COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tranexaminezuur Kabi 10 mg/ml solution for infusion (tranexamic acid)

NL/H/5640/001/DC

Date: 3 May 2024

This module reflects the scientific discussion for the approval of Tranexaminezuur Kabi 10 mg/ml solution for infusion. The procedure was finalised on 8 November 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PDE	Permissible Daily Exposure
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tranexaminezuur Kabi 10 mg/ml solution for infusion, from Fresenius Kabi Nederland B.V.

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

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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, hybrid application.

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

Tranexaminezuur 10 mg/ml Kabi is claimed to be chemically, therapeutically and functionally equivalent to the reference medicinal product Cyklokapron. Both have tranexamic acid as active substance and are intended for parenteral administration as intravenous infusion. However, the new product differs from the innovator in strength (10 mg/mL instead of 100 mg/mL), pharmaceutical form (solution for infusion instead of solution for injection or infusion) and the additional excipient sodium chloride (the innovator contains only water besides tranexamic acid). The new product and the innovator are aqueous solutions for intravenous and may be mixed with most solutions for infusion such as electrolyte solutions prior administration. Therefore, the excipient sodium chloride is not expected to affect the disposition of tranexamic acid. Also, compatibility studies have been submitted. Overall, since the innovator and the new product contain the same active substance and are intended to be administered intravenously as an aqueous solution, in line with “Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, 2010, additional bioequivalence studies are considered not required.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, Germany, Greece, Hungary, Latvia, Lithuania, Northern Ireland, Norway, Portugal, Romania, Slovakia and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Tranexaminezuur Kabi is a clear and colourless solution for infusion, free from visible particles, with a pH value between 6.5 - 8.0 and an osmolality value of 270-330 mOsmol/Kg. Each mL of solution contains 10 mg of tranexamic acid as active substance.

The excipients are sodium chloride and water for injection.

The solution for infusion is presented in 50 mL or 100 mL polyethylene bottles (KabiPac), primary packaging closed with a cap containing rubber discs to allow insertion of the needle or spike.

II.2 Drug Substance

The active substance is tranexamic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder. Freely soluble in water and in glacial acetic acid, practically insoluble in acetone and in ethanol (96%). Tranexamic acid (trans-4-(Aminomethyl)cyclohexanecarboxylic acid) is chiral, it is a stereoisomer of 4-amino-methyl-cyclohexane carboxylic acid.

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 Ph.Eur.

<u>Manufacturing process</u>
A CEP has been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for microbiological quality. Analytical procedures have been adequately described and

sufficiently validated. Batch analytical data demonstrating compliance with this specification have been provided for three batches. The specification is acceptable.

Stability of drug substance
Covered by the CEP.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients has been justified and their functions explained. The MAH has compared the proposed product to the reference product on physicochemical characteristics, assay, and impurity profile. The choice of the sterilisation method has been sufficiently justified. Leachability studies have been adequately conducted. As the test and innovator drug products are to be administered as an infusion and contain the same drug substance in the same quantities, no bioequivalence study is required in accordance with the Guideline on the investigation of bioequivalence. Overall, the pharmaceutical development has been performed adequately.

Manufacturing process
The manufacturing process has been validated. Process validation data on the product have been presented for three batches in accordance with the relevant European/ICH and WHO guidelines. The manufacturing process consist of several steps including the preparation of solution, filtration, storage, filling, sterilisation, inspection, labelling, and packaging. Terminal sterilisation is performed on the medicinal product. Details on the in-process controls and process parameters have been provided. The proposed holding times have been found acceptable.

Control of excipients
The excipients comply with the Ph.Eur. and additional in-house requirements on microbiological quality. The analytical procedures have been adequately described and validated where necessary. These specifications are acceptable.

Microbiological attributes
The drug product is intended to be administered as parenteral (intravenous) solution for infusion. It is a terminally sterilised product and does not contain any antimicrobial preservatives. Adequate information on the microbiological attributes was submitted by the MAH including relevant precautionary measures during production, sterilisation process, controls on the microbiological quality and integrity of the container. Microbiological tests are included in the quality control of the product. The limits for these tests are in accordance with the relevant European guidelines.

