SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Syner-KINASE ® 25,000 IU powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25,000 IU of urokinase produced from human urine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White powder for solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Syner-KINASE® is indicated for the lysis of blood clots in the following conditions:

- thrombosed intravascular catheters and cannulae
- extensive acute proximal deep vein thrombosis
- acute massive pulmonary embolism
- acute occlusive peripheral arterial disease with limb threatening ischemia

4.2 Posology and method of administration

Syner-KINASE® must be restricted to hospital use only. Adequate diagnostic and monitoring techniques should be available.

Posology

The dose of Syner-KINASE may be adjusted individually depending on the clinical condition and response to treatment.

Thrombosed intravascular catheters and cannula

5,000 to 25,000 IU Syner- KINASE® should be dissolved in the volume of solvent required to completely fill the lumen of the catheter or cannula and locked for a duration of 20 to 60 minutes. The lysate is then aspirated and the procedure repeated if necessary.

Alternatively, an infusion of up to 250,000 IU Syner-KINASE® can be administered into the catheter or cannula over a period of 90 to 180 minutes using a solution of 1,000 to 2,500 IU/ml in the solvent.

Extensive acute proximal deep vein thrombosis

An initial loading dose of 4,400 IU/kg body weight dissolved in 15 ml solvent should be infused in a peripheral vein over 10 minutes followed by 4,400 IU/kg/hour for 12-24 hours.

Acute massive pulmonary embolism

An initial loading dose of 4,400 IU/kg body weight dissolved in 15 ml solvent should be infused in a peripheral vein over 10 minutes followed by 4,400 IU/kg/hour for 12 hours. Alternatively, a bolus injection into the pulmonary artery repeated for up to 2 times at 24-hour intervals may be used. An initial dosage of 15,000 IU/kg body weight may be adjusted if necessary for subsequent injections depending on the plasma fibrinogen concentration produced by the previous injection.

Acute occlusive peripheral arterial disease with limb threatening ischaemia

A solution of 2,000 IU/ml (500,000 IU Syner-KINASE® dissolved in 250 ml solvent) should be infused into the clot with angiographic monitoring of progress of treatment. It is recommended that the rate of infusion should be 4,000 IU/minute for 2 hours when angiography should be repeated. Following this, the catheter should be advanced into the occluded segment of vessel and Syner-KINASE® infused at the same rate of 4,000 IU/minute for another 2 hours. The process can be repeated up to 4 times if flow has not been achieved. Once a channel has been created through the blocked segment, the catheter may be withdrawn until it lies proximal to the remaining thrombus. Infusion should continue at the rate of 1,000 IU/minute until the clot has completely lysed. Usually, a dose of 500,000 IU over 8 hours should be sufficient. If the length of the clot has not been reduced by more than 25% after the initial dose of 500,000 IU and further reductions of 10% by subsequent infusions of 500,000 IU, discontinuation of treatment should be considered.

Special populations

Elderly

Available data are limited in patients over 65 years and it is not known whether they respond differently from younger subjects. The initial dosage should be the same as in adults but it may be adjusted subsequently depending on response. Syner-KINASE® 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 or hepatic impairment (see section 5.2). In these cases, the fibrinogen level should not fall below 100 mg/dl.

Paediatric population

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

Syner-KINASE® may be used in children of all ages for the treatment of thrombosed central venous catheters using the same lock procedure as in adults.

Method of administration

The route of administration is by intravenous infusion, intra-arterial injection or local instillation. It must not be given as a subcutaneous or intramuscular injection.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active clinically relevant bleeding
- Recent severe gastrointestinal bleeding
- Recent major surgery
- Recent cerebrovascular accident (e.g. within 2 months)
- Recent trauma including cardiopulmonary resuscitation, thoracic or neurosurgery (e.g. within 2 months)
- Severe hypertension
- Severe hepatic or renal insufficiency unless the patient is receiving renal replacement therapy
- Blood coagulation defects and severe thrombocytopenia
- Aneurysm and arteriovenous malformation
- Intracranial neoplasm or other neoplasm with risk of haemorrhage
- Acute pancreatitis or pericarditis or bacterial endocarditis or sepsis
- Recent obstetric delivery

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 of treatment with urokinase:

- Recent surgery
- Severe cerebrovascular disease
- Moderate coagulation defects including those due to severe renal or hepatic disease
- High likelihood of a left heart thrombus (e.g. mitral stenosis with atrial fibrillation) with possible risk of cerebral embolism
- Cavernous pulmonary diseases
- Genitourinary tract diseases with existing or potential sources of bleeding (e.g. implanted bladder catheter)
- Known septic thrombotic disease
- Elderly patients, especially those over 75 years of age

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. Venipuctures and invasive venous procedures should be performed as infrequently as possible and with care to minimise 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 during systemic treatment with Syner-KINASE®, treatment should be stopped immediately and measures to manage the bleeding implemented (see section 4.9).

Concomitant administration of urokinase with other thrombolytics, anticoagulants or anti-platelet agents may increase the risk of bleeding (see section 4.5).

Concomitant administration of urokinase with angiotensin converting enzyme (ACE) inhibitors, may increase the risk of angioedema (see section 4.5)

Syner-KINASE® contains highly purified urokinase which is obtained from human urine. Products manufactured from human source materials have the potential to transmit infectious agents.

Procedures to control such risks strongly reduce but cannot completely eliminate the risk of transmitting infectious agents.

Therapeutic monitoring

Before thrombolytic therapy the following laboratory tests are indicated: thrombin time (TT), activated partial thromboplastin time (aPTT), prothrombin time (PT), haematocrit and platelet count. If heparin has been given it should be discontinued (unless the patient is receiving haemodialysis) and the TT or aPTT should be less than twice the normal control value before thrombolytic therapy is started.

Therapeutic monitoring should consist of circulating fibrinogen levels and fibrinogen degradation products. However, these tests do not reliably predict efficacy and bleeding complications.

After fibrinolytic therapy has been completed, suitable anticoagulant therapy should be considered provided that the TT or aPTT is less than twice the normal control value.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Loss of activity of urokinase has been noted when dissolved in 5% glucose at a concentration of 1,500 IU/ml and stored in PVC containers (see section 6.2). No information is available regarding other dilutions of urokinase.

Anticoagulants

Concurrent administration of oral anticoagulants or heparin may increase the risk of haemorrhage.

Medicinal products affecting platelet function

Concurrent administration of substances that affect platelet function (e.g. acetylsalicylic acid, clopidogrel, other non-steroidal anti-inflammatory agents, dipyridamole, dextrans) may increase the risk of haemorrhage

Angiotensin converting enzyme (ACE) inhibitors

These agents are able to inhibit the breakdown of bradykinin that can be generated through the fibrinolysis pathway. Therefore, concomitant administration of urokinase with ACE inhibitors may increase the risk of angioedema.

Contrast agents

Contrast agents may delay fibrinolysis.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of urokinase in pregnant women. Syner-KINASE® should not be given during pregnancy or in the immediate post-partum period unless clearly necessary.

Breast-feeding

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

Fertility

No human data on the effect of urokinase on fertility are available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

There are limited data available on the adverse effects of urokinase from controlled clinical trials. The adverse reactions described below reflect the available data from these clinical trials and the clinical use of urokinase in the general population, where it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Haemorrhage

The most frequent and severe adverse effect of urokinase therapy is haemorrhage. 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.

Embolism

Embolic episodes may occur after fragments of clot have been released. Cholesterol embolisms have also been reported.

Hypersensitivity reactions

Urokinase is reportedly non-antigenic but mild hypersensitivity reactions including urticaria, rash, bronchospasm and very rare cases of fatal anaphylaxis have been reported.

Infusion reactions

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

Other infusion reactions 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 urticaria, dyspnoea, hypotension, flushing, rash
Very rare	Anaphylaxis
Nervous system disorders	

Common	Stroke
Vascular disorders	
Very common	Haemorrhage, including from puncture site and wound Epistaxis, gingival bleeding Thromboembolism Embolism, including pulmonary embolism Haematuria (microscopic)
Common	Gastrointestinal haemorrhage, intracranial haemorrhage, retroperitoneal haemorrhage, urogenital haemorrhage, muscle haemorrhage Artery dissection Cholesterol embolism
Uncommon	Intrahepatic haemorrhage
Rare	Vascular pseudoaneurysm Haematuria (macroscopic)
Renal and urinary disorders	
Uncommon	Renal failure
General disorders and administration site conditions	
Common	Fever, chills
Investigations	
Very common	Decrease in haematocrit without clinically detectable haemorrhage Transient increase in transaminases

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Haemorrhage that occurs during treatment with Syner-KINASE® may be controlled with local pressure and treatment continued. If severe bleeding occurs, treatment with Syner-KINASE® must be stopped and inhibitors such as aprotinin, epsilon-amino caproic 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

Pharmacotherapeutic group: antithrombotic agent, ATC code: B01AD04.

