COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Urokinase Devrimed 10,000 IU, 25,000 IU, 100,000 IU, 250,000 IU and 500,000 IU powder for solution for injection or infusion (human urokinase)

NL/H/4884/001-005/MR

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Urokinase Devrimed 10,000 IU, 25,000 IU, 100,000 IU, 250,000 IU and 500,000 IU powder for solution for injection or infusion. The procedure was finalised in the United Kingdom (UK/H/6520/001-005/MR). After a transfer in 2020, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Syner-KINASE

(Human Urokinase)

PL 20675/0001
PL 20675/0002
PL 20675/0003
PL 20675/0004
PL 20675/0005
PL 20675/0006

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Syner-KINASE

(Human Urokinase)

PL 20675/0001
PL 20675/0002
PL 20675/0003
PL 20675/0004
PL 20675/0005
PL 20675/0006

LAY SUMMARY

The MHRA granted Syner-Medica Ltd Marketing Authorisations (licences) for the medicinal products Syner-KINASE 25,000, 100,000, 250,000, 500,000 and 1,000,000 IU (PL 20675/0001-5) and Syner-KINASE 10,000 IU (PL 20675/0006). This medicine is prescription only and is indicated for the lysis of blood clots in the following conditions:

a) Intravascular catheters and cannulae that are blocked by clots.
b) Blockage of blood vessels by clots in conditions such as deep vein thrombosis, pulmonary embolism and peripheral vascular occlusion.

National Marketing Authorisations for PL 20675/0001-5 were granted on 21st September 2006, and subsequently a national Marketing Authorisation for PL 20675/0006 was granted on 15th August 2008.

Syner-KINASE is a powder for solution for injection, which contains the active ingredient human urokinase, an antithrombotic (clot buster) agent. Urokinase is a naturally occurring enzyme which plays an important part in the control of clotting in humans and is a normal constituent of the body. Urokinase is purified from human male urine and it is used as a thrombolytic agent to clear clots in the cardiovascular system or catheters inserted into blood vessels.

As this application was submitted under article 10a – 'well established use'- no specific clinical or non-clinical studies have been carried out using this product. However, a critical review of the supporting literature and the pharmaceutical data presented to the MHRA demonstrated that Syner-KINASE is effective in the lysing of blood clots under the stated conditions. The product has been used on a named patient basis since February 2002 and no adverse events have been reported to the company. The side effects of Syner-KINASE were very similar to those seen with other thrombolytic agents and there were no unexpected safety concerns. It was therefore judged that the benefits of using this product outweighed the risks, hence a Marketing Authorisation has been granted.

Syner-KINASE

(Human Urokinase)

PL 20675/0001
PL 20675/0002
PL 20675/0003
PL 20675/0004
PL 20675/0005
PL 20675/0006

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted Marketing Authorisations to Syner-Medica for the medicinal products Syner-KINASE 25,000, 100,000, 250,000, 500,000 and 1,000,000 IU (PL 20675/0001-5) on 27th September 2006 and Syner-KINASE 10,000 IU (PL 20675/0006) on 15th August 2008. The products are prescription only and intended for use in adults, children and the elderly.

This was a stand-alone, national application for Syner-KINASE, containing the active ingredient urokinase, submitted under Article 10a of Directive 2001/83/EC as amended with supporting literature references for the claim of 'well established use'.

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

a) thrombosed intravascular catheters and cannula that are blocked by fibrin clots,
b) thromboembolic occlusive vascular disease such as deep vein thrombosis, pulmonary embolism, and peripheral vascular occlusion.

The active ingredient, urokinase, is a natural human enzyme which has been isolated from normal human male urine and purified. It is a normal constituent of the human body.

Syner-KINASE is for administration by intravascular injection or infusion only following reconstitution with the correct volume of sterile physiological saline. The lysate is then aspirated and the procedure repeated if necessary. Alternatively, a solution of 5,000 Syner-KINASE dissolved in 200ml sterile physiological saline can be infused into the catheter or cannulae over 30 minutes, but this may be less effective.

QUALITY ASSESSMENT

I. INSPECTION STATUS

Both the bulk drug substance and the finished product are manufactured in Italy and GMP approval by the Italian authorities has been provided for these facilities.

Crude urokinase is manufactured in China. Adequate information has been provided to give confidence that the site and associated QC facilities have suitable levels of GMP compliance. The applicant has provided copies of the original inspection report for the facility where the initial crude urokinase extraction takes place and its associated QC centre. A follow up audit was carried out August 2005, and the complete report has been submitted.

The Company have provided the Audit reports of the Urokinase semi-purified processing unit carried out in October 2004 and the follow up audit in August 2005, confirming an adequate level of GMP compliance at this facility also. The Company has committed to audit/inspect both the manufacturing and QC facilities in every 2-3 years to ensure the level of GMP compliance is maintained while this product is actively marketed within the UK.

II. INTRODUCTION

These are national applications for urokinase intended for intra-vascular administration. The products are presented as powders for solution and injection. The applications are submitted under article 10a of Directive 2001/83/EC as amended with supporting literature references for the claim of 'well established use'. Module III of the application is provided in full.

Urokinase is a serine protease that catalyses conversion of plasminogen to plasmin with resultant fibrinolytic and thrombolytic properties. Urokinase is used in the unblocking of fibrin clots from intravascular catheters and cannulae, and in thromboembolic occlusive vascular disease.

Dosage is dependent on the indication and up to 2 million units may be administered as a bolus in treatment of acute myocardial infarction.

The applicant has provided evidence of a demand for urokinase in the UK, mainly for use in end stage renal disease patients on haemodialysis. This demand is currently met under provisions for unlicensed medicines and, since February 2002, some 85,000 vials of urokinase have been supplied to hospitals in the UK. The urokinase supplied to UK hospitals is Urokinase Crinos and is distributed via Syner-Medica. This product is marketed in Italy and is stated to be identical in composition and source of urokinase and manufactured at the same site as the products in these applications.

III. DRUG SUBSTANCE

III.1 General information

A monograph for urokinase is included in the European Pharmacopoeia. Urokinase is isolated and purified from human urine and consists of mixture high molecular mass (MW~54,000) and low molecular mass (MW~33,000) forms. The HMW fraction accounts for about 95% of the total protein from this source.

III.1.1 Nomenclature

INN: Urokinase
Human urinary-type plasminogen activator (u-PA).

III.1.2 Structure

Satisfactory information on the structure of pro-urokinase (scu-PA) and urokinase (u-PA) has been provided. Primary and two dimensional structures of pro-urokinase have been reproduced from literature. Urokinase is recovered from urine in high (HMW-uk) and low (LMW-uk) forms. The molecular weight of HMW-uk is 53-54,000 and LMW-uk is 33,000.

III.2 Manufacture

III.2.1 Manufacturers

Three manufacturers are involved in the production of urokinase, the site of initial urokinase extraction, the site of semi-purification of urokinase, and the site of purification of bulk urokinase.

III.2.2 Description of Manufacturing Process and Process Controls

Crude urokinase activity 100-300 IU/mg
The applicant has provided adequate assurance that there is minimal likelihood of a viral contamination being present in the product following the appropriate testing regimen of the semi-purified urokinase, the viral clearance factors of the process, and the falling levels of HBV infected donors.

At present the level of the HIV infection in China is 0.05% of the population, and it could be argued that this value is likely to increase. However the population donating urine (5-19 years old) is another factor to help ensure the viral safety of the product, as it is unlikely that the infection rate is anywhere near that of the general population, at least at the present time.

With respect to monitoring donation sites for serious outbreaks of disease, a system is in place to trace individual batches of crude and semi-purified Urokinase back to the period the urine was collected, should there be a notification of a serious disease outbreak either nationally or locally.

The stability data for two recent batches of drug substance has been provided, each with only 6 months data. The Company have committed to provide the full study report on completion of both studies

The drug substance batch data thus presented are acceptable.

Stability data have been provided for 2 batches each of the 100,000 IU and 250,000 IU strengths and 4 batches of the 25,000 IU strength. These studies should be completed this year**.**

The 1,000,000 IU presentation is rarely manufactured. The company has committed to placing the next batch that is manufactured on stability and report the results to the regulatory authorities upon its completion. In the meantime the data from the 500,000 IU presentation confirms the higher concentration stability that is regularly marketed.

A description of the sanitisation process of the ion exchange column has been provided.

The company has evaluated all chromatography steps with respect to bioburden removal, and implemented bioburden monitoring throughout the manufacturing process.

The Company has confirmed that shipping trials for crude, semi-pure and purified Urokinase will be implemented.

Semi-purified urokinase, activity > 50,000 IU/mg
Blended crude urokinase is transferred to the manufacturer of the semi-purified urokinase. Details of the transfer schedule have been provided.

Synthesis of semi-purified urokinase from crude urokinase has been adequately and thoroughly described. The conditions, purifications processes are described.

Appropriate in-process controls are in place, and suitable specifications and test methods are applied to the intermediate product.
Validation reports for viral screening have been provided.

Purified urokinase
Semi-purified urokinase is transferred to the final manufacturer for purification. Storage and transfer conditions have been described and are assessed to be adequate.

III.2.3 Control of Materials

Materials used at each stage of the process have been stated. Certificates of analysis have been provided for all components used and those where identity tests are carried out upon receipt at the manufacturing facility has been highlighted.

Human male urine is the only material of biological origin used in the process. The volume of urine required for production of urokinase mitigates against testing of individual donations, as acknowledged in the CPMP position statement 118/95 concerning products derived from human urine. Viral inactivation and removal stages have been included in the purification process and have been validated for inactivation/removal of viruses.

Each batch of semi-purified and purified urokinase is tested for the absence of HIV-1/2, Hepatitis C and Hepatitis B using validated nucleic acid amplification techniques.

Arginine is produced by bacterial fermentation, no animal-derived materials are used in the production process.

III.2.4 Controls of Critical Steps and Intermediates

Critical steps in the process have been adequately described.

III.2.5 Process Validation and/or Evaluation

All purification stages and viral inactivation and removal steps have been validated.

III.2.6 Manufacturing Process Development

The process is stated to be based on established published methods.

III.3 Characterisation

III.3.1 Elucidation of Structure and other Characteristics

Complete amino acid sequencing has not been conducted since the substance is extracted from human urine without modification. Evidence in support of the molecular structure is provided from peptide mapping and similar chromatographic profiles have been demonstrated with the reference.
Overall, the applicant has provided satisfactory evidence of structure and characteristics such as fibrinolytic activity.

The applicant has not provided immunological characterisation data on account of the human origin of the enzyme and inclusion of a species selective identity control in the substance specification.

III.3.2 Impurities

Impurities can be either derived from the starting material, created during preparation of crude, semi-purified and purified urokinase, caused by contaminants (e.g. bacteria) or substances related to the product itself.

The applicant has discussed the fate of potential impurities arising from the various steps throughout the extraction and purification and these are well summarised in the dossier. The likelihood of significant contamination from urine and chemicals used in the process is discounted on account of the various purification process steps. Likewise, contamination from purification materials is discounted on account of the process design. Other urinary proteins are anticipated to be removed during the initial extraction process for crude urokinase and thereafter through the purification stages. In-process controls and product release data have not provided any evidence of contamination by extraneous proteins.

III.4 CONTROL OF DRUG SUBSTANCE

III.4.1 Drug Substance Specification

The drug substance specification has been provided and is compliant with the Ph. Eur. Monograph.

III.4.2 Analytical Procedures

Non-pharmacopoeial analytical methods have been described.

III.4.3 Validation of Analytical Procedures

All non-compendial release assays have been suitably validated.

III.4.4 Batch Analyses

Appropriate data have been provided on batches of product manufactured at a production scale.
All reported results comply with the specification in place at the time.

III.4.5 Justification of Specification

The specification has been justified in relation to the Ph Eur monograph for urokinase. Proposed limits for chlorobutanol, arginine and aminocaproic acid (ACA) along with aggregates and very low MW fragments (SDS PAGE) are based on batch histories. Chlorobutanol is used as a preservative in other approved UK parenteral products and ACA has also been included in other UK parenteral products, in view of this and the trace levels in these products, no safety concerns arise.

III.5 Reference Standards or Materials

The preparation of all standards has been described. The standards have been suitably characterised and calibrated.

III.6 Container Closure System

This has been described and specifications of the drug substance containers have been provided. Integrity testing data on all containers used in the shipment of partially purified urokinase has been provided.

III.7 Stability

III.7.1 Stability Summary and Conclusions

The data provided generally support the physicochemical and biological stability of the drug substance under the storage and handling conditions described.

III.7.2 Post-Approval Stability Protocol and Stability Commitment

The stability studies reported in the dossier include three production batches studied over the proposed ‘shelf-life’.

III.7.3. Stability Data

Stability studies include long-term testing of three industrial batches produced in 1997, freeze-thaw testing of one batch (1996) and stress testing of a further batch of purified urokinase.

In the long-term testing all batches retained 90% of initial potency over 24 months storage and all other tests complied with the specification.
In the freeze-thaw testing all results were within the variability of the assay and no evidence of a trend was apparent.
Stress test studies indicated that analytical methods for control of the drug substance were sensitive to significant degradation of the drug substance.

IV. DRUG PRODUCT

IV.1 Composition of the Drug Product

Syner-KINASE is presented as a lyophilised powder for solution for injection. The excipients are well known pharmaceutical ingredients. The powder is packed into 8ml colourless glass (Type I) vials and closed with a chlorobutyl rubber stopper and aluminium flip-off cap. The active ingredient comprises about 0.2 (25,000IU) to 8mg (1MIU) of the weight of the vial contents.

IV.2 Pharmaceutical Development

The composition of the product has been discussed in relation to other approved urokinase products on the Italian market. The development pharmaceutics are adequately described.

IV.3 Manufacture

IV.3.1 Batch Formula

Batch formulae have been provided for each of the different strength compositions at two different batch sizes.

IV.3.3 Description of Manufacturing Process and Process Controls

A satisfactory account of the manufacturing process has been provided.

The manufacturing facility has been appropriately described in the dossier and room grades for preparation and filling of the solutions are in accordance with GMP requirements.

The limits for prefiltration bioburden are provided and meet the required specification.

The final filtration step is adequate and a bacterial challenge test has been performed which conforms to that described in Ph. Eur 5.1.1 and is therefore acceptable.

IV.3.4 Control of Critical Steps and Intermediates

The critical steps have been described.

IV.3.5 Process Validation and/or Evaluation

The process was appropriately validated.

Historical batch records have been provided as evidence of the suitability of the manufacturing process. These are acceptable to demonstrate the suitability of the process in relation to the physicochemical and biological properties of the product.

Validation of the new manufacturing facility was carried out using 3 batches each of drug product at the lowest and highest strengths.

All batches used in the validation of lyophilisation samples met the required specifications

Media fill of vials was adequately validated.

The company provided batch analysis data from 3 batches of drug product at the 1 million IU strength. All batches met the required specification. The Company has committed to provide validation data for lyophilisation samples for the highest strength to the competent authorities within 6 months following licensure of the product as a post-approval commitment.

IV.4 Control of Excipients

IV.4.1 Specifications

Mannitol, disodium edetate, disodium phosphate dodecahydrate, sodium hydroxide and water for injections are controlled in accordance with Ph Eur. Certificates of analysis of excipients have been provided, all of which contain microbial counts. The only exception to this are disodium phosphate dodecahydrate and sodium hydroxide, as these are inorganic components and unlikely to support microbial growth. Specifications for all excipients are set following the respective Ph Eur monographs.

No excipients are of human or animal origin.

IV.5 Control of Drug Product

IV.5.1 Finished Product Specification for Syner-KINASE 25,000 IU

The finished product specification has been provided and is compliant with the Ph. Eur. Monograph.

IV.5.2 Analytical Procedures

The non-pharmacopoeial analytical methods have been adequately described.

IV.5.3 Validation of Analytical Procedures

All non-compendial release assays have been suitably validated.

IV.5.4 Batch Analyses

Analytical results have been provided and comply with the specification. Data supports the manufacturing overage as defined by the applicant.

IV.5.5 Characterisation of Impurities

No information in addition to that provided for the drug substance has been submitted. The applicant states that the manufacturing process does not change the impurity profile. This is supported by results of batch analysis and stability studies.

IV.5.6 Justification of Specification(s)

The company has supplied results for urokinase molecular fractions for all the batches placed in stability data studies, all of which met the required specification.

IV.6 Reference Standards or Materials

The reference standards are as described for the drug substance.

IV.7 Container Closure System

The primary container for all product strengths is an 8ml vial composed of colourless, Ph Eur Type I, borosilicate glass. The stopper is composed of chlorobutyl rubber and complies with Ph Eur requirements for Type I closures. An aluminium flip off cap is used to crimp the stopper.

