Tranexamic Acid 500 mg film-coated Tablets
PL 39891/0008

UKPAR

TABLE OF CONTENTS

Lay Summary                      Page 2
Scientific discussion             Page 3
Steps taken for assessment        Page 12
Steps taken after authorisation – summary
Summary of Product Characteristics Page 13
Patient Information Leaflet       Page 14
Labelling                         Page 15
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Double-E Pharma Limited a Marketing Authorisation for the medicinal product Tranexamic Acid 500 mg film-coated Tablets (PL 39891/0008) on 15 November 2012. This medicine is only available on prescription from your doctor.

The active ingredient, tranexamic acid, belongs to a group of medicines called anti-fibrinolytic drugs. These are used to stop or reduce unwanted bleeding. When you bleed your body forms clots to stop the bleeding. In some people these break down causing too much bleeding. Tranexamic acid stops these clots dissolving and so reduces unwanted bleeding.

Tranexamic Acid 500 mg film-coated Tablets are used to prevent or reduce bleeding for a short period of time in many different conditions. Tranexamic Acid 500 mg film-coated Tablets may be prescribed for one of the following:
• following prostate surgery (post-prostatectomy)
• following bladder surgery
• heavy periods (menorrhagia)
• nose bleeds (epistaxis)
• cervical surgery (conisation of the cervix)
• bleeding inside the eye (traumatic hyphaema)
• tooth removal (dental extraction) in haemophiliacs (people who bleed more easily than normal). You will know if this refers to you
• a hereditary disease called angioneurotic oedema (HANO). A doctor will have told you if you have this.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Tranexamic Acid 500 mg film-coated Tablets outweigh the risks and a Marketing Authorisation was granted.
Tranexamic Acid 500 mg film-coated Tablets
PL 39891/0008

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4

Pharmaceutical assessment Page 5

Non-clinical assessment Page 8

Clinical assessment Page 9

Overall conclusions and risk assessment Page 11
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Double-E Pharma Limited a Marketing Authorisation for the medicinal product Tranexamic Acid 500 mg film-coated Tablets (PL 39891/0008) on 15 November 2012. This product is a prescription-only medicine (POM) indicated for short term use for haemorrhage or risk of haemorrhage in those with increased fibrinolysis or fibrinogenolysis. Local fibrinolysis as occurs in the following conditions:

1. a) Prostatectomy and bladder surgery  
   b) Menorrhagia  
   c) Epistaxis  
   d) Conisation of the cervix  
   e) Traumatic hyphaema  
2. Management of dental extraction in haemophiliacs.  
3. Hereditary angioneurotic oedema.

This application was submitted under Article 10(1) of Directive 2001/83/EC (as amended), claiming to be a generic medicinal product of Cyklokapron 500 mg Film-coated Tablets (Meda Pharmaceuticals UK Limited, UK), which was first authorised in the UK on 14 February 2005.

The active ingredient, tranexamic acid, is a derivative of the aminoacid lysine which demonstrates clinical antifibrinolytic efficacy. Tranexamic acid blocks lysine binding sites on plasminogen molecules thereby inhibiting the interaction with lysine residues of fibrin and suppresses fibrin degradation.

One bioequivalence study was submitted to support this application, comparing the applicant’s test product Tranexamic acid 500 mg rapid release tablets with the reference product Cyklokapron 500 mg rapid release tablets (Pharmacia Laboratories Ltd, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Tranexamic Acid 500 mg film-coated Tablets outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Tranexamic acid
Chemical Name: Trans-4-(aminomethyl)cyclohexanecarboxylic acid
Molecular Formula: C₈H₁₅NO₂

Structure

Molecular weight: 157.2
Appearance: A white or almost white crystalline powder.
Solubility: Freely soluble in water and in glacial acetic acid, practically insoluble in acetone and in ethanol (96%).

Tranexamic acid is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients in the tablet core and coating namely cellulose microcrystalline, povidone (K 90), croscarmellose sodium, silica colloidal anhydrous, talc, magnesium stearate, methacrylate polymers, titanium dioxide (E171), talc, magnesium stearate and macrogol (8000). Appropriate justifications for the inclusion of each excipient have been provided.
All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contains materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**
The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product Cyklokapron 500 mg Film-coated Tablets (Meda Pharmaceuticals UK Limited, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and the reference product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Based on production-scale batches, the manufacturing process has been validated and has shown satisfactory results.

**Control of Finished Product**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The tablets are packaged in polyvinyl chloride/aluminium blisters. These are packed into cardboard cartons with Patient Information Leaflets in pack sizes of 60 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage conditions ‘Do not store above 30°C. Store in the original package.’

**Bioequivalence**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective. User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant that makes reference to the user test of the PIL for Tranexamic Acid 500 mg film coated tablets (PL 33155/0010; Rivopharm UK Limited, UK).

MAA (Marketing Authorisation Application) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of tranexamic acid are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of tranexamic acid is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study:

A randomised, open label, single-dose, two-period, crossover study to compare the pharmacokinetics of the test product Tranexamic acid 500 mg rapid release tablets (Rivopharm S.A., Switzerland) versus the reference product Cyklokapron 500 mg rapid release tablets (Pharmacia Laboratories Limited, UK) in healthy adult male and female subjects under fasting conditions.

The subjects were administered two tablets (2x500 mg) of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 14 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (geometric means±SD, ratios and confidence intervals [CI]) of tranexamic acid

<table>
<thead>
<tr>
<th></th>
<th>Geometric Means±SD</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tranexamic acid</td>
<td>Cyklokapron</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500mg (Test)</td>
<td>500mg (Reference)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>12251±1.26</td>
<td>11268±1.27</td>
<td>109</td>
</tr>
<tr>
<td>AUC0-t (ng hr/ml)</td>
<td>6760±1.24</td>
<td>6355±1.24</td>
<td>107</td>
</tr>
<tr>
<td>AUC0-inf (ng hr/ml)</td>
<td>7032±1.24</td>
<td>66198±1.24</td>
<td>107</td>
</tr>
</tbody>
</table>

Cmax = maximum plasma concentration
AUC0-t = area under the plasma concentration-time curve from time zero to t hours
AUC0-inf = area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from ln-transformed data
SD=standard deviation

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and Cmax values. Thus, the data support the claim that the applicant’s test product Tranexamic acid 500 mg rapid release tablets is bioequivalent to the reference product Cyklokapron 500 mg rapid release tablets (Pharmacia Laboratories Limited, UK) under fasting conditions.

EFFICACY
The efficacy of tranexamic acid is well-known. No new efficacy data have been submitted and none are required for this type of application.
SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are satisfactory from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Tranexamic Acid 500 mg film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of tranexamic acid are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s Tranexamic acid 500 mg rapid release tablets (Rivopharm S.A., Switzerland) and the reference product Cyklokapron 500 mg rapid release tablets (Pharmacia Laboratories Limited, UK) under fasting conditions.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of tranexamic acid is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tranexamic acid is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 04 October 2011.
2 Following standard checks and communication with the applicant the MHRA considered the application valid on 02 November 2011.
3 Following assessment of the application the MHRA requested further information relating to the dossier on 20 January 2012 and 06 July 2012.
4 The applicant responded to the MHRA’s requests, providing further information on the dossier on 22 June 2012 and 31 August 2012.
5 The application was granted on 15 November 2012.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.