

Annex II

Scientific conclusions

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Urokinase is a serine protease that catalyses conversion of plasminogen to plasmin with resultant fibrinolytic and thrombolytic properties. Urokinase is used 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 and acute occlusive peripheral arterial disease with limb threatening ischemia.

Urokinase is considered to have a well-established use in the above indications within the European Union and on 29 September 2006, Syner-Kinase was granted a marketing authorisation in the UK according to Article 10(a) of Directive 2001/83/EC. In January 2018, Syner-Medica Ltd submitted a mutual recognition application for Syner-Kinase 10,000 IU, 25,000 IU, 100,000 IU, 250,000 IU and 500,000 IU powder for solution for injection or infusion in France, Germany, Spain and the Netherlands with the United Kingdom as the reference Member State (RMS).

The mutual recognition procedure was closed on day 90, with the four concerned Member States raising potential serious risk to public health (PSRPH) in relation to the lack of bridging data between the product applied for and the product(s) described in literature that was used to demonstrate the benefit/risk of Syner-Kinase, the adventitious agent safety with respect to viral and prion clearance and the lack of adequate quality of the process validation of the semi-purified urokinase and lifetime of columns used for urokinase purification. A referral was thus triggered at the CMD(h) but at D60 of the procedure, the PSRPH issues remained unresolved. The UK therefore triggered a referral under Article 29(4) of Directive 2001/83/EC.

As part of this procedure, the CHMP requested the applicant to justify that the available data on Syner-Kinase, including its comparison to the urokinase products mentioned in the literature, are adequate to support its positive benefit/risk balance in the proposed indications. The CHMP also requested the MAH/applicant to provide further information to support the viral and prion clearance capacity of the process and justify the adequacy of the procedures to support the suitability of viral and prion removal, including transmissible spongiform encephalopathies (TSE) infectivity reduction. Finally, the CHMP requested the MAH/applicant to provide further information to demonstrate that the manufacturing steps for semi-purified urokinase have been satisfactorily validated, and also that the control strategy for column lifetime during the manufacture of the active pharmaceutical ingredient is suitable. Furthermore, confirmation was required that the semi-purified urokinase is manufactured in accordance with GMP.

Overall summary of the scientific evaluation by the CHMP

The MAH/applicant has provided relevant data to justify the extrapolation of the data available in the literature on the benefit and risks of urokinase in the indications applied for. The MAH/applicant has provided further comparative studies between Syner-Kinase active ingredient (API) and the API's in the urokinase products used in the literature studies cited in the submission, as well as data demonstrating the consistency of the product overtime despite the changes made to the product during its lifecycle.

Based on the data provided, it is considered that the comparability of Syner-Kinase and urokinase products used in the literature studies cited in the submission has been sufficiently demonstrated.

The MAH/applicant has successfully demonstrated that the virus removal/inactivation steps are appropriately controlled and will provide the final reports of the virus and TSE removal studies and the updated risk assessment analysis by 31 May 2019 to the relevant national competent authorities.

Finally, evidence has been provided that the manufacture of semi-purified urokinase is adequately validated and controlled and in compliance with good manufacturing practices and all concerns raised over the quality and manufacturing of Syner-Kinase are considered solved.

The CHMP considered, as a consequence, that the benefit-risk balance of Syner-Kinase is favourable.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC,
- The Committee considered the totality of the data submitted by the MAH/applicant in relation to the objections raised as potential serious risk to public health.
- The Committee concluded that Syner-Kinase is comparable to the urokinase products mentioned in the published literature, and that the data available are adequate to support its proposed use.
- The Committee concluded that the purification process of the active substance is suitable for the removal of possible viral and prion impurities.
- The Committee concluded that manufacture of the semi-purified urokinase is adequately validated and controlled, and that reassurance has been provided that this intermediate is manufactured at a site that complies with the principles and guidelines of Good Manufacturing Practice (GMP).

The Committee, as a consequence, considers that the benefit-risk balance of Syner-Kinase and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion.

The product information remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.