Certificate of conformity for the glass vials confirm that they meet the requirements of the Ph.Eur. general monograph 3.2.1 for Hydrolytic Resistance and Arsenic levels.
Certificate of conformity for the rubber stoppers meet the requirements of the Ph.Eur. general monograph 3.2.9 for Type I rubber closures.

IV.8 Stability

IV.8.1 Stability Summary and Conclusion

Results from long-term, accelerated and reconstitution study comply with the specification. On the basis of these data a shelf-life of 2 years is proposed with the storage conditions ‘Do not store above 25°C’. After reconstitution the solution should be used within 2 hours, if stored at room temperature. Solutions stored in the refrigerator are physically, chemically and biologically stable for up to 48 hours.

The applicant has provided 24 months stability for 250 000 and 100 000 IU strengths Twelve months stability data has also been provided for the 250,000IU strength, and 6 months for the 100, 000 IU strength manufactured at the new facility.

Actual results for molecular fractions over the storage intervals have been reported which fall within the required specification.

Data from 3 batches of the 25,000IU strength manufactured at the new site has been provided with 24 months stability data. In addition, data from 1 batch of the 25,000IU strength manufactured at the new site has been provided with 18 months stability data. All batches conform to specifications at this time. The applicant has committed to supply further results as they become available. It should be noted that HPLC determination of HMW-uk can not be determined at this concentration of Urokinase due to interference from excipients present.

IV.8.2 Post-approval Stability Protocol and Stability Commitment

A commitment to enter one additional batch of 100,000IU and one batch of 1,000,000IU into the long-term stability programme has been provided.

IV.8.3 Stability Data

Reported stability studies include one batch of each strength proposed for marketing. These batches were manufactured in the previous manufacturing facility and are packed into an 18ml volume container. The vial size for the market presentation is 8ml and the larger container in the stability study can be accepted as 'worst case' scenario in relation to headspace.

The 'shelf-life' specification is in line with the 'release' specification and includes additional controls for purity. Acceptance limits for related substances are wider than those in the drug substance specification. Limits for molecular fractions have been widened for HMW-uk in line with Ph Eur monograph for urokinase, and limits for VLMW-uk and aggregates are specified although it is unclear if this is for individual degradants or the total.

Stability samples were stored under long-term and accelerated storage conditions and these reflect ICH recommended conditions at the time of the study. A study of solutions reconstituted in saline according to label instructions and stored for 2 hours at 25°C exposed to light and for 48 hours at 2-8°C has also been conducted for 100,000 and 1,000,000 IU strengths.

The accelerated studies have been completed for all product strengths. Long term storage results are reported out to 36 months storage for one batch each of 100,000, 250,000 and 1,000,000 IU, manufactured in 1997 and for 6 months only for the 25,000 IU presentation which was entered later into the studies.

Batches tested complied with pyrogens, sterility and abnormal toxicity tests after 24 months long-term storage.

The study of reconstituted solutions investigated appearance of solution, pH, potency, molecular fractions, and purity. Storage conditions results and potency results are within the defined limits.

The SPC includes reference to infusions in saline delivered over 8 hours. The stability of infusion solutions under these conditions has been demonstrated and evidence provided.

V. APPENDICES

V.1 Facilities and Equipment

Details of product manufacturing facilities are acceptable.

V.2 Adventitious Agents Safety Evaluation

Prion safety
The applicant complies with CSM precautionary principles (March 2003) for sourcing of plasma and urinary derived medicinal products, in so much as there are no reports of vCJD (or BSE) in China and urine used for the manufacture of the product is restricted to single country origin. No alternative (non-urine) origin urokinase is approved or under assessment in the UK at this time.

Viral safety
Urine donations are not screened for contaminating viruses on account of the large number of donations involved. The semi-purified and purified urokinase is tested for HIV-1/2, Hepatitis B and Hepatitis C using validated nucleic acid amplification techniques and two viral clearance steps are included in the manufacturing process. Both stages have been validated for viral elimination.
An adequate range of challenge viruses were used in these studies.

The validation studies provide assurance of the efficacy of the process for removal of viral contaminants.

Measures to minimise the risk of bacterial contamination have been described in the description of the manufacture of the drug substance and finished product.

V.3 Novel Excipients

Not applicable.

VI. REGIONAL INFORMATION

VII 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 vial labels comply with the minimum requirement for small containers. This is accepted in view of the small pack size (8ml).

The colour differentiation between 100,000 and 500,000 IU strengths was changed to make them more distinct.

VII.2.2 Comment on Expert report

The expert report was prepared by a regulatory consultant with appropriate experience.

VII.2.3 MAA form

Acceptable.

VIII ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

The demand for urokinase for injection in the UK is currently met by importation of product approved for use in Italy, under UK provisions for unlicensed medicines.

The distributor of the Italian product is seeking UK marketing authorisations based on data from the same drug substance and finished product manufacturers as used for product on the Italian market.

The origin of human male urine for separation and purification of urokinase is the Peoples Republic of China.

No cases of vCJD (or BSE) have been reported in China.

Information on purification and control of urokinase and manufacture of the finished product is adequately described from the Nanjing New Century Company, China.

Adequate information on donor screening and of criteria for assessing the suitability of urine donations has been provided and processes involved in the preliminary purifications steps are adequately described. As such it has been decided that the Marketing Authorisation license is approvable.

PRECLINICAL ASSESSMENT

INTRODUCTION

These are national applications for Syner-KINASE under article 10.1a on the basis of "well established use".

Syner-KINASE is a urokinase product derived from human urine and is presented as a powder in vials each containing 10,000, 25,000, 100,000, 250,000, 500,000 or 1,000,000 IU of human urokinase. It is a powder for solution for injection. It is intended for intravascular administration after reconstitution with sterile physiological saline.

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

a) Intravascular catheter or intravenous cannulae that are blocked by fibrin clots.
b) Thromboembolic occlusive vascular disease such as deep vein thrombosis, pulmonary embolism, and peripheral vascular occlusion.

Presentations of urokinase identical to the candidate product are stated to have been registered in Italy and in Spain to other marketing authorisation holders for many years. All of these products are produced by the same contract manufacture as Syner-KINASE (Crinos) to the same formulation and using the same source of urokinase.

The largest area of use for urokinase in the UK is in End Stage Disease Patients on haemodialysis. There has been no registered source in the UK, however, since November 1999 when Serono withdrew their registered urokinase product, Ukidan. Consequently, Syner-Medica Ltd, a sister company to Syner-Med (Pharmaceutical Products) Ltd, was requested by a number of UK clinicians to assist in making urokinase available for managing effectively their respective patients.

Syner-Medica now wishes to formalise the situation by applying for a marketing authorisation in the UK for all six presentations of Syner-KINASE.

The applicant states that it has not been possible to extrapolate to the originator's pre-clinical or clinical data simply because such information would have been generated so many years ago. Indeed it is extremely likely that the original licence was the Italian equivalent of a product licence of right.

Accordingly, no new nonclinical or clinical studies have been conducted in support of this application. Publications and reviews have been referred to which confirm that urokinase is a natural human enzyme and that it has been used for over 20 years since purified material was made available.

The applicant states that evidence of the correct structure of the urokinase active substance and evidence of the absence of potential impurities i.e. other urine-derived proteins and process reagents has been provided in the submission (see pharmaceutical assessment, module III, section III).

The excipients in the Syner-KINASE presentations i.e. mannitol, disodium edetate and disodium phosphate, are recognised for use in parenteral preparations. In addition, these excipients are sufficiently stabilising to allow storage of the products at room temperature without the inclusion of human serum albumin.

NON-CLINICAL ASSESSMENT

Urokinase is a well established product. No non-clinical testing has been conducted. The product is a natural human enzyme which has been isolated from normal human urine and is therefore a normal constituent of the body. The production methods are stated to have removed unwanted substances from the urine and the preparation is stated to comply with relevant European Pharmacopoeial specifications for purity and efficacy. The inactive ingredients are commonly used excipients and the lyophilised product is reconstituted with sterile physiological saline prior to administration.

The product has over 25 year clinical use as a thrombolytic agent. Therefore non-clinical studies are not required.

ENVIRONMENTAL RISK ASSESSMENT

The applicant has not submitted a conventional ERA. However, 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.

NON CLINICAL OVERVIEW

The non-clinical overview has been written by suitably qualified experts.

