Syner-KINASE® is a registered trademark

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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 cannulae
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).

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**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**
25,000 IU, 100,000 IU strengths – 4 Years
10,000 IU, 250,000 IU and 500,000 IU strengths – 3 Years
Use reconstituted material immediately.

**6.4 Special precautions for storage**
Do not store above 25°C.
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.
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-aminocaproic acid, p-aminomethylbenzoic 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 preclinical 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

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 thrombolitics, 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.
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.

The following frequency convention was used as a basis for the evaluation of undesirable effects:

<table>
<thead>
<tr>
<th>Frequency</th>
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<tr>
<td>Very common</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥ 1/100 to &lt; 1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥ 1/1,000 to &lt; 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥ 1/10,000 to &lt; 1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000</td>
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### 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