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CBG MEB

Public Assessment Report

Scientific discussion

Tranexaminezuur Mylan 100 mg/ml, solution for injection

(tranexamic acid)

NL/H/3875/001/DC

Date: 8 May 2018

This module reflects the scientific discussion for the approval of Tranexaminezuur Mylan 100 mg/ml, solution for injection. The procedure was finalised on 15 November 2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

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

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 B.V. since 31 July 1968.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Tranexaminezuur Mylan 100 mg/ml is a clear, colourless solution with pH value between 6.5 and 8.0. Each ml contains 100 mg tranexamic acid.

The solution for injection is packed in type I glass ampoules.

The only excipient is 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, freely soluble in water and glacial acetic acid, practically insoluble in acetone and in alcohol.

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 the Ph.Eur monograph and the additional requirements from the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 production scaled batches.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 equivalent to the reference product Cyklokapron. The choices of the packaging, manufacturing process and final sterilisation are justified in relation to the innovator. In accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence, a bioequivalence study is not required as the product is administrated as an aqueous intravenous solution containing the active drug substance in the same concentration and as the reference product Cyklokapron. In addition, just as the reference product the formulation contains water for injection as solvent.

Manufacturing process
The manufacturing process includes preparation of solution, filtration and terminal sterilisation. The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been adequately presented for three batches each for two batch sizes and each fill volume. The manufacturing process has been adequately validated.

Control of excipients
The specification and testing methods for the excipient used in the manufacture of the product comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, extractable volume, acidity or alkalinity, identification, particulate contamination, bacterial endotoxins, sterility, related substances and assay. The release and shelf-life requirements are identical, except for assay. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two production-scale batches for two fill volumes (10 ml and 5 ml), demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided 17 production-scale batches stored at 25°C/60% RH (up to 36 months), 30°C/75% RH (up to 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.

Specific measures for the prevention of the transmission of animal spongiform encephalo-pathies
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 Mylan 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 Mylan 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 Mylan 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Tranexaminezuur Mylan 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 Mylan.

- Summary table of safety concerns as approved in RMP

Important identified risks	– Thromboembolism – Vision disturbances, including visual impairment, vision blurred, and impaired colour vision – Convulsions – Disseminated intravascular coagulation (DIC) – Hypotension due to rapid injection
Important potential risks	None
Missing information	– Use in pregnancy – Use in lactation – Use in paediatrics

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 package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tranexaminezuur Mylan 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 Tranexaminezuur Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 November 2017.

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