SmPC

This is acceptable.

CONCLUSION

There are no preclinical objections to the grant of this application.

CLINICAL ASSESSMENT

1. INTRODUCTION

These are national applications for urokinase intended for intra-vascular administration. The products are presented as powders for solution and injection. The applications are submitted under article 10a of Directive 2001/83/EC as amended with supporting literature references for the claim of 'well established use'.

Urokinase is a serine protease that catalyses conversion of plasminogen to plasmin with resultant fibrinolytic and thrombolytic properties. Urokinase is used in unblocking of fibrin clots from intravascular catheters and cannulae and in thromboembolic occlusive vascular disease.

2. INDICATIONS

The proposed indications are as follows:

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

a) thrombosed intravascular catheters and cannula that are blocked by fibrin clots.
b) thromboembolic occlusive vascular disease such as deep vein thrombosis, pulmonary embolism, and peripheral vascular occlusion.

3. DOSE & DOSE SCHEDULE

The proposed posology is as follows:

Syner-KINASE® must be reconstituted before use with the correct volume of sterile physiological saline (not provided).
The route of administration is by direct intravenous injection or infusion. It must not be given by subcutaneous or intramuscular injection.

Adults:

a) *Thrombosed intravascular catheters and cannula*

5000 to 25,000 IU Syner-KINASE® dissolved in 2 ml sterile physiological saline is instilled into the intravenous catheter or cannula which is then clamped for up to 4 hours

The lysate is then aspirated and the procedure repeated if necessary. Alternatively, a solution of 5,000 IU Syner-KINASE® dissolved in 200 ml sterile physiological saline

can be infused into the catheter or cannulae over 30 minutes but this may be less effective.

b) *Thromboembolic occlusive vascular disease*

Deep vein thrombosis: an initial loading dose of 4,400 IU/kg body weight dissolved in 15 ml saline infused over 10 minutes followed by 4,400 IU/kg/hour for 12-24 hours.

Pulmonary embolism: an initial loading dose of 4,400 IU/kg body weight dissolved in 15 ml sterile physiological saline infused 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.

Peripheral vascular occlusion: infusion of a solution of 2,500 IU/ml (500,000 IU Syner-KINASE® dissolved in 250 ml sterile physiological saline) into the clot with angiographic monitoring of progress of treatment. It is recommended that the rate of infusion should be 4000 IU/minute (96ml/hour) 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 4000 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 1000 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.

After fibrinolytic therapy has been completed, suitable anticoagulant therapy should be considered.

Elderly:

The initial dosage as in adults should be used but the dosage may be adjusted depending on response.

Children: The company have committed to investigate the paediatric use of all strengths of Syner-KINASE within two years with consequential changes to the SPC

4. CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics

Urokinase elimination is rapid with a half-life of between 5 and 10 minutes. It is cleared from the circulation by the liver.

4.2 Pharmacodynamics

Urokinase activates the naturally occurring fibrinolytic, plasmin, by cleaving plasminogen.

5. EFFICACY

As this application was submitted under article 10a - 'well established medicinal use' - no clinical studies have been carried out. The applicant has therefore provided a literature review and report in the dossier. The report summarised the clinical safety and efficacy of generic urokinase in the following proposed indications:

- Thromboembolic occlusive vascular disease.
- Thrombosed intravascular catheters or intravenous cannulae.

The publications were organised according to their level of evidence according to the study design:

Definitions of level of evidence

Level	Type of evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomised, controlled clinical trial
II	Evidence obtained from at least one well-designed experimental study or low-power randomised, controlled clinical trial
III	Evidence obtained from well-designed, quasi-experimental studies such as non-randomised, controlled single-group, pre-post, cohort, time or matched case-control series
IV	Evidence obtained from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence obtained from case reports and clinical examples

5.1 Deep vein thrombosis (DVT)

There is level II evidence that locoregional urokinase combined with heparin provides similar lysis of DVT when compared with rt-PA (type not specified) plus heparin (Schweizer et al, 1998). There is also level II evidence that urokinase or rt-PA, both administered with heparin, provide for similar reduction of serious post-thrombotic changes compared with heparin alone (Schweizer et al, 1998). Additionally, Meissner et al (2002) provide level IV evidence of the efficacy of urokinase administered using a catheter-directed approach. Furthermore, there is level IV evidence of significantly improved health-related quality of life (HRQOL) outcomes in patients receiving urokinase for DVT when compared with those receiving heparin (Comerota et al, 2000).

5.2 Pulmonary embolism (PE)

There is level II evidence that urokinase plus heparin provides a significant improvement in PE outcomes when compared with heparin alone as indicated by pulmonary arteriogram, haemodynamic and lung perfusion data (UKPET Study Group, 1970). There is also level II evidence that urokinase plus heparin provides similar improvement of pulmonary arteriogram, haemodynamic and lung perfusion data when compared with SK plus heparin in patients with PE (UKPET Study Group, 1974). Furthermore, there is level II evidence showing urokinase (2 hour infusion) plus heparin is as effective in PE thrombus dissolution as rt-PA (alteplase) plus heparin (Goldhaber et al, 1992).

5.3 Peripheral vascular occlusion

Level II evidence shows that urokinase therapy provides for similar limb salvage as operative intervention in patients with peripheral vascular occlusion with a significant improvement in cumulative survival secondary to operative cardiopulmonary risks (Ouriel et al, 1994). Additionally, in recent studies, urokinase has been added to investigational platelet receptor antibody therapy; urokinase has been referred to by such trialists as '… a long-standing thrombolytic agent of choice…' (Duda et al, 2001). Further supportive evidence is provided in 11, level III–V studies.

Conclusion: No prospective study of peripheral arterial thrombolysis has demonstrated complete clot lysis in substantially greater than ¾ of patients, regardless of infusion duration or type of thrombolytic agent. This ratio may, therefore, represent a success level that cannot be improved upon, possibly due to technical and anatomical features present in the remaining one fourth of patients who never achieve complete lysis (Ouriel et al, 1999). Thus, the level II–III evidence presented indicates that urokinase is efficacious-in the treatment of peripheral vascular occlusion.

5.4 Intravascular catheters and cannula

Ten level III–V evidence studies provide efficacy data regarding the use of urokinase in thrombosed intravascular catheters and cannula. The angiographic success rate of thrombolysis was ≥70% in all bar one of these studies. In this study (Wever et al, 1995) 50% of patients achieved complete thrombolysis, and 12% reached partial thrombolysis. In addition, two level II and one level IV evidence study demonstrate that prophylactic urokinase administration is efficacious in reducing the incidence of catheter thromboses and associated complications such as bacteremia (Aquino et al, 2002; Ray et al, 1999 and Kalmanti et al, 2002).

5.5 Further studies

A further six, level III evidence studies comparing urokinase administration with conventional therapy or rt-PA in treating coronary stenoses associated with AMI, appear to support the efficacy of urokinase in increasing patency rates or improving clinical outcomes.

In four out of five level IV evidence studies that have reported patency rates associated with urokinase administration, the rate was >70%; the fifth study reported a reperfusion rate of 37% with a dose range of 4,000IU/min to 2,000,000U.

Four level V studies have also reported similar patency rates following urokinase administration.

5.6 *Assessor's comment*

Urokinase, a physiologic thrombolytic agent that is produced in renal parenchymal cells has been used for a number of years for thrombolysis in the proposed conditions. Currently, there is no licensed product since other product licences with similar indications were withdrawn or cancelled.

The Applicant has performed a thorough literature search for all studies conducted with urokinase for the proposed indications and submitted a critical review of the publications.

Although the review refers to publications, case reports and clinical examples, rather than full study reports, they support the use of urokinase in the amended proposed indications (the indication "*hyphaema (haemorrhage into the anterior chamber of the eye)* has been deleted).

The SmPCs have been amended to reflect up-to-date knowledge regarding this product.

Conclusion

The submitted literature review indicates that urokinase appears to be at least as efficacious as SK and rt-PA (alteplase).

6. SAFETY

The applicant has provided evidence of use of the same product as Syner-KINASE in Italy and in Spain, as a registered product, and in the United Kingdom as an unlicensed product distributed on a named-patient basis. These currently used products are identical in composition to Syner-KINASE and the urokinase active ingredient and finished product are made by the same manufacturers.

Up to the end of April 2005, 701,365 vials of this same urokinase product had been distributed in Italy and 522,334 in Spain. Since commencement of urokinase production and initiation of clinical use in 1994, the marketing authorisation holder of this product have received no notification or reports of any adverse events, serious adverse events or fatal reports in its use.

From January 2000 up to the end of April 2005, 153,035 vials of the 25,000 IU strength of Syner-KINASE, 2547 vials of the 100,000 IU strength and 232 vials of the 250,000 IU strength have been distributed to hospitals in the United Kingdom on a named patient basis.
To date, Syner-Medica Ltd has not been notified or received any reports of any adverse events, serious adverse events or fatal reports.

Currently the majority of Syner-KINASE supplied to the NHS is used to treat patients with end stage renal disease patients receiving haemodialysis or peritoneal dialysis and those with long-term central venous catheters or peripheral vascular access catheters required to administer chemotherapy.

The product has been used on a named patient basis since Feb 2002 with 85.000 vials having been distributed. Apparently, no adverse events have been reported to the company. The company have given a critical analysis of the supporting literature.

6.1 Deep vein thrombosis (DVT)

A study provided level IV evidence of the safety of urokinase administered using a catheter-directed approach.

6.2 Pulmonary embolism (PE)

Level II data indicates that urokinase has a similar safety profile to SK and rt-PA (alteplase).

6.3 Peripheral vascular occlusion

Level II–III evidence presented indicates that urokinase is safe in the treatment of peripheral vascular occlusion.

6.4 Further studies

A further six, level III evidence studies comparing urokinase administration with conventional therapy or rt-PA in treating coronary stenoses associated with AMI, did not reveal any safety concerns related to urokinase therapy.

6.6 *Assessor's Conclusion*

The submitted literature review indicates that urokinase has a similar mortality rate and overall safety profile as SK and rt-PA (alteplase) including the expected incidence of haemorrhagic complications.

7. EXPERT REPORT

The clinical expert report was written by a consultant agency.

It is a very brief document with only citations of 10 of the 32 submitted references without any critical review. Further, there is no indication as to how the literature search was carried out.

8. SUMMARY OF PRODUCT CHARACTERISTICS

This is satisfactory.

9. DISCUSSION

The application includes a critical review of the submitted literature and a description of how the literature search was carried out. Safety and efficacy have been justified and the risk/benefit profile of this product is satisfactory.

10. CONCLUSIONS

There is adequate documentation and sufficient justification for efficacy and safety for the proposed indications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Syner-KINASE 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.

PRECLINICAL

Urokinase is a well established product and, as such, no non-clinical testing was conducted. The product has over 25 year clinical use as a thrombolytic agent.

EFFICACY

The indication is lysis of blood clots under the following conditions:

a) thrombosed intravascular catheters and cannulae that are blocked by fibrin clots.
b) thromboembolic occlusive vascular disease such as deep vein thrombosis, pulmonary embolism, and peripheral vascular occlusion.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant clinical safety concerns were identified, and some benefit has been shown to be associated with Syner-KINASE. The risk benefit is therefore considered to be positive.

Syner-KINASE

(Human Urokinase)

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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on the 17th October 2003.
2 Following assessment, a request for supplementary information was sent to the applicant on the 22nd March 2004.
3 The applicant submitted its response to supplementary information request in a letter dated 29th March 2004.
4 The application was considered by the Biologicals and Vaccines Expert Advice Group (BVEAG) on the 22nd March 2004.
5 The application was considered by the Committee on Human Medicines (CHM) at their meeting on the 7th April 2004 where the application was rejected on quality grounds in relation to safety, clinical safety and efficacy.
6 The Company appealed against the decision on the 5th May 2004.
7 A clarification meeting was held on the 10th April 2006 at the request of the Company, to address points from the April 2004 CHM letter.
8 The MHRA received appeal data from the Company on the 1st June 2005.
9 Following assessment of the response data, the application was considered by the Biological sub group of the CHM on the 10th October 2005 at a pre-hearing and by the CHM on the 12th October 2005 at a hearing.
10 A clarification meeting was held on the 10th April 2006 between representatives of the Company and members of BVEAG at the request of the Company, to address points from the April 2004 CHM letter.
11 Following the company's response from the 10th/12th October 2005 meetings, the application was considered by BVEAG at the meeting on 10th April 2006.
12 The application then went to the Commission on Human Medicines (CHM) for a pre-hearing on the 20th April 2006 and a hearing on the 18th May 2006.
13 The application was determined on the 21st September 2006.
14 The MHRA received a marketing authorisation application for a new strength of 10,000 IU on 14th September 2007.
15 Following assessment, a request for supplementary information was sent to the applicant on the 3rd of April 2008.
16 The applicant submitted its response to supplementary information request in a letter dated 2nd May 2008.
17 The application was determined on the 15th August 2008.

Syner-KINASE

(Human Urokinase)

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
07/11/2010	National Variation Type 1B	To update sections 2 (Qualitative and quantitative composition), 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Pregnancy and lactation), 4.8 (Undesirable effects), 5.2 (Pharmacokinetic properties), 6.2 (Incompatibilities), 6.5 (Nature and contents of container), 6.6 (Instructions for use and handling) & 9 (Date of first authorisation/renewal of authorisation) of the SPC following a request from the MHRA to update product information before MRP submission. The PIL is updated accordingly.	Granted 12/05/2011

SUMMARY OF PRODUCT CHARACTERISTICS

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
Syner-KINASE® 1,000,000 IU

Powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10,000, 25,000, 100,000, 250,000, 500,000 or 1,000,000 IU of human urokinase.

For excipients, see 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 these conditions:

a) thrombosed intravascular catheters and cannula that are blocked by fibrin clots.
b) thromboembolic occlusive vascular disease such as deep vein thrombosis, pulmonary embolism, and peripheral vascular occlusion.

4.2 Posology and method of administration

Syner-KINASE® must be reconstituted before use with the correct volume of sterile physiological saline (not provided).
The route of administration is by direct intravenous injection or infusion. It must not be given by subcutaneous or intramuscular injection.

Adults:

a) *Thrombosed intravascular catheters and cannula*

5000 to 25,000 IU Syner-KINASE® dissolved in 2 ml sterile physiological saline is instilled into the intravenous catheter or cannula which is then clamped for up to 4 hours

The lysate is then aspirated and the procedure repeated if necessary. Alternatively, a solution of 5,000 IU Syner-KINASE® dissolved in 200 ml sterile physiological saline can be infused into the catheter or cannulae over 30 minutes but this may be less effective.

b) *Thromboembolic occlusive vascular disease*

Deep vein thrombosis: an initial loading dose of 4,400 IU/kg body weight dissolved in 15 ml saline infused over 10 minutes followed by 4,400 IU/kg/hour for 12-24 hours.

Pulmonary embolism: an initial loading dose of 4,400 IU/kg body weight dissolved in 15 ml sterile physiological saline infused 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.

Peripheral vascular occlusion: infusion of a solution of 2,000 IU/ml (500,000 IU Syner-KINASE® dissolved in 250 ml sterile physiological saline) into the clot with angiographic monitoring of progress of treatment. It is recommended that the rate of infusion should be 4000 IU/minute (96ml/hour) 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 4000 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 1000 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.

After fibrinolytic therapy has been completed, suitable anticoagulant therapy should be considered.

Elderly:

The initial dosage as in adults should be used but the dosage may be adjusted depending on response.

4.3 Contraindications

Hypersensitivity to urokinase or to any of the excipients. The risk of haemorrhage should be balanced against the dangers of untreated occlusion particularly in the situation of recent bleeding such as following: surgery, cerebro-vascular bleeding, severe hypertension, pregnancy and the immediate post-partum period, severe hepatic or renal insufficiency unless the patient is receiving renal replacement therapy.

4.4 Special warnings and special precautions for use

If bleeding occurs following systemic treatment with Syner-KINASE®, infusion should be stopped immediately. However, the risks of haemorrhage must be balanced against the risk of stopping treatment.

Care should be taken in patients known to have peptic ulcer disease or at risk of other gastrointestinal bleeding. Also due caution should be exercised in patients who have had recent repeated intravascular or intracardiac puncture as in those who have undergone recent cardio-pulmonary resuscitation.

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 1500 IU/ml and stored in PVC containers. No information is available regarding higher strengths of Syner-KINASE®.

4.6 Pregnancy and lactation

Syner-KINASE® should not be given during pregnancy or in the immediate post-partum period. Breast feeding should be avoided.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Local sensations of warmth, dull ache or pain may be felt locally in the vessel being treated. Overt bleeding and haemorrhagic complications may occur. Pyrexia and haematuria have been reported.

Embolic episodes have been noted after fragments of clot have been released. Cholesterol embolism may occur.
Allergic reactions have been reported.

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. As it is of human origin, it is not antigenic although allergic reactions have been reported following the use of urokinase.

5.2 Pharmacokinetic properties

Syner-KINASE® is eliminated rapidly from the circulation by the liver with a half-life of up to 20 minutes. Elimination is delayed in patients with liver disease and impaired kidney function.

5.3 Preclinical safety data

There is 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 with sterile physiological saline. It has been reported to lose 15-20% of its activity in solutions of 5% glucose containing 1500 units/ml in PVC containers. No information is available regarding higher strengths of Syner-KINASE®.
Patel J P, *et al*. Activity of urokinase diluted in 0.9% sodium chloride injection or 5% dextrose injection and stored in glass or plastic syringes. *Am. J. Hosp. Pharm.* 1991; **48**; 1511-1514

6.3 Shelf life

2 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 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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Syner-Medica Ltd
Beech House
840 Brighton Road
Purley
Surrey
CR8 2BH
Telephone No. 0845 634 2100

8. MARKETING AUTHORISATION NUMBERS

PL 20675/0001
PL 20675/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2006 (PL 20675/0001-5)
15/08/2008 (PL 20675/0006)

10 DATE OF REVISION OF THE TEXT

15/08/2008

Patient Information Leaflet

Syner-KINASE

(Human Urokinase)

PL 20675/0001
PL 20675/0002
PL 20675/0003
PL 20675/0004
PL 20675/0005
PL 20675/0006

PACKAGE LEAFLET

Syner-KINASE®

INFORMATION FOR THE USER

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
Syner-KINASE® 1,000,000 IU
Powder for solution for injection or infusion

Read all of this leaflet carefully before you start taking/using this medicine. It contains a summary of the information available on Syner-KINASE. The information in this leaflet applies only to your medicine.

- keep this leaflet. You may need to read it again
- if you have further questions, please ask your doctor or your 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 become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor

This leaflet answers the following questions:

1. **What Syner-KINASE is and what it is used for**
2. **Before you are given Syner-KINASE**
3. **How Syner-KINASE is given**
4. **Possible side-effects**
5. **How to store Syner-KINASE**
6. **Further information**

1. What Syner-KINASE is and what it is used for:
The name of your medicine is Syner-KINASE. The active ingredient is urokinase a thrombolytic that can help to dissolve blood clots that may form in:

- intravenous catheters or cannulae (surgical tubes used to withdraw fluids from, or introduce fluids into the body)
- lungs
- deep veins
- peripheral blood vessels (vessels away from the heart)

This medicine will be administered as an injection or infusion into a blood vessel or directly into a catheter or cannula.

2. Before you are given Syner-KINASE:
Do not use Syner-KINASE
If you are allergic (hypersensitive) to urokinase or any of the other ingredients of Syner-KINASE
(See Section 6)

Take special care with Syner-KINASE if you:

- have had recent bleeding such as following surgery
- have a history of stroke
- have severe high blood pressure
- have severe liver or kidney disease
- are pregnant or have recently given birth.

In all these circumstances your doctor will decide whether or not you should be given Syner-KINASE.

Special care must also be taken if you have stomach ulcers or have had bleeding from elsewhere in the intestine, or if you have recently had repeated blood tests taken or any other procedures which may be associated with a high risk of bleeding.

Taking or using other medicines:
Please inform your doctor if you are taking, or have recently taken any other medicine, including medicines obtained without a prescription.

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

If bleeding occurs following treatment:
If bleeding occurs following treatment with Syner-KINASE the infusion may be stopped, but the risk of stopping treatment has to be balanced against the risk of continuing. Your doctor will decide.

3. How Syner-KINASE is given:
Syner-KINASE will be given to you by a doctor or nurse. You will not normally be asked to administer Syner-KINASE to yourself.

Before you are given Syner-KINASE it will be dissolved in saline (solution of salt and water). It should never be injected into a muscle or under the skin

- if you are being treated for a blocked intravascular catheter or cannula, Syner-KINASE may be injected directly into the catheter or cannula and left for a while before removing the fluid. This may be repeated several times
- if you are being treated for blood clots in your lungs, deep veins or peripheral blood vessels, an initial loading dose may be given, followed by an infusion of Syner-KINASE. Progress of the treatment may be checked by special X-rays. After the clot has been dissolved, you may be put on anticoagulant therapy (blood thinning) to prevent a recurrence
- the amount and duration of Syner-KINASE treatment will be decided by your doctor

4. Possible side-effects:
Like all medicines, Syner-KINASE can have side-effects but not everybody will get them. If any of the following occur please tell your doctor:

Effects on your blood and lymph system
You may experience unusual bleeding, particularly from recent cuts or puncture wounds; rarely some smaller fragments of the blood clot or even cholesterol crystals may be released and pass along the blood vessel and cause a blockage elsewhere. You may also experience low blood pressure making you feel faint.

Effects on your breathing and chest
You may experience an allergic reaction such as wheezing, tightness in your chest or difficulty with breathing.

Effects on your skin
You may experience an allergic reaction such as skin rashes and urticaria (nettle rash).

Effects on your kidneys and bladder
You may notice some blood in your urine.

Effects on your whole body and the injection site
You may experience a sensation of warmth, or dull ache or pain where the infusion is being given. Your temperature may rise.

If you experience any of the above side effects, or if you notice anything else which is unusual, and not mentioned in this leaflet, please inform your doctor or pharmacist immediately.

5. How to store Syner-KINASE:
- keep out of the reach and sight of children
- do not store above 25°C
- do not keep reconstituted material for later use
- store in the original container and package in order to protect from light
- do not use after the expiry date stated on the label. The expiry date refers to the last day of the month
- do not use if the contents of the vial are discoloured
- medicines should not be disposed of via waste water or household waste

Ask your pharmacist how to dispose of medicines no longer required. These measurements will help to protect the environment.

6. Further information:
The active ingredient is urokinase.
The other ingredients are: Mannitol, Disodium Edetate, Disodium Phosphate Dodecahydrate, Sodium Hydroxide.

What Syner-KINASE looks like and contents of the pack:
Each pack contains one vial (small bottle). The white powder contents are Syner-KINASE.

There are different strengths available:
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
Syner-KINASE® 1,000,000 IU

Marketing Authorisation Holder (MAH)
Syner-Medica Ltd
Beech House
840 Brighton Road
Purley, Surrey
UK
CR8 2BH

Manufacturer
Sirton Pharmaceuticals SpA
Piazza XX Settembre, 2
22079 Villa Guardia (CO)
Italy

Sales & Distribution
Syner-Med (Pharmaceutical Products) Ltd
Beech House
840 Brighton Road
Purley, Surrey
UK
CR8 2BH
0845 634 2100
mail@syner-med.com

For further information please contact
Medical Information Department
Syner-Med (Pharmaceutical Products) Ltd
Beech House
840 Brighton Road
Purley, Surrey
UK
CR8 2BH
0845 634 2100
mail@syner-med.com

