Public Assessment Report

Decentralised Procedure

TRANEXAMIC ACID 500MG/5ML SOLUTION FOR INJECTION

Procedure No: UK/H/5039/001/DC

UK Licence No: PL 20046/0098

FOCUS PHARMACEUTICALS LIMITED
LAY SUMMARY

On 25 February 2013, Ireland and the UK agreed to grant a marketing authorisation to Focus Pharmaceuticals Limited for the medicinal product Tranexamic Acid 500mg/5ml Solution for Injection (PL 20046/0098; UK/H/5039/001/DC). This prescription-only medicine (POM) is used for:

- heavy periods in women;
- gastrointestinal bleeding;
- haemorrhagic urinary disorders after having an operation on the prostate gland or urinary tract;
- after having an operation on the ear, nose or throat;
- after having heart, abdominal or gynaecological surgery;
- bleeding after treatment with another medicine to break down blood clots.

This product contains tranexamic acid which belongs to a group of medicines called antihaemorrhagics; antifibrinolytics, aminoacids. Tranexamic acid is used in adults and children above one year of age for the prevention and treatment of bleeding due to a process that inhibits blood clotting called fibrinolysis.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Tranexamic Acid 500mg/5ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted. A national licence was granted in the UK on 26 March 2013.
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Module 1
Information about initial procedure

<table>
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<tr>
<th>Product Name</th>
<th>Tranexamic Acid 500mg/5ml Solution for Injection</th>
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<tr>
<td>Type of Application</td>
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<td>Form</td>
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<td>MA Holder</td>
<td>Focus Pharmaceuticals Ltd, Unit 5 Faraday Court, First Avenue, Centrum 100, Burton-upon-Trent, DE14 2WX</td>
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<td>Reference Member State (RMS)</td>
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<td>Concerned Member States (CMS)</td>
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Module 2
Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.

Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
On 25 February 2013, Ireland and the UK agreed to grant a marketing authorisation to Focus Pharmaceuticals Limited for the medicinal product Tranexamic Acid 500mg/5ml Solution for Injection (PL 20046/0098; UK/H/5039/001/DC). This is a prescription-only medicine (POM) indicated for the Prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from 1 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.

This application was submitted via the decentralised procedure as an abridged application according to Article 10(1) of Directive 2001/83/EC, claiming to be a generic medicinal product of Cyklokapron Injection 500mg/5ml solution for injection, which was initially granted a licence to Pharmacia Limited in February 1987.

Tranexamic acid is an antifibrinolytic drug which is used to control bleeding by preventing clot breakdown (fibrinolysis). It is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a generic medicinal product for a solution for injection. Bioequivalence is confirmed through the qualitative and quantitative composition of the product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

After a subsequent national phase, a licence was granted in the UK on 26 March 2013.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Tranexamic Acid 500mg/5ml Solution for Injection |
| Name(s) of the active substance(s) (INN) | Tranexamic acid |
| Pharmacotherapeutic classification (ATC code) | Tranexamic acid (B02AA02) |
| Pharmaceutical form and strength(s) | Solution for injection 500mg/5ml |
| Reference numbers for the Mutual Recognition Procedure | UK/H/5039/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Ireland |
| Marketing Authorisation Number(s) | PL 20046/0098 |
| Name and address of the authorisation holder | Focus Pharmaceuticals Ltd, Unit 5 Faraday Court, First Avenue, Centrum 100, Burton-upon-Trent, DE14 2WX |

## III. SCIENTIFIC OVERVIEW AND DISCUSSION

### III.1 QUALITY ASPECTS

#### S. Active substance – Tranexamic acid

**INN:** Tranexamic acid  
**Chemical name:** Trans-4-(aminomethyl) cyclohexanecarboxylic acid  
**Structure:**

![Structure of Tranexamic Acid](image)

**Molecular formula:** C₈H₁₅NO₂  
**Molecular weight:** 157.2  
**Physical form:** A white or almost white crystalline powder, freely soluble in water and glacial acetic acid, practically insoluble in acetone and ethanol

Tranexamic acid is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug 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.

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.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

**P. Medicinal Product**

**Other ingredients**

Other ingredients consist of the pharmaceutical excipient water for injection, which is controlled to its European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for water for injection showing compliance with its respective monograph.

None of the excipients used contain material of animal or human origin.

**Pharmaceutical development**

The aim of the pharmaceutical development was to create an injectable solution containing 500mg of tranexamic acid per 5ml of product that could be considered a generic medicinal product of Cyklokapron Injection 500mg/5ml (Pharmacia Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative physico-chemical characteristics have been provided for the proposed product versus the originator product, and pharmaceutical equivalence has been shown.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on production-scale batches. The results are satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Test methods have been described and have been 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 finished product is stored in clear Type I glass ampoules, which are packed into cardboard cartons in pack sizes of 10 ampoules.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 30 months (unopened) with the storage conditions “Do not store above 25°C. Store in the original packaging. Do not refrigerate or freeze.” It should be noted that this products should be used immediately on opening and any unused portion should be discarded.

**Bioequivalence/bioavailability**

No bioequivalence study is submitted with this application. Essential similarity with the reference product is shown by the qualitative and quantitative composition.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is pharmaceutically satisfactory.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
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.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected. Therefore, no environmental risk assessment is required for this application.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Clinical Pharmacology and Efficacy
No bioequivalence study is submitted with this application. Essential similarity with the reference product is shown by the qualitative and quantitative composition.

Safety
No new data have been submitted and none are required for an application of this type.

SmPC, PIL and Labels
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

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.
Clinical Expert Report
The clinical expert report has been 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.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Tranexamic Acid 500mg/5ml Solution for Injection 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 and none are required for an application of this type.

CLINICAL
No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the qualitative and quantitative composition of the product versus that of the reference product, Cyklokapron Injection 500mg/5ml solution for injection (Pharmacia Limited, UK).

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product. (Pharmacia Limited).

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s product and the reference product Cyklokapron Injection 500mg/5ml solution for injection (Pharmacia Limited, UK) are interchangeable. Extensive clinical experience with tranexamic acid is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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