

# **Public Assessment Report**

## **Decentralised Procedure**

**Tranexamic Acid 100 mg/ml solution for injection**

**Procedure No: UK/H/5436/001/DC**

**UK Licence No: PL 31745/0028**

**Ibigen S.r.l.**

## Lay Summary

### Tranexamic Acid 100 mg/ml solution for injection (tranexamic acid)

This is a summary of the public assessment report (PAR) for Tranexamic Acid 100 mg/ml solution for injection (PL 31745/0028; UK/H/5436/001/DC). It explains how Tranexamic Acid 100 mg/ml solution for injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Tranexamic Acid 100 mg/ml solution for injection.

For practical information about using Tranexamic Acid 100 mg/ml solution for injection, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

#### **What is Tranexamic Acid 100 mg/ml solution for injection and what is it used for?**

Tranexamic Acid 100 mg/ml solution for injection is a 'generic medicine'. This means that it is similar to a 'reference medicine', already authorised in the European Union (EU) called Cyklokapron Injection, 500 mg/5 ml solution for injection.

Tranexamic Acid 100 mg/ml solution for injection 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. Specific conditions include: heavy periods in women; gastrointestinal bleeding; haemorrhagic urinary disorders, after having an operation on your prostate gland or urinary tract; after having an operation on your ear, nose or throat; after having heart, abdominal or gynaecological surgery; and, bleeding after you have been treated with another medicine to treat blood clots.

#### **How does Tranexamic Acid 100 mg/ml solution for injection work?**

Tranexamic Acid 100 mg/ml solution for injection contains the active substance tranexamic acid. Tranexamic acid belongs to a group of medicines called 'anti-haemorrhagics' or 'anti-fibrinolytics'. Tranexamic acid works as an anti-haemorrhagic medicine in the body by inhibiting the activation of a protein that leads to blood clot breakdown (fibrinolysis).

#### **How is Tranexamic Acid 100 mg/ml solution for injection used?**

Tranexamic Acid 100 mg/ml solution for injection should be given to the patient by a slow injection into a vein. It should not be injected into a muscle.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The prescribing doctor will decide the correct dose and for how long Tranexamic Acid 100 mg/ml solution for injection should be taken for. In adults, the usual dose for the treatment of local fibrinolysis is 500 - 1000 mg (5 - 10 ml) three times a day, and the usual dose for the treatment of general fibrinolysis is 1000 mg (10 ml) every 6 to 8 hours, or up to 15 mg per kg of body weight.

The medicine can only be obtained with a prescription.

**What benefits of Tranexamic Acid 100 mg/ml solution for injection have been shown in studies?**

No additional studies were needed as Tranexamic Acid 100 mg/ml solution for injection is a generic medicine that is given by intravenous injection and contains the active substance in the same quantity as the reference medicine, Cyklokapron Injection, 500 mg/5 ml solution for injection.

**What are the possible side effects from Tranexamic Acid 100 mg/ml solution for injection?**

Like all medicines, this medicine can cause side effects although not everybody gets them.

For information about side effects that may occur with using Tranexamic Acid 100 mg/ml solution for injection, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Why is Tranexamic Acid 100 mg/ml solution for injection approved?**

It was concluded that, in accordance with EU requirements, Tranexamic Acid 100 mg/ml solution for injection has been shown to have comparable quality and to be comparable to Cyklokapron Injection, 500 mg/5 ml solution for injection. Therefore, the view was that, as for Cyklokapron Injection, 500 mg/5 ml solution for injection, the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Tranexamic Acid 100 mg/ml solution for injection?**

A Risk Management Plan (RMP) has been developed to ensure that Tranexamic Acid 100 mg/ml solution for injection is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Tranexamic Acid 100 mg/ml solution for injection**

Ireland, Malta and the UK agreed to grant a marketing authorisation for Tranexamic Acid 100 mg/ml solution for injection on 16 October 2014. The marketing authorisation in the UK was granted on 03 November 2014.

The full PAR for Tranexamic Acid 100 mg/ml solution for injection follows this summary.

For more information about treatment with Tranexamic Acid 100 mg/ml solution for injection, read the PIL or contact your doctor or pharmacist.

This summary was last updated in December 2014.

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## I Introduction

Based on the review of the data on quality, safety and efficacy, the member states have granted a marketing authorisation (MA) for the medicinal product Tranexamic Acid 100 mg/ml solution for injection. The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland and Malta as Concerned Member States (CMSs).

Tranexamic Acid 100 mg/ml solution for injection is a prescription-only medicine (POM), 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

This application was made under made under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product. The reference medicinal product, which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area, is Cyklokapron Injection, 500 mg/5 ml solution for injection. This reference medicinal product was authorised to Pharmacia Laboratories Limited in the UK on 09 February 1987 (PL 00022/0004R). On 01 November 2001, the marketing authorisation for the reference product was updated by a change of ownership to Pharmacia Limited (PL 00032/0314), and then again on 30 August 2012 to the current marketing authorisation holder Pfizer Limited (PL 00057/0952).

The medicinal product contains the active substance tranexamic acid, which exerts an anti-haemorrhagic activity by inhibiting the fibrinolytic properties of plasmin. Tranexamic acid inhibits the activation of plasminogen to plasmin by forming a complex with plasminogen.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No clinical studies were performed as part of this application. A bioequivalence study was not necessary to support this application for an aqueous parenteral product, containing the same active substance as the reference product. Comparative physico-chemical characteristics have been provided for the proposed product versus the originator product, and pharmaceutical equivalence has been shown.

The RMS 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.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Since Tranexamic acid 500mg/5ml solution for injection 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.

The RMS and CMSs considered that the application could be approved at the end of procedure (Day 205) on 16 October 2014. After a subsequent national phase, a licence was granted in the UK on 03 November 2014.

## II Quality aspects

### II.1 Introduction

The application is submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has specified Cyklokapron Injection, 500 mg/5 ml solution for injection, authorised in the UK (PL 00057/0952; MA holder: Pfizer Limited) as the reference medicinal product for the purpose of determining the expiry period of data exclusivity.

The product is formulated as a clear, solution for injection, free of particles, containing the active substance tranexamic acid at a concentration of 100 mg/ml. The excipients present are water for injections, sodium hydroxide and hydrochloric acid.

The oral solution is presented in Type I glass 5 ml (5 ml fill volume) and 10ml (10 ml fill volume) ampoules, which are further packed in cardboard boxes of 1, 5, 10, 20 and 50 ampoules.

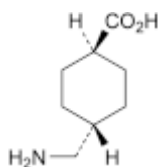
### II.2 Drug Substance

#### Tranexamic acid

INN: Tranexamic acid

Chemical Name: *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid

Structure:



Molecular formula: C<sub>8</sub>H<sub>15</sub>NO<sub>2</sub>

Molecular weight: 157.2

Appearance: White or almost white, crystalline powder.

Solubility: Freely soluble in water and in glacial acetic acid, practically insoluble in acetone and in ethanol (96 per cent).

Tranexamic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, tranexamic acid, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

### II.3 Medicinal Product

#### Pharmaceutical development

The aim of the pharmaceutical development was to obtain a generic finished product essentially similar to the UK reference medicinal product, Cyklokapron, 500 mg/5 ml solution for injection.

All the excipients used in the manufacture of the proposed formulation comply with their respective European Pharmacopoeial monographs.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

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

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

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

### **Manufacture of the product**

Satisfactory batch formulae have been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated for manufacture of the smallest-scale production batch size. A commitment has been provided that process validation for manufacture of the finished product will be performed on three batches for each of the larger production-scale batches. Validation protocols reflecting the larger production-scale batches were provided and are satisfactory.

### **Finished Product Specification**

The finished product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided from two production-scale batches that comply with the release specification. Certificates of analysis have been provided for all working standards used.

### **Stability of the product**

Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months (unopened) with special storage conditions of “Do not refrigerate or freeze”. Once the ampoule is opened the product should be used immediately. After opening, any unused product should be discarded.

Suitable post approval stability commitments have been provided.

## **II.4 Discussion on chemical, pharmaceutical and biological aspects**

The grant of a marketing authorisation is recommended.

