

# **Public Assessment Report**

## **Scientific discussion**

**Tranexaminezuur Sandoz 100 mg/ml,  
solution for injection**

**(tranexamic acid)**

**NL/H/3153/001/DC**

**Date: 18 March 2015**

<p>This module reflects the scientific discussion for the approval of Tranexaminezuur Sandoz 100 mg/ml, solution for injection. The procedure was finalised on 19 December 2014. For information on changes after this date please refer to the module 'Update'.</p>
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## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tranexaminezuur Sandoz 100 mg/ml, solution for injection from Sandoz B.V.

The product is indicated for prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year.

Specific indications include:

- Haemorrhage caused by general or local fibrinolysis such as:
  - Menorrhagia and metrorrhagia
  - Gastrointestinal bleeding
  - Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract
- Ear Nose Throat surgery (adenoidectomy, tonsillectomy, dental extractions)
- Gynaecological surgery or disorders of obstetric origin
- Thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery
- Management of haemorrhage due to the administration of a fibrinolytic agent.

A comprehensive description of the indications and posology is given in the SmPC.

Tranexamic Acid is an antifibrinolytic drug used to control bleeding by preventing clot breakdown (fibrinolysis). Its structural formula is trans-4-(aminomethyl)cyclohexanecarboxylic acid (C<sub>8</sub>H<sub>15</sub>NO<sub>2</sub>). Tranexamic acid exerts an anti haemorrhagic activity by inhibiting the fibrinolytic properties of plasmin.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Cyklokapron solution for injection 100 mg/ml (NL license RVG 05573), which has been registered in the Netherlands by Pfizer since 31 July 1968.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

## II. QUALITY ASPECTS

### II.1 Introduction

Tranexaminezuur Sandoz 100 mg/ml is a colourless solution with pH value between 6.5 and 7.5.

The solution for injection is packed in type I glass ampoules containing 100 mg in 1 ml.

The excipients are: hydrochloric acid 37% (for pH adjustment) and water for injection.

### II.2 Drug Substance

The active substance is tranexamic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white crystalline powder.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

#### Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance

The drug substance specification is in line with CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 industrial scaled batches.

#### Stability of drug substance

Stability data on the active substance have been provided for 6 industrial scaled batches stored at 25°C/60% RH (36 months) and 40°C/75%RH (6 months). No trends or changes are observed, the active substance remains stable at both storage conditions. A retest period of 36 months without any special storage conditions is considered acceptable.

### **II.3 Medicinal Product**

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The objective of the pharmaceutical development was to get a tranexamic acid 100 mg/ml solution which is essentially similar to the reference product Cyklokapron. The choices of the packaging and manufacturing process are justified in relation to the innovator. The choice of final sterilisation is justified. In accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence, a bioequivalence study is not required as the product is administered as an aqueous intravenous solution containing the active drug substance in the same concentration as the currently authorized product Cyklokapron by Pfizer.

#### Manufacturing process

A bulk solution is manufactured and the ampoules are filled. The ampoules are then steam sterilized. The manufacturing process has been adequately validated according to relevant European guidelines. The applied steam sterilization process is acceptable. Process validation data on the product has been adequately presented for 3 full-scale batches.

#### Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

#### Quality control of drug product

The product specification includes tests appearance, extractable volume, pH, particulate matter, identity, assay, impurities, sterility and bacterial endotoxins. The release and shelf-life requirements are identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 production-scale batches, demonstrating compliance with the release specification.

#### Stability of drug product

Stability data on the product has been provided 5 production-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended ampoules. No changes or trends can be observed at both storage conditions. A photostability test confirmed that the product is not sensitive to light. The proposed shelf-life of 36 months without any special storage conditions is considered acceptable.

Although the product is only intended for injection, compatibility has been demonstrated with the following infusion solutions/diluents, which are included in the innovator SmPC: 5% dextrose, 0.9% Sodium chloride IV, Dextran 40 in 5% dextrose IV, Dextran 40 in 0.9% Sodium chloride, Aminogen 10% (crystalline amino acid solution) and Heparin 1000 USP units/ml in 2 ml vials. Mixtures were stable for 24 hours after dilution at 25°C. It is not expected that missing information on compatibility with other infusion solutions (fructose, invertose, Ringer lactate) will lead to problems in practice, as the drug product will only be used for injection.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

#### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Tranexaminezuur Sandoz 100 mg/ml, solution for injection has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

### **III. NON-CLINICAL ASPECTS**

#### **III.1 Ecotoxicity/environmental risk assessment (ERA)**

Since Tranexaminezuur Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

#### **III.2 Discussion on the non-clinical aspects**

This product is a generic formulation of Cyklokapron, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

### **IV. CLINICAL ASPECTS**

#### **IV.1 Introduction**

Tranexamic acid is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

#### **IV.2 Pharmacokinetics**

##### Biowaiver

Tranexaminezuur Sandoz 100 mg/ml solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Tranexaminezuur Sandoz 100 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

#### **IV.3 Risk Management Plan**

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tranexaminezuur Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> <li>– Thromboembolism</li> <li>– Vision impairment – incl. impaired colour vision</li> <li>– Convulsions</li> <li>– Hypersensitivity reactions</li> <li>– Hypotension due to rapid injection</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>– None</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>– Use in pregnant and lactating women</li> <li>– Use in post pubertal females under 15 years of age</li> </ul>

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

#### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cyklokapron. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The MAH provided a bridging report with reference to the successful user test for the package leaflet (PL) of the innovator. The PL of the applied product and the innovator are sufficiently similar in content and the layout and design of the PL of the applied product is identical to the well established MAH's company layout. Therefore, the bridging report is considered acceptable and a user test is not necessary.

#### Information for the healthcare professional

In accordance with the "Guideline on the readability of the labelling and package leaflet of medicinal products for human use" (ENTR/F/2/SF/jr (2009)D/869) section 9.2, for a product administered by a healthcare professional, information from the SmPC for the healthcare professional (e.g. the instructions for use) could be included at the end of the patient leaflet.

The MAH has added a brief section with information for the healthcare professional, based on the same information provided in the package leaflet for the innovator. Since RMS accepted the proposal not to include information in the SmPC about compatibility with solutions, the PL has been updated to include only the following sentence in that section:

'The following information is intended for healthcare professionals only:

Tranexaminezuur Sandoz solution for injection should not be added to blood for transfusion, or to injections containing penicillin.'

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tranexaminezuur Sandoz 100 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Cyklokapron solution for injection 100 mg/ml. Cyklokapron is a well-known medicinal product with an established favourable efficacy and safety profile

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Cyklokapron solution for injection 100 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 December 2014.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached