution for injection or infusion should only be used by physicians experienced in the management of thrombotic diseases in hospitals where adequate diagnostic and monitoring techniques are available.

Urokinase UKR powder for solution for injection or infusion may be used in children of all ages only for the indication of treatment of thrombosed central venous catheters using the same lock procedure as in adults. There is very limited experience with urokinase in children with thromboembolic occlusive vascular disease and urokinase should not be used in this indication.

Depending on the indication, the route of administration Urokinase UKR powder for solution for injection or infusion is by systemic intravenous infusion, by local intra-arterial catheter-directed infusion during arteriography, or by local instillation. Urokinase UKR powder for solution for injection or infusion must not be given by subcutaneous or intramuscular injection.

Urokinase UKR powder for solution for injection or infusion was granted a license on 17th March 2010.

QUALITY ASSESSMENT

INSPECTION STATUS
The manufacturer of the active ingredient (urokinase purified bulk) and the unlabelled finished dosage form in bulk has been certified for Good Manufacturing Practice (GMP) by the relevant competent supervising authorities.
Medac Gesellschaft für klinische Spezialpräparate, Fehlandtstr.3, D- 20354 Hamburg / Germany is the marketing authorisation holder of the pharmaceutical products.

INTRODUCTION
This is a national application for a purified form of naturally occurring human urokinase extracted from urine. The Applicant (UKR Regulatory Affairs Ltd.) has submitted an application according to Article 10a of Directive 2001/83/EC, as amended, a well-established use, or bibliographic, application.

The active ingredient in Urokinase UKR 10,000 IU powder for solution for injection or infusion is urokinase. Urokinase is extracted from human urine. Each vial contains 10,000 IU of human urokinase extracted from human urine.

Urokinase UKR powder for solution for injection or infusion is in pharmacotherapeutic group: antithrombotics, ATC code: B01 AD 04.

DRUG SUBSTANCE

General Information
The applicant has submitted a satisfactory dossier containing information on the drug substance and drug product.

Manufacture
Urokinase (purified bulk) enzyme, extracted from human urine, activates plasminogen. It consists of a mixture of low-molecular-mass (LMM) (Mr 33,000) and high molecular-mass (HMM) (Mr 54,000) forms, the high-molecular-mass form being dominant. Urokinase purified bulk is manufactured from crude urokinase (semi-purified urokinase).

The applicant has provided satisfactory information regarding the production and control of the semi-purified urokinase. Fresh human male urine is collected in China. The collection sites are limited to high schools, colleges, and universities. Medical schools and hospitals are not used as collection sites. Details of the collection procedure and the operating requirements were provided by the manufacturers and are included in Module 3.

The applicant has adequately described the drug substance manufacturing process and process controls.

Characterisation
Urokinase [EC 3.4.99.26] is a polypeptide with fibrinolytic action that is isolated from human urine. Urokinase occurs in different molecular forms, with a distinction being made between a high and low molecular weight forms. The mean molecular weight of the high molecular weight form is approximately 54,000 Daltons while that of the low molecular weight form is given as approx. 33,000 Daltons.

The structure of the drug substance has been adequately described.

Analytical procedures
Pharmacopoeial methods are used where applicable and the relevant SOPs are provided. Validation data have been submitted for thromboplastin, albumin content and the viral marker tests and are satisfactory.

REFERENCE STANDARDS OR MATERIALS
Details of the urokinase reference material have been provided and are satisfactory.

CONTAINER CLOSURE SYSTEM
Details of the urokinase (purified bulk) container closure system have been provided and are satisfactory.

STABILITY
Study on several production batches confirmed that urokinase (purified bulk) was stable when stored in vials for 12 months at ≤ -30°C.
The temperature of ≤ –30°C was found to be a good condition for storing the urokinase (purified bulk) before entering into the manufacturing process of the finished products.

DRUG PRODUCT

Description and composition of the drug product
Urokinase is a polypeptide with fibrinolytic action that is isolated from human urine. The excipients are disodium phosphate dodecahydrate, sodium dihydrogen phosphate dehydrate and human albumin.

Pharmaceutical development
The development pharmaceutics of Urokinase UKR powder for solution for injection or infusion are adequately described.

Manufacture
Description of Manufacturing Process and Process Controls
A satisfactory account of the manufacturing process has been provided and is in accordance with current good manufacturing practice (GMP) requirements.

Process Validation
Validation reports for the non-standard operations; filling (media fills) and lyophilisation are provided and are satisfactory. A comprehensive aseptic validation study demonstrated that the process was satisfactory and both environmental and contamination criteria were met.

Validation study data confirm that the lyophilisation process results in a satisfactory consistent product.

Several batches of urokinase finished product have been manufactured for the stability test program and all met the defined finished product specification.

Control of Excipients
The excipients and reagents used in the manufacture of the urokinase powder for injection are pharmacopoeial grade.

Control of Drug Product
Finished Product Specification

The finished product specification has been provided. Satisfactory control tests are applied at the time of release.

Analytical Procedures
Pharmacopoeial methods are used where applicable and the relevant SOPs are provided. Analytical batch data have been provided for several batches, all of which complied with the release specification.

Validation of Analytical Procedures
Appropriate validation data have been supplied and are considered adequate.

Batch Analyses
Analytical batch data have been provided for several batches, all of which complied with the release specification.

Justification of Specifications
The applicant has provided the specifications for Urokinase UKR powder for solution for injection or infusion and has justified the acceptance limits adequately.

Reference Standards or Materials
The reference standards are listed and are satisfactory.

Container Closure System
The container and stopper have been described and are acceptable.

Stability Data
The shelf life specification for urokinase finished product is based on the release specification with the exception of potency. Supporting data are provided from a stability study using several batches each of urokinase 10,000, 50,000, 100,000, 250,000 and 500,000 IU.

The current stability study demonstrated strength-related decease of potency by statistical evaluation of stability data according to the recommendations of ICH guide of Evaluation of Stability Data. An individual decrease of potency per month was obtained for each urokinase strength. Considering limits of potency both in the release specification and the shelf life specification, the applicant has calculated a shelf life for each strength.

The proposed shelf lives are considered appropriate. The applicant has provided a summary of the stability data which is satisfactory.

APPENDICES
Facilities and Equipment
Details of product manufacturing facilities and equipment are acceptable.

Adventitious Agents Safety Evaluation
The applicant has adequately dealt with issues of prion and viral safety. This is satisfactory.

Novel Excipients
None.
REGIONAL INFORMATION
Not applicable.

ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Summary of Product Characteristics
The SPC is satisfactory.

Patient Information Leaflet
The PIL is satisfactory.

Labels
The labels are acceptable.

MAA form
Acceptable.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
The application is approvable.

PRECLINICAL ASSESSMENT

INTRODUCTION

This is a national application for a purified form of naturally occurring human urokinase extracted from urine. The product has been granted a marketing authorisation under the name Urokinase HS medac since 1980 in Germany, since 1988 in Luxembourg and Switzerland, and since 1989 in the Netherlands under the name Medacinase. The Marketing Authorisation Holder is Medac GmbH.

The Applicant (UKR Regulatory Affairs Ltd.) has submitted an application according to Article 10a of Directive 2001/83/EC, as amended, a well-established use, or bibliographic, application.

The active ingredient in Urokinase is urokinase (Ph. Eur.).

Urokinase UKR is indicated for (from the SPC):

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

The Applicant has submitted a fully bibliographic application for the non-clinical part of the dossier.

NON-CLINICAL ASSESSMENT

Urokinase is a well established product. No further non-clinical testing has been conducted in support of this application. The product is a natural human enzyme which has been isolated from normal human urine and is therefore a normal constituent of the body.

According to the SPC the product contains in addition to the active ingredient the following excipients: disodium phosphate dodecahydrate, sodium dihydrogen dehydrate. All excipients and reagents used in the manufacture of urokinase powder for injection are pharmacopoeial grade.

Urokinase has over 20 years clinical use as a thrombolytic agent. Furthermore, its pharmaco-toxicological properties have been well documented. Therefore further non-clinical studies are not required.

NON-CLINICAL OVERVIEW

The applicant has submitted an up to date non-clinical overview which is a detailed summary of the non-clinical information available in the literature up to 2008 and is acceptable. The overview was written by Dr. Martin Guppy who is appropriately qualified.

ENVIRONMENTAL RISK ASSESSMENT

The applicant has not submitted an ERA. Since urokinase is a naturally occurring substance and the excipients are all commonly used compounds, the product is not considered to present a risk to the environment. Urokinase is exempt from ERA according to the relevant guideline.

SPC
Section 5.3 of the SPC is acceptable.

ASSESSOR'S OVERALL CONCLUSIONS
There are no objections to the grant of a marketing authorisation from the non-clinical point of view.

CLINICAL ASSESSMENT REPORT

INTRODUCTION
Urokinase UKR powder for solution for injection or infusion is in pharmacotherapeutic group: antithrombotics, ATC code: B01 AD 04.

TYPE OF APPLICATION AND REGULATORY BACKGROUND
This is a national application for a purified form of naturally occurring human urokinase extracted from urine. The product has been granted a marketing authorisation under the name Urokinase HS medac since 1980 in Germany, since 1988 in Luxembourg and Switzerland, and since 1989 in the Netherlands under the name Medacinase. The Marketing Authorisation Holder is Medac GmbH.

The Applicant (UKR Regulatory Affairs Ltd.) has submitted an application according to Article 10a of Directive 2001/83/EC, as amended, a well-established use, or bibliographic, application.

INDICATION
Urokinase UKR powder for solution for injection or infusion is indicated for the 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

POSOLOGY AND METHOD OF ADMINISTRATION
Urokinase UKR is formulated as a powder for solution for injection or infusion. Five strengths are available: 10,000 – 50,000 – 100,000 – 250,000 and 500,000 I.U.
It must be reconstituted before use with the correct volume of sterile physiological saline (not provided). Various doses are recommended depending on the indication.

CONSIDERATION FOR PAEDIATRIC USE
The SPC states that there is very limited experience with urokinase in children with thromboembolic occlusive vascular disease and urokinase should not be used in this indication.

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

CLINICAL PHARMACOLOGY
INTRODUCTION
Urokinase is a fibrinolytic enzyme produced by the kidneys and excreted in the urine. Urokinase preparations have historically been isolated from human urine (e.g. Urokinase medac, Syner-kinase) or human kidney tissue cultures (Abbokinase) and can further be produced by recombinant DNA technology.

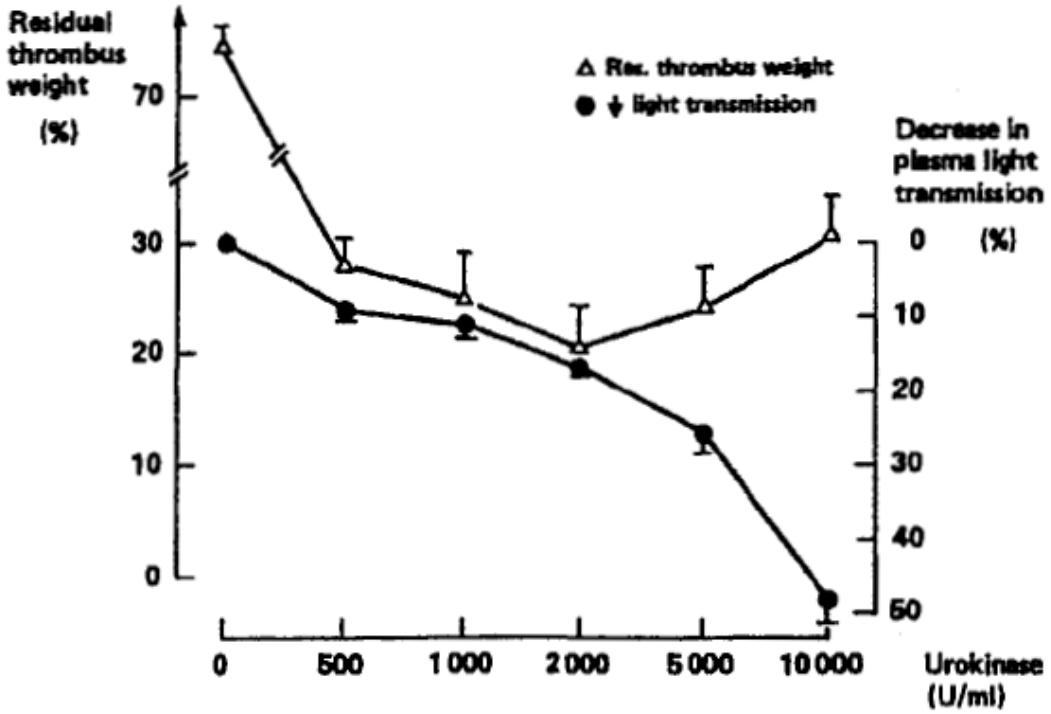
It is a trypsine-like two-chain serine protease and exists in two molecular entities, a low molecular weight form (≈ 32,000 daltons) and a high molecular weight form (≈ 54,000 daltons). The latter is the native form of the molecule, which is probably degraded to the low molecular weight form through proteolysis. Commercial preparations contain various proportions of the two forms and the applicant states in their Clinical Overview that “the

proportions do, however, not alter the thrombolytic properties of the compound as the high molecular form is converted to the low molecular form during thrombolytic treatment and both forms are equipotent plasminogen activators". Although no composition is provided by the applicant in their Clinical dossier, the Quality dossier indicates that Urokinase medac contains more than 85% of high molecular weight form. Other urokinases extracted from human urine are known to contain both forms in various proportions whereas Abbokinase predominantly contains the low molecular weight form and the recombinant form developed by Abbot Laboratories has a high molecular weight (48,000 daltons).

PHARMACODYNAMICS

Urokinase converts plasminogen to the active enzyme plasmin through cleavage of an arginine-valine peptide bond in a direct catalytic reaction. Plasmin may degrade any protein/peptide with an arginyl-lysyl amino acid sequence, including fibrin, for which it has a high affinity, but also clotting factors (e.g. factors II, V or VIII). Thus, a systemic state of fibrinolysis can be created.

To evaluate the possibility that platelet activity impairs the lysis of thrombi, the effects of aspirin and platelet-deaggregating prostaglandin E1 on thrombolysis with urokinase have been studied by Terres et al (1989). Combined platelet and fibrin thrombi were produced in vitro. Urokinase medac (500-10,000 units/ml) caused a dose dependent weight loss of the thrombi that was maximal at 2,000 units/ml. However, plasma light transmission further declined when the concentrations of urokinase exceeded that value (see figure below).



In vitro lysis with urokinase of combined platelet and fibrin thrombi was enhanced by the addition of platelet-deaggregating prostaglandin E1 and by pretreatment with aspirin. Numerous other interactions are known, such as with other platelet inhibitors, anticoagulants, antifibrinolytics, contrast media.

PHARMACOKINETICS

Urokinase activity was initially measured; later, specific anti-urokinase antibodies were developed. Today, commercially available ELISA kits are used to quantify urokinase in human tissue and serum samples but different sets of antibodies and standards provided with the kits may lead to discrepancies among various kits used.

Information on the pharmacokinetics of urokinase in humans is limited and can be found in general reviews.

CONCLUSIONS

The clinical pharmacology of urokinase has been documented in published papers, including one on Urokinase medac (the same product as Urokinase UKR). No new clinical pharmacology data are required for this type of application and none are provided by the applicant. This is satisfactory.

The applicant has estimated that their product has been administered to 4000 - 5000 patients per year in the four European countries where it is marketed (Germany, Switzerland, The Netherlands, Luxembourg) and the scientific interest in the use of urokinase is reflected in the published literature.

Various types of urokinase have been used in the trials reported in the literature. Sometimes a mainly High Molecular Weight (HMW) urinary product is specified but more often the Low Molecular Weight (LMW) product produced from human neonatal kidney cells (Abbokinase) or a recombinant HMW product is specified. The applicant has submitted a large number of literature references stating that all literature is relevant since their urokinase complies with the European Pharmacopoeia, i.e. contains more than 85% HMW-form. This may be considered acceptable for an extraction product.

The applicant has also provided an overview of thrombolytic agents (Gulba et al, 1996) that describes the differences between the HMW and LMW forms. Both are equipotent plasminogen activators but they differ in their binding and activation properties of the two forms (Glu- and Lys-) of plasminogen. However, during therapy, there is a continuous conversion by proteolysis of HMW- into LMW-urokinase, which suggests that the thrombolytic properties of all urokinases are similar. The paper comparing Abbokinase to a urinary urokinase (Marder et al, 1978) supports this line of reasoning although the evidence is not robust due to the limited number of patients studied. Nevertheless, even if some slight variability in effects exists amongst the various types of urokinase it may not be critical since the dose is adjusted individually. Finally, it is reassuring that the applicant's urokinase has been used in the EU for more than 25 years. Thus, safety data are available from wide clinical practice with the product intended for marketing.

In conclusion, reliance on the literature submitted by the Applicant is considered acceptable.

CLINICAL EFFICACY

INDICATIONS

The indications are in line with current guidelines on the use of thrombolytics in general. Each indication and its specific dosing regimen are supported by a range of relevant publications.

CONCLUSIONS
The efficacy of Urokinase UKR powder for solution for injection or infusion has been documented in published papers. No new clinical efficacy data are required for this type of application and none are provided by the applicant. This is satisfactory.

CLINICAL SAFETY
DATA PROVIDED
Apart from a review of the literature, two Periodic Safety Update Reports (PSURs) have been submitted.

The first report covers the period from 1980 to 2001, and according to the MAH Medac GmbH, the number of patients exposed over this period amounted to approximately 84,000 patients. Twenty cases of spontaneous reports were received: 8 serious and 12 non-serious.

Serious reports include haemorrhages [cerebral (3), retroperitoneal (1)], lack of efficacy (1), pericardial effusion (1), fever (1), and anaphylactoid reaction (1). Non serious reports include fever/chills (4), lack of efficacy (4), thrombophlebitis (2), bronchitis (1), and swollen extremities (1).

The second report covers the period from 2001 to 2005, and according to the MAH Medac GmbH, the number of patients exposed over this period amounted to approximately 23,500 patients. No case of spontaneous report was received. The MAH has sponsored a trial in patients with critical limb ischemia (e.g. diabetic foot), who were treated for 21 days with a daily infusion of urokinase (500,000 or 1,000,000 IU); 70 patients have been enrolled. Three serious cases were reported: cerebellar haemorrhage, haemorrhage in both lower legs, hypotension (80/40 mmHg).

CONCLUSIONS
The safety of Urokinase UKR powder for solution for injection or infusion has been documented in published papers and two PSURs. This is satisfactory.

PHARMACOVIGILANCE AND RISK MANAGEMENT SYSTEM
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The applicant has provided a Risk Management Plan that is considered to adequately monitor identified and potential risks in relation to suspected adverse reactions.

PRODUCT LITERATURE

SPC
As proposed by the applicant. The final SmPC is satisfactory.

PATIENT INFORMATION LEAFLET
The PIL is in line with the approved SmPC is considered to be satisfactory.

LABEL
Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

OVERALL CONCLUSION

In principle, the benefit/risk balance of Urokinase UKR powder for solution for injection or infusion is positive in the indications proposed by the Applicant and this application is approvable.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Urokinase UKR powder for solution for injection or infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL

No new preclinical data were submitted and none are required for an application of this type. The literature has not revealed any evidence of untoward toxicity on the part of the active ingredient, or the excipients of Urokinase UKR powder for solution for injection or infusion.

EFFICACY AND SAFETY

The published literature supports the efficacy of Urokinase UKR powder for solution for injection or infusion. The literature review identifies no new safety issues or concerns.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with urokinase is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

Urokinase UKR (10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, 500,000 IU) powder for solution for injection or infusion

(Urokinase)

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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application 26th April 2007
2 Following standard checks the MHRA informed the applicant that its application was considered valid on 1st August 2007
3 Following assessment of the submitted data, a request for supplementary information was sent to the applicant on 23rd January 2008
4 The applicant submitted its responses to the supplementary information request in letters dated 29th October 2008 and 11th February 2009
5 A further request for supplementary information was sent to the applicant on 2nd June 2009
6 The applicant submitted its response to the supplementary information request in a letter dated 29th September 2009
7 A further request for supplementary information was sent to the applicant on 11th December 2009
8 The applicant submitted its response to the supplementary information request in a letter dated 21st January 2010
9 A further request for supplementary information was sent to the applicant on 27th January 2010
10 The applicant submitted its response to the supplementary information request in a letter dated 11th February 2010
11 The application was finalised on 17th March 2010

Urokinase UKR (10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, 500,000 IU) powder for solution for injection or infusion

(Urokinase)

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Urokinase UKR (10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, 500,000 IU) over for solution for injection or infusion

(Urokinase)

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Urokinase UKR 10,000 IU

Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Thrombosed arteriovenous haemodialysis shunts
Urokinase UKR 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 IU/ml up to a total dose of 250,000 IU If necessary, the application can be repeated every 30 – 45 minutes up to a maximum of 2 hours.

Thrombosed central venous catheters
Urokinase UKR should be dissolved in physiological saline at a concentration of 5,000 IU/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 UKR 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 UKR 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 UKR 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	≥ 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

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

Investigations

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

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 UKR 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 UKR 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 ºC.
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 IU vial use 2 ml of water for injection.

After reconstitution the solution must be clear and colourless.

7 MARKETING AUTHORISATION HOLDER

UKR Regulatory Affairs Ltd.
The Bull Pen
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/03/2010

10 DATE OF REVISION OF THE TEXT

17/03/2010

1 NAME OF THE MEDICINAL PRODUCT

Urokinase UKR 50,000 IU

Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50,000 IU 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 UKR 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 UKR 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 UKR should be administered by intravenous infusion into a peripheral vein using an initial dose of 4,400 IU/kg bodyweight infused over 10 – 20 min, followed by a maintenance dose of 100,000 IU per hour for 2 – 3 days.

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

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

Thrombosed arteriovenous haemodialysis shunts
Urokinase UKR 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 IU/ml up to a total dose of 250,000 IU If necessary, the application can be repeated every 30 – 45 minutes up to a maximum of 2 hours.

Thrombosed central venous catheters
Urokinase UKR should be dissolved in physiological saline at a concentration of 5,000 IU/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 UKR 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 UKR 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 UKR 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	≥ 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

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

Investigations

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

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 UKR 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 UKR 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

32 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 ºC.
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 50,000 IU vial use 2 ml of water for injection.

After reconstitution the solution must be clear and colourless.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/03/2010

10 DATE OF REVISION OF THE TEXT

17/03/2010

1 NAME OF THE MEDICINAL PRODUCT

Urokinase UKR 100,000 IU

Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Thrombosed arteriovenous haemodialysis shunts
Urokinase UKR 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 IU/ml up to a total dose of 250,000 IU If necessary, the application can be repeated every 30 – 45 minutes up to a maximum of 2 hours.

Thrombosed central venous catheters
Urokinase UKR should be dissolved in physiological saline at a concentration of 5,000 IU/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 UKR 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 UKR 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 UKR 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	≥ 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

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

Investigations

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

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 UKR 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 UKR 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

32 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 ºC.
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 100,000 IU vial use 2 ml of water for injection.

After reconstitution the solution must be clear and colourless.

7 MARKETING AUTHORISATION HOLDER

UKR Regulatory Affairs Ltd.
The Bull Pen
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/03/2010

10 DATE OF REVISION OF THE TEXT

17/03/2010

1 NAME OF THE MEDICINAL PRODUCT

Urokinase UKR 250,000 IU

Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250,000 IU 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 UKR 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 UKR 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.

<u>Deep vein thrombosis</u>

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

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

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

Thrombosed arteriovenous haemodialysis shunts
Urokinase UKR 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 IU/ml up to a total dose of 250,000 IU If necessary, the application can be repeated every 30 – 45 minutes up to a maximum of 2 hours.

Thrombosed central venous catheters
Urokinase UKR should be dissolved in physiological saline at a concentration of 5,000 IU/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 UKR 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 UKR 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 UKR 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	≥ 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

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

Investigations

Very common	Decrease in haematocrit without clinically detectable haemorrhage

Transient increase in transaminases

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 UKR 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 altons) and a low molecular weight (approximately 33,000 daltons). Urokinase UKR 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

32 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 ºC.
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 250,000 IU vial use 5 ml of water for injection.

After reconstitution the solution must be clear and colourless.

7 MARKETING AUTHORISATION HOLDER

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Home Farm
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OX27 8TG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/03/2010

10 DATE OF REVISION OF THE TEXT

17/03/2010

1 NAME OF THE MEDICINAL PRODUCT

Urokinase UKR 500,000 IU

Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500,000 IU 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 UKR 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 UKR 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 UKR should be administered by intravenous infusion into a peripheral vein using an initial dose of 4,400 IU/kg bodyweight infused over 10 – 20 min, followed by a maintenance dose of 100,000 IU per hour for 2 – 3 days.

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

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

Thrombosed arteriovenous haemodialysis shunts
Urokinase UKR 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 IU/ml up to a total dose of 250,000 IU If necessary, the application can be repeated every 30 – 45 minutes up to a maximum of 2 hours.

Thrombosed central venous catheters
Urokinase UKR should be dissolved in physiological saline at a concentration of 5,000 IU/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 UKR 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 UKR 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 UKR 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.

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 effects 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	≥ 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

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

Investigations

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

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 UKR 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 UKR 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

34 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 ºC.
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 500,000 IU vial use 10 ml of water for injection.

After reconstitution the solution must be clear and colourless.

7 MARKETING AUTHORISATION HOLDER

UKR Regulatory Affairs Ltd.
The Bull Pen
Home Farm
Banbury Road
Caversfield
Nr Bicester
OX27 8TG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/03/2010

10 DATE OF REVISION OF THE TEXT

17/03/2010

Patient Information Leaflet

Urokinase UKR (10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, 500,000 IU) powder for solution for injection or infusion

(Urokinase)

PL 19364/0023
PL 19364/0024
PL 19364/0025
PL 19364/0026
PL 19364/0027

Urokinase UKR · 82100-VPGB · AA · 01.10 · Pharma-Code: 266
Format: 296 x 132 mm · HKS 44 N · Corrective action: KV01_lindauer_22.02.10 / KV02_bk_22.02.10 / KV03_bk_23.02.10

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Urokinase UKR 10,000 I.U.
powder for solution for injection or infusion

Urokinase UKR 50,000 I.U.
powder for solution for injection or infusion

Urokinase UKR 100,000 I.U.
powder for solution for injection or infusion

Urokinase UKR 250,000 I.U.
powder for solution for injection or infusion

Urokinase UKR 500,000 I.U.
powder for solution for injection or infusion

Human urokinase

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT UROKINASE UKR IS AND WHAT IT IS USED FOR

The name of your medicine is Urokinase UKR. The active substance is urokinase which is a thrombolytic medicine that can help to dissolve blood clots in:
- lungs
- deep veins
- peripheral arteries (such as in the leg)
- intravenous central catheters (catheter placed into a large vein in the neck, chest, or groin) and haemodialysis shunts (surgically created connection between an artery and a vein that is used to filter blood)

2. BEFORE YOU ARE GIVEN UROKINASE UKR

Urokinase UKR treatment is administered by a doctor or nurse who is experienced in this type of treatment. You will not be asked to administer Urokinase UKR to yourself.

Urokinase UKR will not be used if you
- are allergic (hypersensitive) to urokinase or any of the other ingredients of Urokinase UKR
- are currently bleeding
- have any abnormal blood vessel
- have any cancer that has a risk of bleeding
- have abnormal blood clotting, or are taking anticoagulant (blood thinning) medicines
- have severe uncontrolled high blood pressure
- have infection of the pancreas, heart, or any other severe infection
- have had a stroke in the past 2 months
- have recently had any major surgery or medical investigations such as lumbar puncture

Special care will be taken with Urokinase UKR if you
- have recently had bleeding from the stomach or elsewhere in the intestines
- have recently had surgery
- have cavities in your lungs
- have problems with your urinary tract that could result in bleeding (e.g. bladder catheter)
- have problems with your heart, particularly the mitral valve, or have abnormal heart rhythm e.g. atrial fibrillation
- have a severe liver or kidney disease
- are pregnant or have recently given birth
- have a severe blood vessel disease especially in the brain
- are elderly, particularly if you are aged over 75 years

In these circumstances your doctor will decide whether or not you should be given Urokinase UKR. Whilst receiving Urokinase UKR, special care will also be taken if you need repeated blood tests taken or intramuscular injections or any other procedures which may be associated with a high risk of bleeding, such as any procedure performed on an artery.

Taking or using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines, or any other medicines, even those obtained without a prescription:
- heparin, dipyridamole and other anticoagulants or other medicines that may affect clotting
- acetylsalicylic acid (aspirin)
- non-steroidal anti-inflammatory drugs
- dextrans

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Urokinase UKR must not be used in pregnancy or immediately after delivery unless clearly necessary.

It is unknown whether urokinase is excreted into human breast milk. For this reason, do not breast-feed during treatment with Urokinase UKR.

Driving and using machines
If your medicine makes you have side effects that may reduce your ability to concentrate, do not drive or operate machinery.

3. HOW UROKINASE UKR IS USED

The amount and duration of Urokinase UKR treatment will be decided by your doctor and will depend on the condition for which you are being treated. Urokinase UKR must **never** be injected into a muscle or under the skin.
- If you are being treated for blood clots in your lungs or deep veins, Urokinase UKR will be injected into a vein (usually in the arm) during several hours and up to 3 days. Progress of the treatment may be checked by special X-rays. After the clot has been dissolved, you may be put on anticoagulant (blood thinning) therapy to prevent a recurrence.
- If you are being treated for blood clots in an artery, Urokinase UKR will be injected directly into the artery until dissolution of the clot.
- If you are being treated for a blocked central venous catheter Urokinase UKR may be injected directly into the catheter and left for up to an hour before removing the fluid. This may be repeated several times.

Urokinase UKR · 82100-VPGB · AA · 01.10 · Pharma-Code: 266
Format: 296 x 132 mm · HKS 44 N · Corrective action: KV01_lindauer_22.02.10 / KV02_bk_22.02.10 / KV03_bk_23.02.10

- If you are being treated for a blocked haemodialysis shunt, Urokinase UKR will be instilled into both branches of the shunt. This may be repeated several times.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Urokinase UKR can cause side effects, although not everybody gets them.

Urokinase UKR can on rare occasions cause severe reactions. **Tell your doctor immediately** if you:
- observe any spontaneous bleeding, since urokinase may increase the risk for bleeding.
- get symptoms of an allergic reaction/hypersensitivity such as
  - tightness of the chest or difficulty with breathing
  - swelling of eyelids, face or lips
  - skin rashes or lumps, itchiness
  - collapse (fall in blood pressure) or turning blue (cyanosis)

Other side effects that may occur:
Some patients may experience a sensation of warmth or cold (fever or chills), nausea and vomiting (feeling or being sick), back pain or shortness of breath within one hour of starting the infusion.

Very common side effects (occur in more than 1 in 10 people)
- bleeding
  - unusual bleeding, particularly from recent cuts or puncture wounds
  - small amounts of blood in the urine
  - nose bleeds
  - bleeding gums
  - bruising
- changes in some blood tests

Common side effects (occur in between 1 in 10 and 1 in 100 people)
- fever
- chills
- bleeding (into the brain, from the stomach, in the urine, into the muscles)
- some smaller fragments of the clot or even cholesterol crystals may be released and pass along the blood vessel and cause a blockage elsewhere.

Uncommon side effects (occur in between 1 in 100 people and 1 in 1000 people)
- bleeding into the liver

If any of these side effects happen, or if you notice anything else unusual, you must tell the doctor as soon as possible. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE UROKINASE UKR

Keep out of the reach and sight of children.
Do not store above 25 °C.
Store in the original container and package in order to protect from light.
Do not use after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
Do not use Urokinase UKR if the contents of the vial are discoloured.
Use reconstituted medicine immediately. Do not keep reconstituted material for later use.

6. FURTHER INFORMATION

What Urokinase UKR contains
There are different strengths available and each vial contains the active substance human urokinase.

The other ingredients are: disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.

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

Each pack contains one vial. There are different strengths of Urokinase UKR approved for marketing:
Urokinase UKR 10,000 I.U.
Urokinase UKR 50,000 I.U.
Urokinase UKR 100,000 I.U.
Urokinase UKR 250,000 I.U.
Urokinase UKR 500,000 I.U.

Not all strengths may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder (MAH):
UKR Regulatory Affairs Ltd.
The Bull Pen
Home Farm
Banbury Road
Caversfield
Nr Bicester
OX27 8TG
United Kingdom

Manufacturer:
medac Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstr. 3
20354 Hamburg
Germany

This leaflet was revised 01/2010.

Labelling

Urokinase UKR (10,000 IU, 50,000 IU, 100,000 IU, 250,000 IU, 500,000 IU) powder for solution for injection or infusion

(Urokinase)

PL 19364/0023
PL 19364/0024
PL 19364/0025
PL 19364/0026
PL 19364/0027


Lot:
Urokinase UKR
10,000 I.U.
powder for solution for injection or infusion Human urokinase
Active ingredient: human urokinase 10,000 I.U. Excipients: Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Intravenous use only. Do not store above 25 °C. Keep the container in the outer carton to protect from light. One vial of 10,000 I.U. lyophilized urokinase is to be reconstituted with 2 ml of water for injection. MA no.:
UKR Regulatory Affairs Ltd.
The Bull Pen, Home Farm, Banbury Road,
Caversfield, Nr Bicester, OX27 8TG,
United Kingdom
EXP:
POM
AA
06.09
82100-VEGB
266
Lot:
Urokinase UKR
50,000 I.U.
powder for solution for injection or infusion Human urokinase
Active ingredient: human urokinase 50,000 I.U. Excipients: Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Intravenous use only. Do not store above 25 °C. Keep the container in the outer carton to protect from light. One vial of 50,000 I.U. lyophilized urokinase is to be reconstituted with 2 ml of water for injection. MA no.:
UKR Regulatory Affairs Ltd.
The Bull Pen, Home Farm, Banbury Road,
Caversfield, Nr Bicester, OX27 8TG,
United Kingdom
EXP:
POM
AA
06.09
82105-VEGB
267
Lot:
Urokinase UKR
100,000 I.U.
powder for solution for injection or infusion Human urokinase
Active ingredient: human urokinase 100,000 I.U. Excipients: Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Intravenous use only. Do not store above 25 °C. Keep the container in the outer carton to protect from light. One vial of 100,000 I.U. lyophilized urokinase is to be reconstituted with 2 ml of water for injection. MA no.:
UKR Regulatory Affairs Ltd.
The Bull Pen, Home Farm, Banbury Road,
Caversfield, Nr Bicester, OX27 8TG,
United Kingdom
EXP:
POM
AA
06.09
82110-VEGB
268

Lot:

Urokinase UKR

250,000 I.U.

AA

06.09

powder for solution for injection or infusion Human urokinase

Active ingredient: human urokinase 250,000 I.U. Excipients: Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Intravenous use only. Do not store above 25 °C. Keep the container in the outer carton to protect from light. One vial of 250,000 I.U. lyophilized urokinase is to be reconstituted with 5 ml water for injection. MA no.:

82115-VEGB

UKR Regulatory Affairs Ltd.
The Bull Pen, Home Farm, Banbury Road,
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United Kingdom

POM

EXP:

269

Lot:

Urokinase UKR

500,000 I.U.

AA

06.09

powder for solution for injection or infusion Human urokinase

Active ingredient: human urokinase 500,000 I.U. Excipients: Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Intravenous use only. Do not store above 25 °C. Keep the container in the outer carton to protect from light. One vial of 500,000 I.U. lyophilized urokinase is to be reconstituted with 10 ml water for injection. MA no.:

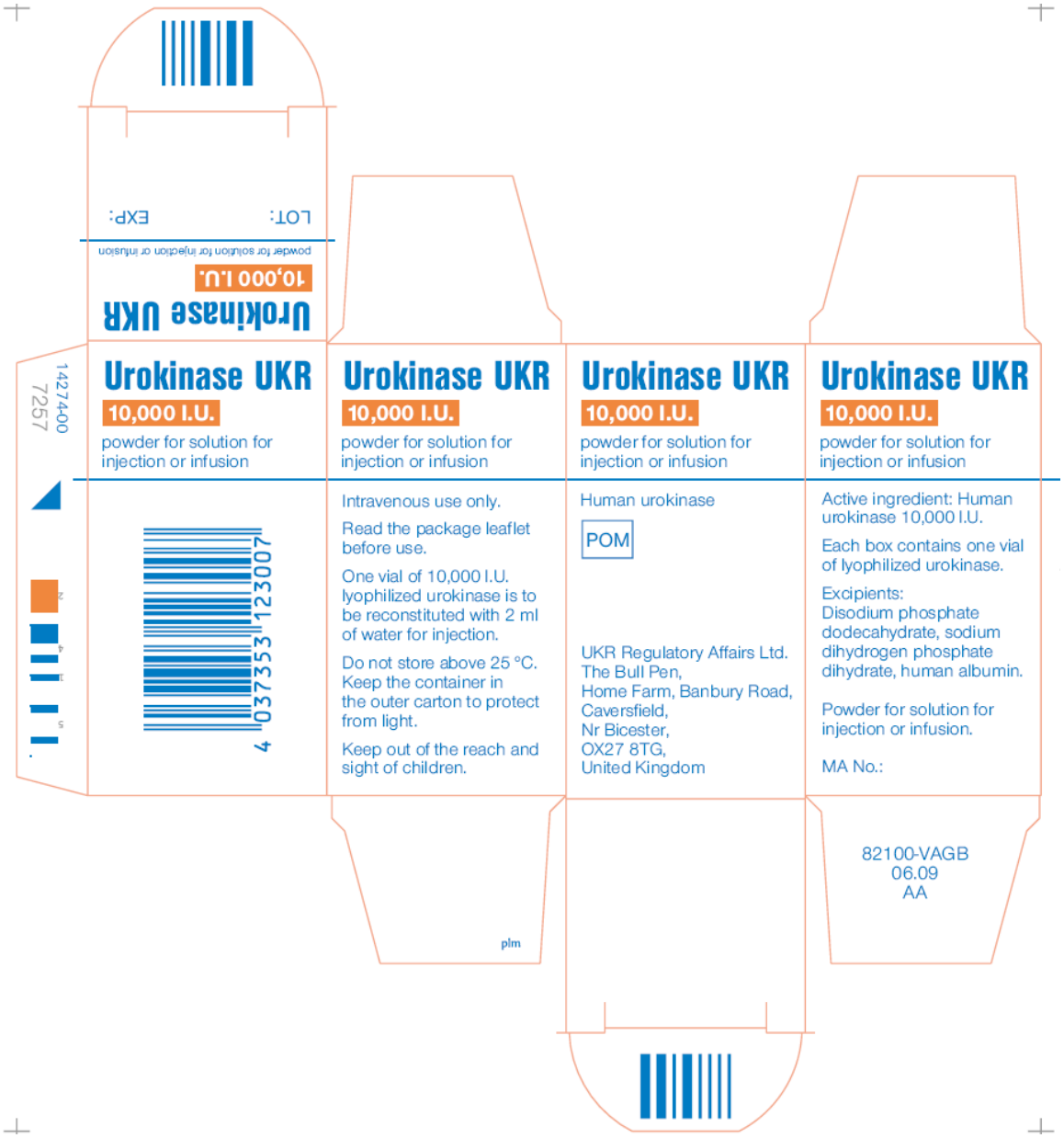
82120-VEGB

UKR Regulatory Affairs Ltd.
The Bull Pen, Home Farm, Banbury Road,
Caversfield, Nr Bicester, OX27 8TG,
United Kingdom

POM

EXP:

270


Urokinase UKR
10,000 I.U.
powder for solution for injection or infusion
LOT:
EXP:
Urokinase UKR
10,000 I.U.
powder for solution for injection or infusion
14274-00
7257
4 037353 123007
Urokinase UKR
10,000 I.U.
powder for solution for injection or infusion
Intravenous use only.
Read the package leaflet before use.
One vial of 10,000 I.U. lyophilized urokinase is to be reconstituted with 2 ml of water for injection.
Do not store above 25 °C. Keep the container in the outer carton to protect from light.
Keep out of the reach and sight of children.
Urokinase UKR
10,000 I.U.
powder for solution for injection or infusion
Human urokinase
POM
UKR Regulatory Affairs Ltd.
The Bull Pen,
Home Farm, Banbury Road,
Caversfield,
Nr Bicester,
OX27 8TG,
United Kingdom
Urokinase UKR
10,000 I.U.
powder for solution for injection or infusion
Active ingredient: Human urokinase 10,000 I.U.
Each box contains one vial of lyophilized urokinase.
Excipients:
Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Powder for solution for injection or infusion.
MA No.:
82100-VAGB
06.09
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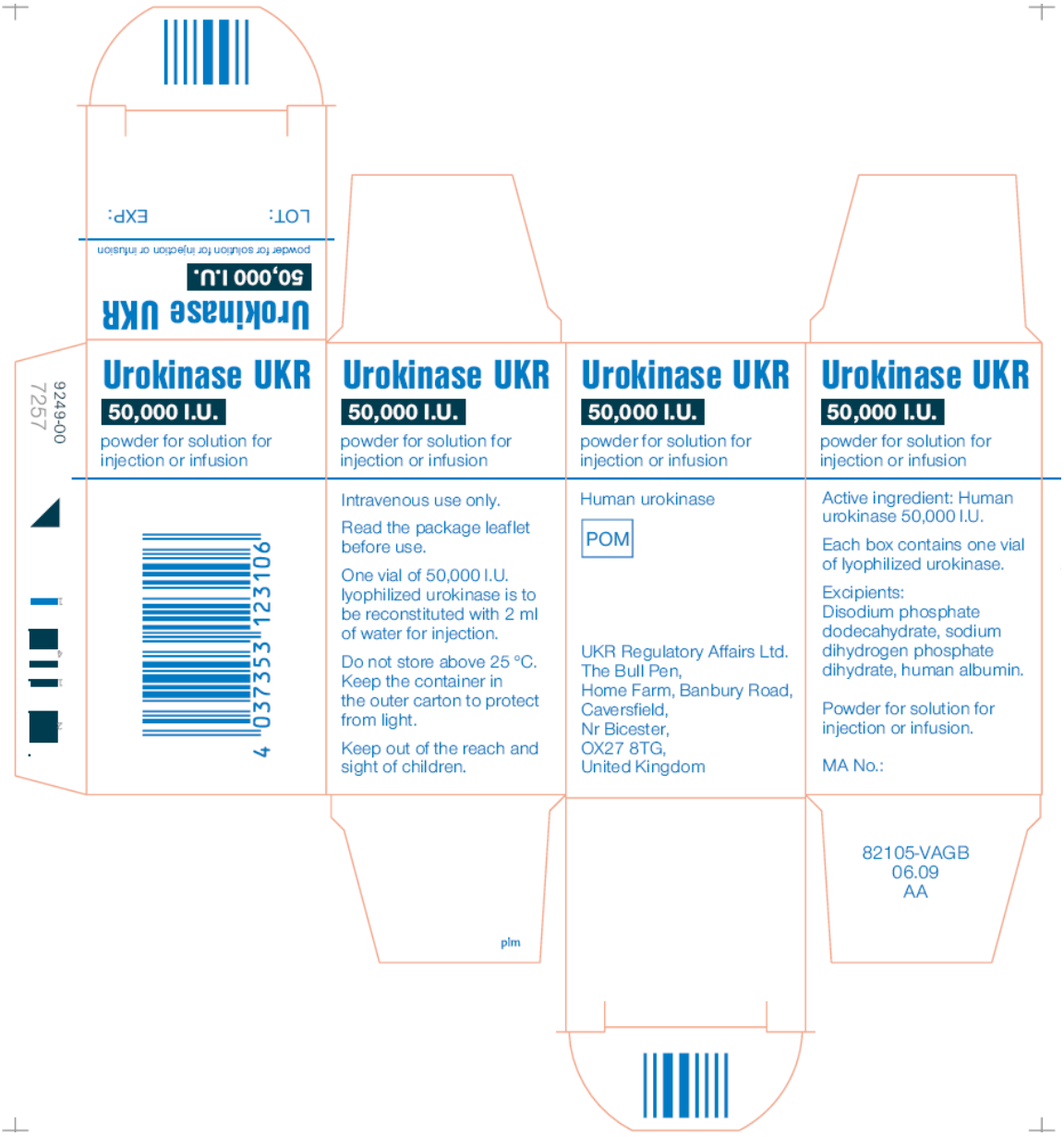
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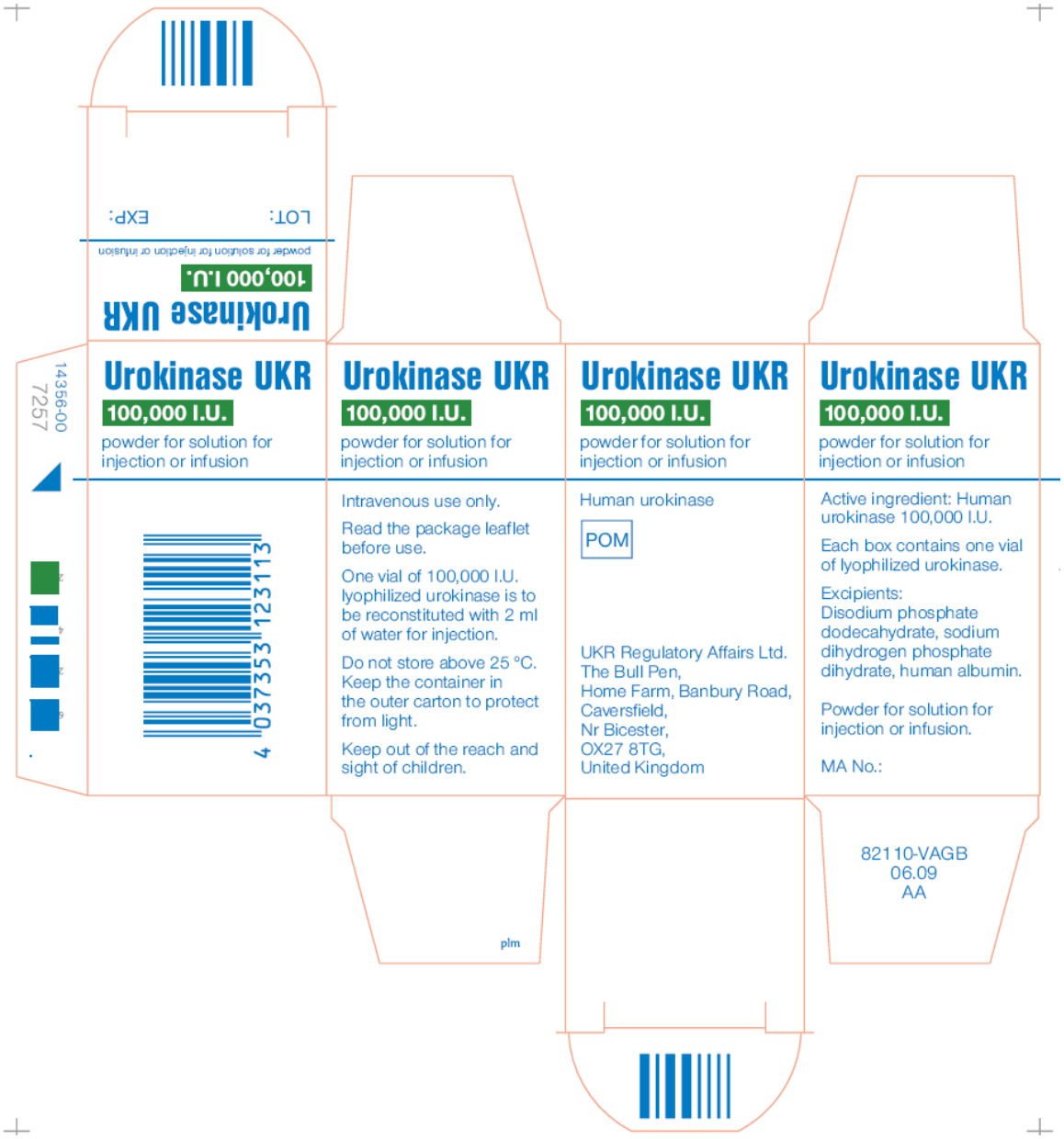
50,000 I.U.
powder for solution for injection or infusion
LOT:
EXP:
9249-00
7257
Urokinase UKR
50,000 I.U.
powder for solution for injection or infusion
4 037353 123106
Urokinase UKR
50,000 I.U.
powder for solution for injection or infusion
Intravenous use only.
Read the package leaflet before use.
One vial of 50,000 I.U. lyophilized urokinase is to be reconstituted with 2 ml of water for injection.
Do not store above 25 °C. Keep the container in the outer carton to protect from light.
Keep out of the reach and sight of children.
plm
Urokinase UKR
50,000 I.U.
powder for solution for injection or infusion
Human urokinase
POM
UKR Regulatory Affairs Ltd.
The Bull Pen,
Home Farm, Banbury Road,
Caversfield,
Nr Bicester,
OX27 8TG,
United Kingdom
Urokinase UKR
50,000 I.U.
powder for solution for injection or infusion
Active ingredient: Human urokinase 50,000 I.U.
Each box contains one vial of lyophilized urokinase.
Excipients:
Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Powder for solution for injection or infusion.
MA No.:
82105-VAGB
06.09
AA