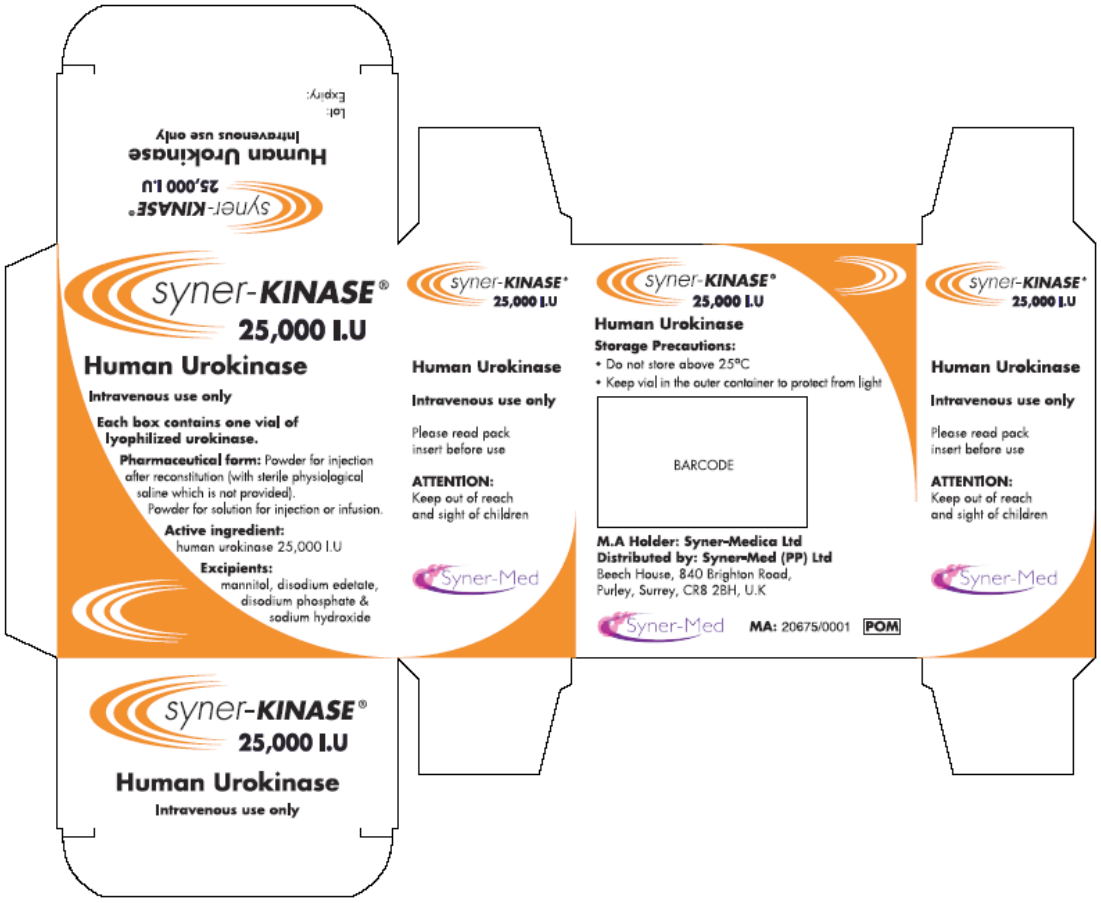
This leaflet was revised August 2009

Labelling

Syner-KINASE

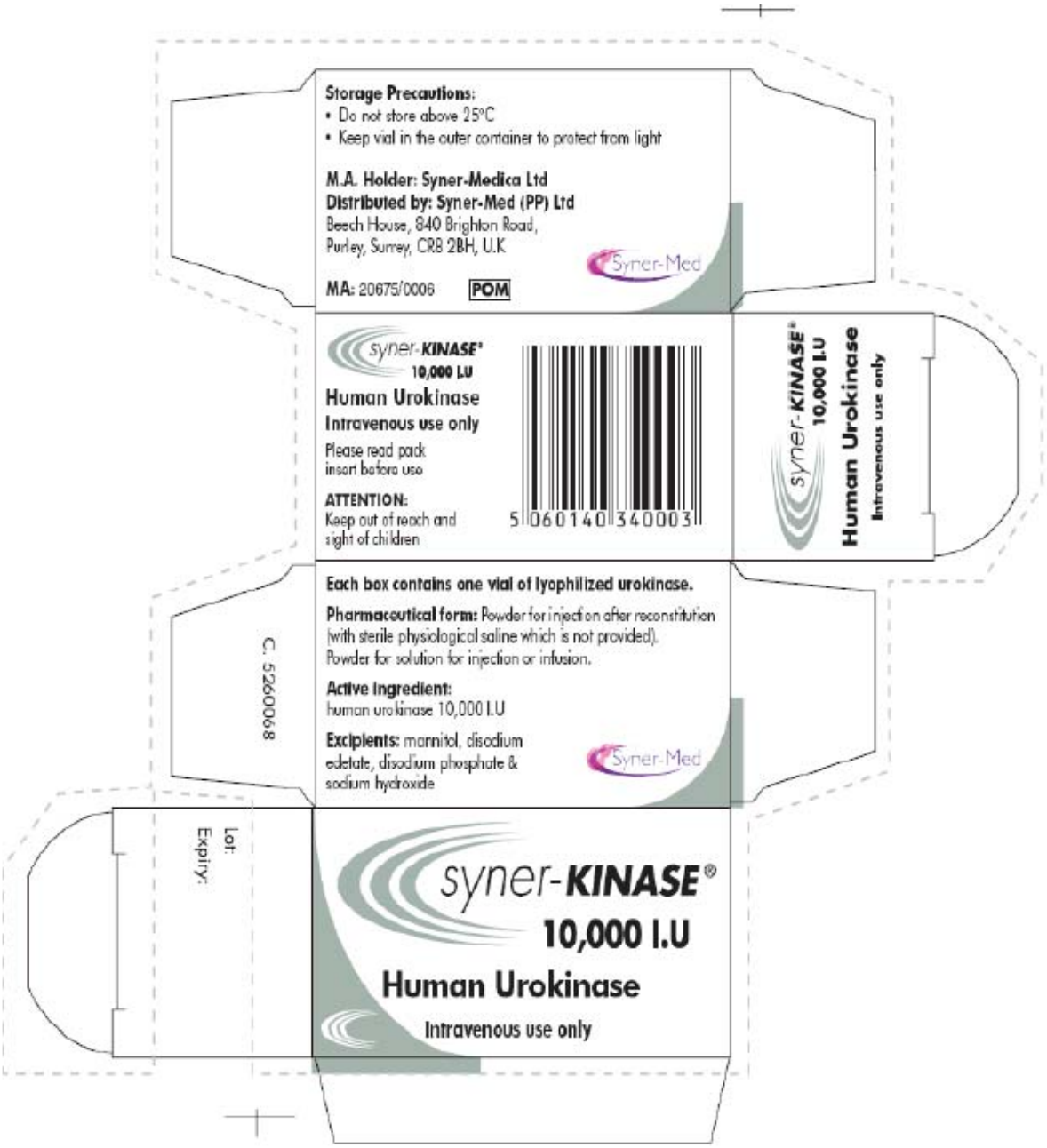
(Human Urokinase)

PL 20675/0001
PL 20675/0002
PL 20675/0003
PL 20675/0004
PL 20675/0005
PL 20675/0006


Lot:
Expiry:
Intravenous use only
Human Urokinase
25,000 I.U
syner-KINASE®
syner-KINASE®
25,000 I.U
Human Urokinase
Intravenous use only
Each box contains one vial of lyophilized urokinase.
Pharmaceutical form: Powder for injection after reconstitution (with sterile physiological saline which is not provided).
Powder for solution for injection or infusion.
Active ingredient:
human urokinase 25,000 I.U
Excipients:
mannitol, disodium edetate, disodium phosphate & sodium hydroxide
Please read pack insert before use
ATTENTION:
Keep out of reach and sight of children
Syner-Med
Storage Precautions:
• Do not store above 25°C
• Keep vial in the outer container to protect from light
BARCODE
M.A Holder: Syner-Medica Ltd
Distributed by: Syner-Med (PP) Ltd
Beech House, 840 Brighton Road,
Purley, Surrey, CR8 2BH, U.K
MA: 20675/0001
POM

Actual Label size 60mm x 27mm

300% Enlargement of Actual Label size (for content use only)


Storage Precautions:
• Do not store above 25°C
• Keep vial in the outer container to protect from light
M.A. Holder: Syner-Medica Ltd
Distributed by: Syner-Med (PP) Ltd
Beech House, 840 Brighton Road,
Purley, Surrey, CR8 2BH, U.K
Syner-Med
MA: 20675/0006
POM
syner-KINASE®
10,000 I.U
Human Urokinase
Intravenous use only
Please read pack insert before use
ATTENTION:
Keep out of reach and sight of children
5 060140 340003
syner-KINASE®
10,000 I.U
Human Urokinase
Intravenous use only
Each box contains one vial of lyophilized urokinase.
Pharmaceutical form: Powder for injection after reconstitution (with sterile physiological saline which is not provided).
Powder for solution for injection or infusion.
Active ingredient:
human urokinase 10,000 I.U
Excipients: mannitol, disodium edetate, disodium phosphate & sodium hydroxide
Syner-Med
C. 5260068
Lot:
Expiry:
syner-KINASE®
10,000 I.U
Human Urokinase
Intravenous use only


M.A. Holder: Syner-Medica Ltd
MA: 20575/0005
Distribution: Syner-Med (PR) Ltd
Beech House, 64 Bridgham Road,
Pulley, Surrey, CR5 2EH, U.K.
syner-KINASE+
10,000 I.U
Human Urokinase Intravenous use only
One vial of lyophilized urokinase to be reconstituted with sterile physiological saline
Active ingredient: human urokinase 10,000 I.U
Excipients: mannitol, disodium edetate, disodium phosphate & sodium hydroxide
Storage Precautions: • Do not store above 25°C
• Keep vial in the outer container to protect from light
Syner-Med
Lot
Expiry

Annex 1

Our Reference:	PL 20675/0001 - 0017
Product:	PL 20675/0001 Syner-KINASE injection 25,000 IU
Marketing Authorisation Holder:	Syner-MEDICA Limited
Active Ingredient(s):	Urokinase

Reason:
To update sections 2 (Qualitative and quantitative composition), 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Pregnancy and lactation), 4.8 (Undesirable effects), 5.2 (Pharmacokinetic properties), 6.2 (Incompatibilities), 6.5 (Nature and contents of container), 6.6 (Instructions for use and handling) & 9 (Date of first authorisation/renewal of authorisation) of the SmPC following a request from the MHRA to update product information before MRP submission. The PIL is unchanged.

