SYNER-KINASE

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Syner-KINASE® 10,000 IU
Syner-KINASE ® 25,000 IU
Syner-KINASE® 100,000 IU
Syner-KINASE® 250,000 IU
Syner-KINASE® 500,000 IU

Powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10,000, 25,000, 100,000, 250,000 or 500,000 IU of urokinase produced from human urine.

For a 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® should be restricted to hospital use only. Adequate diagnostic and monitoring techniques should be available.

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.

Instructions on reconstitution with the recommended solvent are provided in section 6.6.

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 3 times in 24 hours 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
The initial dosage as in adults should be used but the dosage may be adjusted 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).

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.

4.3 Contraindications

- Hypersensitivity to urokinase or to any of the excipients
- Active clinically relevant 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
- Aneurysm
- Intracranial neoplasm
- Acute pancreatitis or pericarditis or bacterial endocarditis

4.4 Special warnings and special 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 severe gastrointestinal bleeding
- Recent surgery
- Recent obstetric delivery
- Severe cerebrovascular disease
- Moderate coagulation defects including those due to severe renal or hepatic disease
- High likelihood of a left heart thrombus
- Known septic thrombotic disease
- Elderly patients, especially those over 75 years of age

If severe bleeding occurs during systemic treatment with Syner-KINASE®, treatment should be stopped immediately (see section 4.9). Bleeding from puncture sites may be controlled with local pressure.

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

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, other non-steroidal anti-inflammatory agents, dipyridamole, and dextrans) may increase the risk of haemorrhage.

4.6 Fertility, pregnancy and lactation

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.

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

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.

The most frequent and severe adverse effect of urokinase therapy is haemorrhage, with puncture site being the most common location. Intracranial (including fatal cases), hepatic and gingival haemorrhages have also been reported.

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

Urokinase is reportedly non-antigenic but hypersensitivity reactions including urticaria and very rare cases of fatal anaphylaxis have been reported. Infusion reactions including fever and shaking chills (rigors) have also been reported.

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 Anaphylaxis

Nervous system disorders

Common	Stroke

Vascular disorders

Very Common	Haemorrhage, including from puncture site and wound Epistaxis Thromboembolism Embolism, including pulmonary embolism Haematuria (microscopic)
Common	Haematoma, including intracranial, retroperitoneal and at puncture site Gastrointestinal haemorrhage, intracranial haemorrhage

	Artery dissection
	Cholesterol embolism
Rare	Vascular pseudoaneurysm
	Hematuria (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

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

ATC code: B01A D04, antithrombotic agent.

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.

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 Instructions for use and handling

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.

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	MA20675/0006
Syner-KINASE®	25,000 IU	MA20675/0001
Syner-KINASE®	100,000 IU	MA20675/0002
Syner-KINASE®	250,000 IU	MA20675/0003
Syner-KINASE®	500,000 IU	MA20675/0004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Syner-KINASE® 25,000 IU, 100,000 IU, 250,000 and 500,000 IU
21st September 2006.

Syner-KINASE® 10,000 IU: 15th August 2008.

10. DATE OF REVISION OF THE TEXT

29 February 2016