LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tranexa
(tranexamic acid)

Asp no 2015-1352

This module reflects the scientific discussion for the approval of Tranexa. The procedure was finalised on 2016-10-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Tranexa, 500 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, 2care4 ApS, Tomrervej 9 DK-6710 Esbjerg V, applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cyklokapron, 500 mg, film-coated tablet authorised in Denmark since 1969, with Meda A/S as marketing authorisation holder.

The reference product used in the bioequivalence study is Cyklokapron, 500 mg, film-coated tablets from Germany with Meda A/S as marketing authorisation holder.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Tranexa, 500 mg, film-coated tablet with Cyklokapron, 500 mg, film-coated tablet under fasting conditions. The dose was 1 g given as 2x500 mg. The study was conducted at Arab Pharmaceutical industry Consulting in Jordan between 20/2/2015 and 10/03/2015. Blood samples were collected pre-dose and up to 14 hours post-dose. The study design is considered acceptable. Plasma concentrations of tranexamic acid were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for tranexamic acid, n=30.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**57.25 ± 14.22**	**10.41 ± 2.78**	**2.50 1.50-4.50**
Reference	**55.97 ± 13.46**	**10.04 ± 3.05**	**3.00 2.00-4.50**
***Ratio (90% CI)**	**101.37 (91.56-112.23)**	**103.42 (92.33-115.84)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Based on the submitted bioequivalence study, Tranexa 500 mg film-coated tablet is considered bioequivalent with cyklokapron 500 mg film-coated tablet.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Tranexa.

Safety specification (updated)
Summary table of safety concerns as approved in RMP

Important identified risks	□ Hypersensitivity to the active substance. □ Thrombosis in patients with medical history of thromboembolic events. □ Haematuria from the upper urinary tract. □ Overdose in patients with renal impairment.
Important potential risks	□ Restriction of blood supply in patients with subarachnoid bleeding. □ Severe thrombosis in patients with disseminated intravascular coagulation. □ Misdiagnose of patients with irregular menstrual bleeding.
Missing information	□ Adolescents with menorrhagia below 15 years. □ Use during pregnancy. □ Use during lactation.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

The RMP is approved

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 language used for the purpose of user testing the PIL was English.
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

The quality of the product, Tranexa, is found adequate. There are no objections to approval of product name, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Tranexa, 500 mg, film-coated tablet was approved in the national procedure on 2016-10-20.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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