Compatibility
Tranexaminezuur 10 mg/ml Kabi is a ready to use infusion solution, which means is administrated without the need of further dilutions. In the SmPC, the following is stated: “Tranexamic acid may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solution. Heparin may be added to

Tranexamic acid solution for infusion". The MAH has provided literature evidence that the medicinal product is compatible with these solutions. Additionally, the MAH has performed compatibility studies. No trends were observed and the measured values were well within the acceptance criteria. Based on these results, compatibility was demonstrated.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance of solution, degree of colouration, pH, extractable volume, identification, assay, purity tests (any individual unspecified degradation product, total degradation products), particulate contamination subvisible and visible particles, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The nitrosamine risk assessment was found to be acceptable. The elemental impurities risk assessment was performed according to ICH Q3D for parenteral dosage forms. The risk assessment process has not identified any potential elemental impurities with levels above the 30% of the established permissible daily exposure (PDE) at the currently used amounts.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scale batches of each packaging size stored during 18 months for long term at 25°C/40% RH, intermediate conditions at 30°C/35% RH and accelerated conditions at 40°C/25% RH. The tested stability indicating parameters are appearance of solution, degree of colouration, pH, weight loss, extractable volume, identification, assay, purity tests (any individual unspecified degradation product, total degradation products), particulate contamination subvisible and visible particles, bacterial endotoxins and sterility. The stability was tested in accordance with applicable European guidelines. Photostability studies according to the ICH Q1B have been provided, demonstrating that the product is photostable. A thermal cycling study was performed, confirming that the product should not be frozen, as it leads to an assay drop.

On basis of the data submitted, a shelf life was granted of 30 months. The labelled storage conditions are: "This medicinal does not require any special storage conditions. Do not freeze".

In-use storage time and conditions are not applicable as in the SmPC (section 6.3 Shelf life) of the product the following is stated: "The solution for infusion is for single use only. Unused solution must be discarded. From a microbiological point of view, the product should be used immediately after opening. Otherwise, the in-use storage time and conditions prior to use are in the responsibility of the user".

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

III.2 Discussion on the non-clinical aspects

As tranexamic acid is a widely used, well-known active substance with known pharmacodynamic, pharmacokinetic and toxicological properties, the MAH has not provided additional studies. Instead, an adequate 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

Tranexaminezuur Kabi 10 mg/ml solution for infusion is a well-known active substance with established efficacy and tolerability. An adequate clinical overview on the clinical pharmacology, efficacy and safety has been provided, which is based on scientific literature. No bioequivalence study has been performed because the product concerns an aqueous solution for intravenous use and the excipient sodium chloride is not expected to affect the disposition of tranexamic acid. The strength of Tranexaminezuur Kabi differs from the reference product Cyklokapron (10 mg/mL instead of 100 mg/mL). However, 10 mL of Tranexaminezuur Kabi is infused per minute instead of 1 mL/min as in the reference. Therefore, the dose administered is the same. The difference between increased infusion

volume is not considered clinically relevant for the proposed indications. Overall, the MAH has adequately justified why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 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 Kabi 10 mg/ml.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	Thromboembolism.
Important potential risks	None
Missing information	None

The differences in pharmaceutical form and administration rate compared to the reference product do not result in the addition or deletion of a safety concern. This is endorsed. The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

The application contains an adequate review of published clinical data. No bioequivalence study has been performed. The MAH has adequately justified why there is no need to generate additional clinical data. Based on the submitted data, therapeutic equivalence between the product and the reference was demonstrated. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Tranexamsäure Baxter 100 mg/ml solution for injection/infusion (DE/H/6097/001/DC) for content and to Amikacin 5 mg/ml solution for infusion (DE/H/5638/001/DC) and Potassium Chloride 0.15% w/v & Sodium Chloride 0.9% w/v, solution for infusion (PT/H/1153/001/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tranexaminezuur Kabi 10 mg/ml solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Cyklokapron® 100 mg/mL, solution for injection/infusion. 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 Tranexaminezuur Kabi 10 mg/ml solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 November 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-