Urokinase UKR
100,000 I.U.
powder for solution for injection or infusion
LOT:
EXP:
14356-00
7257
4 037353 123113
Urokinase UKR
100,000 I.U.
powder for solution for injection or infusion
Intravenous use only.
Read the package leaflet before use.
One vial of 100,000 I.U. lyophilized urokinase is to be reconstituted with 2 ml of water for injection.
Do not store above 25 °C. Keep the container in the outer carton to protect from light.
Keep out of the reach and sight of children.
Urokinase UKR
100,000 I.U.
powder for solution for injection or infusion
Human urokinase
POM
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The Bull Pen,
Home Farm, Banbury Road,
Caversfield,
Nr Bicester,
OX27 8TG,
United Kingdom
Urokinase UKR
100,000 I.U.
powder for solution for injection or infusion
Active ingredient: Human urokinase 100,000 I.U.
Each box contains one vial of lyophilized urokinase.
Excipients:
Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Powder for solution for injection or infusion.
MA No.:
82110-VAGB
06.09
AA
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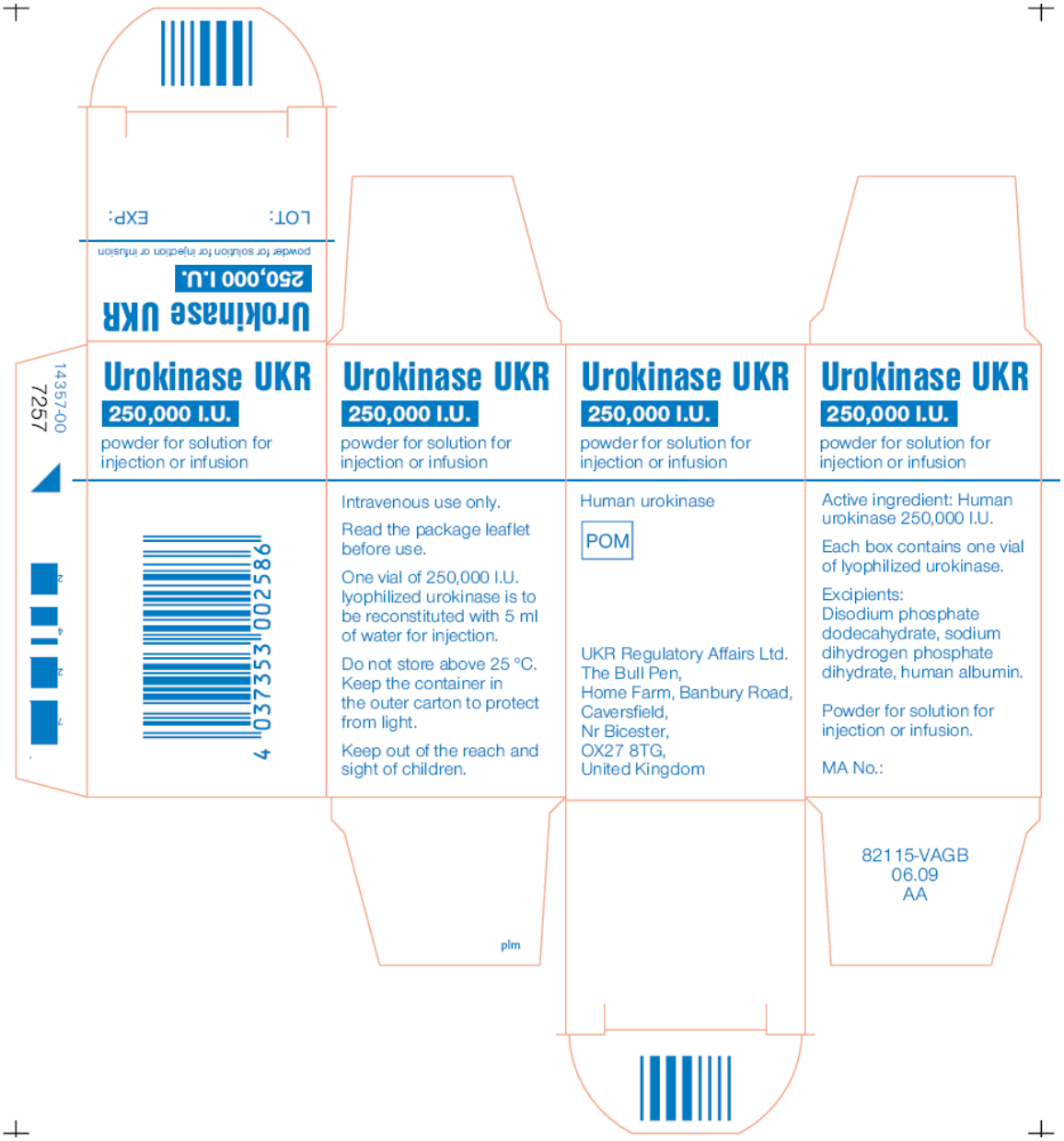
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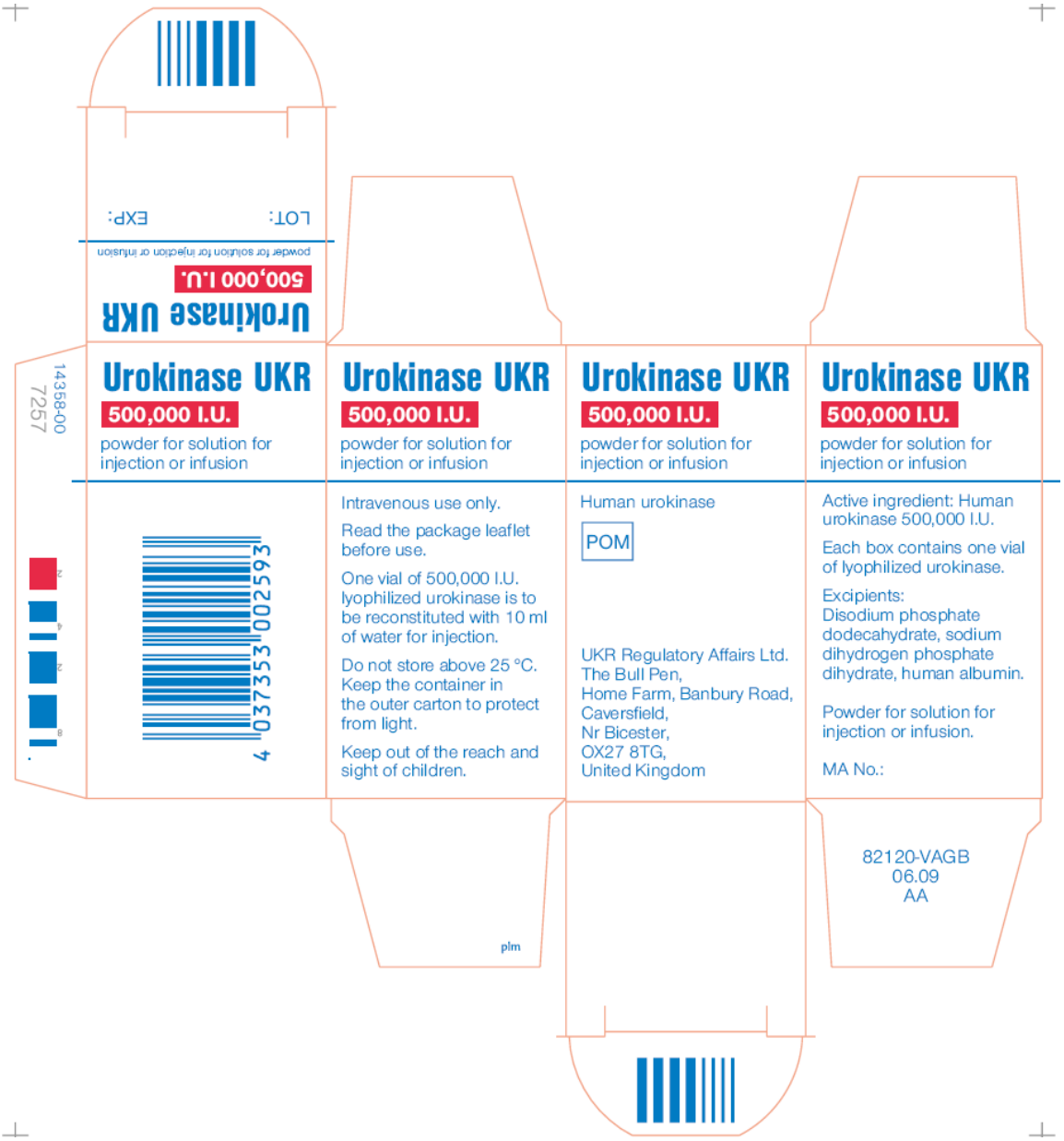
250,000 I.U.
powder for solution for injection or infusion
LOT:
EXP:
14357-00
7257
4 037353 002586
Urokinase UKR
250,000 I.U.
powder for solution for injection or infusion
Intravenous use only.
Read the package leaflet before use.
One vial of 250,000 I.U. lyophilized urokinase is to be reconstituted with 5 ml of water for injection.
Do not store above 25 °C. Keep the container in the outer carton to protect from light.
Keep out of the reach and sight of children.
plm
Urokinase UKR
250,000 I.U.
powder for solution for injection or infusion
Human urokinase
POM
UKR Regulatory Affairs Ltd.
The Bull Pen,
Home Farm, Banbury Road,
Caversfield,
Nr Bicester,
OX27 8TG,
United Kingdom
Urokinase UKR
250,000 I.U.
powder for solution for injection or infusion
Active ingredient: Human urokinase 250,000 I.U.
Each box contains one vial of lyophilized urokinase.
Excipients:
Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Powder for solution for injection or infusion.
MA No.:
82115-VAGB
06.09
AA


Urokinase UKR
500,000 I.U.
powder for solution for injection or infusion
LOT:
EXP:
14358-00
7257
4 037353 002593
Urokinase UKR
500,000 I.U.
powder for solution for injection or infusion
Intravenous use only.
Read the package leaflet before use.
One vial of 500,000 I.U. lyophilized urokinase is to be reconstituted with 10 ml of water for injection.
Do not store above 25 °C. Keep the container in the outer carton to protect from light.
Keep out of the reach and sight of children.
plm
Urokinase UKR
500,000 I.U.
powder for solution for injection or infusion
Human urokinase
POM
UKR Regulatory Affairs Ltd.
The Bull Pen,
Home Farm, Banbury Road,
Caversfield,
Nr Bicester,
OX27 8TG,
United Kingdom
Urokinase UKR
500,000 I.U.
powder for solution for injection or infusion
Active ingredient: Human urokinase 500,000 I.U.
Each box contains one vial of lyophilized urokinase.
Excipients:
Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, human albumin.
Powder for solution for injection or infusion.
MA No.:
82120-VAGB
06.09
AA