Syner-KINASE® is a highly purified form of naturally occurring human urokinase extracted from urine. It is a thrombolytic agent which converts plasminogen into plasmin (fibrinolysin) a proteolytic enzyme that breaks down fibrin as well a 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 fibrinogen 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 up to 20 minutes. The inactive degradation products are excreted primarily by the kidneys and in bile. Elimination is delayed in patients with liver disease and impaired kidney function.

5.3 Preclinical safety data

There are no pre-clinical safety data of additional value to the prescribing physician.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Disodium edetate

Disodium phosphate dodecahydrate

Sodium hydroxide

6.2 Incompatibilities

Syner-KINASE® should be reconstituted before use only with the solvent described in Section 6.6. It has been reported to lose 15-20% of its activity in solutions of 5% glucose containing 1,500 units/ml in PVC containers. No information is available regarding other dilutions of urokinase.

Syner-KINASE® must not be mixed with other medicinal products.

6.3 Shelf life

25,000IU, 100,000IU strengths – 4 years

10,000IU, 250,000IU and 500,000IU strengths – 3 years

Use reconstituted material immediately

6.4 Special precautions for storage

Do not store above 25ºC.

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

6.5 Nature and contents of container

All single pack presentations are contained in borosilicate clear type 1 (8 ml) glass vials closed with chlorobutyl rubber stoppers and sealed with an aluminium flip-off cap.

Each vial size is colour coded:

10,000 IU - Grey

25,000 IU - Orange

100,000 IU - Green

250,000 IU - Red

500,000 IU - Purple

6.6 Special precautions for disposal

Syner-KINASE® must be reconstituted before use with the correct volume of 9 mg/ml (0.9%) sodium chloride solution for injection (not provided). This produces a colourless solution.

There are no special requirements for the handling of this product.

Posology summary – see details and special populations in section 4.2

Extensive acute proximal deep vein thrombosis

Initial infusion

Loading dose	4,400 IU/kg of body weight
Volume of solvent	15 ml
Infusion time	10 min

Subsequent infusion

Dose	4,400 IU/kg of body weight/hour
Infusion time	12-24 hours

Acute massive pulmonary embolism – infusion or bolus injections

Infusion

Initial infusion

Loading dose	4,400 IU/kg of body weight
Volume of solvent	15 ml
Infusion time	10 min

Subsequent infusion

Dose	4,400 IU/kg of body weight/hour
Infusion time	12 hours

OR

Bolus Injection

Dose	15,000 IU/kg of body weight
Repeat bolus dose	Once every 24 hours, can be repeated up to x2. The dose of the subsequent bolus injections can be adjusted if necessary.

Acute occlusive peripheral arterial disease with limb threatening ischaemia (do not administer intravenously)

Initial dose	500,000 IU
Volume of solvent	250 ml
Recommended infusion rate	4,000 IU/min (2 ml/min)
Infusion time	2 hours
Repeat infusion	Advance catheter into occluded segment of vessel and repeat infusion
This process can be repeated up to 4 times if flow has not been achieved.	

If the length of the clot has not been reduced by >25% after the initial dose of 500,000 IU and further reduced by 10% by subsequent infusions of 500,000 IU, discontinuing treatment should be considered.

Once a channel has been created through blocked segment

Infusion rate	1,000 IU/min
Additional dose	500,000 IU over 8 hours depending on clinical condition and response to treatment.

Instructions on administration are provided in Section 4.2.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

Syner-KINASE® 10,000 IU powder for solution for injection/infusion
20675-0006
Syner-KINASE ® 25,000 IU powder for solution for injection/infusion
20675-0001
Syner-KINASE® 100,000 IU powder for solution for injection/infusion
20675-0002
Syner-KINASE® 250,000 IU powder for solution for injection/infusion
20675-0003
Syner-KINASE® 500,000 IU powder for solution for injection/infusion
20675-0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2006-09-21

10 DATE OF REVISION OF THE TEXT

23/12/2024