Linked/related variation(s) or case(s):
The Assessment Report covers the following submissions PL 20675/0005 - 0014, PL 20675/0006 - 0013, PL 20675/0002 - 0017, PL 20675/0004 - 0014, PL 20675/0003 - 0014.

Type of application
Although this should have been a type II variation, the MHRA has accepted it as a type IB national standard variation, which has been submitted by Syner-MEDICA Limited for Syner-KINASE injection 25,000 (PL 20675/0001).

Supporting evidence
In support of this National variation application, the applicant has submitted the following documents:

- an expert report based on literature search to update the indications, contraindications, warnings, interactions, use in pregnancy, and pharmacokinetic properties
- an expert report based on literature search for the use in the paediatric population
- a literature search on adverse events to urokinase with estimates of ADR frequencies
- a bridging statement for the changes to the PIL.

Evaluation
Following requests for further information from the MAH, all proposed changes have been adequately justified based on appropriate documentation, including a full analysis of relevant literature. Consequentially, it was also required that the PIL should be updated accordingly.

Conclusion
After discussion with the MAH, suitable changes were made to the SmPC such that the following text was accepted for sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.2, 6.2, 6.5, 6.6, 9. In addition, the PIL was updated accordingly.
The text below is for PL 20675/0001, Syner-KINASE 25,000 IU. In all sections, the text is identical for all PLs apart from section 2 where the quantity in IU is different for each strength, i.e.
PL 20675/0002 - 0017, Syner-KINASE 100,000 IU.
PL 20675/0003 – 0014, Syner-KINASE 250,000 IU.

PL 20675/0004 - 0014, Syner-KINASE 500,000 IU.
PL 20675/0005 - 0014, Syner-KINASE 1,000,000 IU.
PL 20675/0006 - 0013, Syner-KINASE 10,000 IU.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

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®.

4.8 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

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.

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% dextrose 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.

6.5 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
1,000,000 IU – Blue

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.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st September 2006

PACKAGE LEAFLET

Syner-KINASE®

INFORMATION FOR THE USER

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
Syner-KINASE® 1,000,000 IU
Powder for solution for injection or infusion.

Read all of this leaflet carefully before you start taking/using this medicine. It contains a summary of the information available on Syner-KINASE. The information in this leaflet applies only to your medicine.
- keep this leaflet. You may need to read it again
- if you have further questions, please ask your doctor or your 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 become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor

This leaflet answers the following questions:

1. What Syner-KINASE is and what it is used for
2. Before you are given Syner-KINASE
3. How Syner-KINASE is given
4. Possible side-effects
5. How to store Syner-KINASE
6. Further information

1. What Syner-KINASE is and what it is used for:

The name of your medicine is Syner-KINASE. The active ingredient is urokinase, a thrombolytic that can help to dissolve blood clots that may form in:
- intravenous catheters or cannulae (surgical tubes used to withdraw fluids from, or introduce fluids into the body)
- lungs
- deep veins
- peripheral arteries (blood vessels away from the heart, such as in the leg)

2. Before you are given Syner-KINASE:

Syner-KINASE will not be given to you if you:
- are allergic (hypersensitive) to urokinase or any of the other ingredients of Syner-KINASE (See Section 6)
- are currently bleeding
- had a major surgical operation or a stroke recently (in the past 2 months)
- have severe high blood pressure
- have abnormal blood clotting
- have abnormal blood vessels
- have cancer of the brain
- have infection of the pancreas or heart
- have severe liver or kidney disease

Special care will be taken with Syner-KINASE if you:
- have been recently bleeding from the stomach or intestines
- had surgery or have given birth recently
- have severe blood vessel disease in your brain
- have problems with your heart
- are elderly, particularly if you are aged over 75 years

In all these circumstances your doctor will decide whether or not you should be given Syner-KINASE.

Taking or using other medicines:
Please inform your doctor if you are taking, or have recently taken any of the following medicines, or any other medicines, including medicines obtained without a prescription:
- heparin or other anticoagulants
- acetylsalicylic acid (aspirin)
- non-steroidal anti-inflammatory agents
- dipyridamole
- dextrans

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

Syner-KINASE must not be used in pregnancy or immediately after delivery unless otherwise recommended by your doctor.

Do not breast-feed during treatment with Syner-KINASE.

3. How Syner-KINASE is given:

Syner-KINASE will be given to you by a doctor or nurse. You will not be asked to administer Syner-KINASE to yourself.

Before you are given Syner-KINASE it will be dissolved in saline (solution of salt and water). It should never be injected into a muscle or under the skin. The amount and duration of Syner-KINASE treatment will be decided by your doctor.
- if you are being treated for a blocked intravascular catheter or cannulae, Syner-KINASE may be injected directly into the catheter or cannulae and left for a while before removing the fluid. This may be repeated several times. Syner-KINASE may also be injected into the blocked tube over a period of time.
- if you are being treated for blood clots in your lungs, deep veins or peripheral arteries, Syner-KINASE may be injected into a vein (usually in the arm) or directly into the blocked vessel. Progress of the treatment may be checked by special X-rays. After the clot has been dissolved, you may be put on anticoagulant therapy (blood thinning) to prevent a recurrence.

Use in children:
Syner-KINASE can be used in children to dissolve blood clots in intravenous catheters or cannulae.

4. Possible side-effects:
Like all medicines, Syner-KINASE can have side-effects but not everybody will get them.
Tell your doctor immediately if you notice:
- any bleeding
- any sign of an allergic reaction, such as difficulty with breathing, swelling of face, lips or throat, skin rash or hives

Other side effects include:
Very common side effects (affects more than 1 user in 10)
- unusual bleeding, particularly from puncture wounds or nose bleeds
- blood detected in the urine after a urine test
- blood clots: small fragments of a blood clot may be released and pass along the blood vessel and cause blockage elsewhere, such as in the lungs, heart or limbs
- a decrease in haematocrit (a red blood cell test) and a temporary increase in certain liver enzymes

Common side effects (affects 1 to 10 users in 100)
- bleeding in the stomach or into/around the brain or at puncture sites
- stroke
- tearing of an artery wall
- blockage of blood vessels due to cholesterol (fat)
- fever, chills and/or shivering

Uncommon side effects (affects 1 to 10 users in 1000)
- kidney failure

Rare side effects (affects 1 to 10 users in 10,000)
- visible blood in the urine
- injury and swelling in an artery wall

If you experience any of the above side effects, or if you notice anything else which is unusual, and not mentioned in this leaflet, please inform your doctor or pharmacist immediately.

5. How to store Syner-KINASE:
- keep out of the reach and sight of children
- do not store above 25˚C
- do not keep reconstituted material for later use
- store in the original container and package in order to protect from light
- do not use after the expiry date stated on the label. The expiry date refers to the last day of the month
- do not use if the contents of the vial are discoloured
- medicines should not be disposed of via waste water or household waste

6. Further information:
The active ingredient is urokinase.
The other ingredients are: Mannitol, Disodium Edetate, Disodium Phosphate Dodecahydrate, Sodium Hydroxide.

What Syner-KINASE looks like and contents of the pack:
Each pack contains one vial (small bottle). The wh powder contents are Syner-KINASE.

There are different strengths available:
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
Syner-KINASE® 1,000,000 IU

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Decision – Granted
Date 12/05/11