## **III Non-clinical aspects**

The pharmacology, pharmacokinetics and toxicology of tranexamic acid are well-known and are adequately described in the non-clinical overview. No new non-clinical studies were conducted in support of this application, which is acceptable for a generic product.

An adequate justification has been provided for the absence of an Environmental Risk Assessment (ERA). The product is intended for generic substitution and will not lead to an increase in exposure to the environment.

The product literature is in line with the harmonised text for tranexamic acid that has been published following a CHMP Article 31 referral of antifibrinolytic agents.

In conclusion, this application is approvable from a non-clinical point of view.

## IV Clinical aspects

### IV.1 Introduction

No new clinical data have been submitted for this application. The applicant's clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately qualified person and is adequate. The proposed indications and posology are identical to those of the reference product.

Antifibrinolytic agents, including tranexamic acid, were the subject of a CHMP Article 31 referral, which concluded in February 2012 (EMEA/H/A-31/1267). No new safety concerns were revealed for tranexamic acid, though the Committee requested more information on optimal dosing in children. Harmonised prescribing information has been published for tranexamic acid and the SmPC of Tranexamic Acid 100 mg/ml solution for injection is in line with this information.

### IV.2 Pharmacokinetics

No bioequivalence studies have been performed. A biowaiver is sought, on the basis that both the reference product and Tranexamic Acid 100 mg/ml solution for injection are aqueous solutions intended to be administered intravenously, containing the same active substance as the currently approved product. This is in accordance with the *Guideline On The Investigation Of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1)* and is acceptable.

### IV.3 Pharmacodynamics

No new studies have been performed and none are required for this type of application.

### IV.4 Clinical efficacy

No new studies have been performed and none are required for this type of application.

### IV.5 Clinical safety

No new safety data were submitted with this application and none were required.

### IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP, 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 Tranexamic Acid 100 mg/ml solution for injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

**Summary table of safety concerns**

Important identified risks	<p>The important identified risks associated with medicinal products with tranexamic acid as active substances are detailed the SmPC of the original product Cyklokapron, and also reported in the proposed SmPC in annex 2:</p> <ul style="list-style-type: none"> <li>• visual disturbances, including visual impairment, vision blurred, impaired colour vision (section 4.4; 4.8);</li> <li>• thromboembolic events (section 4.3; 4.4; 4.5; 4.8);</li> </ul>
Important potential risks	<p>According to the SmPC of the original product Cyklokapron, important potential risk can be</p> <ul style="list-style-type: none"> <li>• renal insufficiency (section 4.2; 4.3).</li> </ul> <p>This information is reported also in the proposed SmPC (annex 2).</p>
Important missing information	<p>According to the SmPC:</p> <ul style="list-style-type: none"> <li>• There is insufficient clinical data on the use of tranexamic acid in pregnant women. As a result, although studies in animals do not indicate teratogenic effects, as precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy.</li> <li>• Limited clinical data of the use of tranexamic acid in different clinical haemorrhagic settings during the second and third trimesters did not identify deleterious effect for the foetus. Tranexamic acid should be used throughout pregnancy only if the expected benefit justifies the potential risk.</li> <li>• There are no clinical data on the effects of tranexamic acid on fertility</li> <li>• No studies have been performed on the ability to drive and use machines.</li> <li>• In children over one year old: While studied in very few patients, the limited data suggest that continuous infusion is preferable, since it would maintain therapeutic plasma concentration throughout surgery. No specific dose-effect study or PK study has been conducted in children.</li> </ul>
	<ul style="list-style-type: none"> <li>- The efficacy, posology and safety of tranexamic acid in children undergoing cardiac surgery have not been fully established.</li> </ul>

**Summary table of risk minimisation measures**

<b>Safety concern</b>	<b>Routine risk minimisation measures</b>	<b>Additional risk minimisation measures</b>
Important identified risks	Routine pharmacovigilance activities.	None proposed.
Important potential risks	Routine pharmacovigilance activities.	None proposed.
Important missing information	Routine pharmacovigilance activities.	None proposed.

**IV.7 Discussion on the clinical aspects**

The grant of a marketing authorisation is recommended for this application.

**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, as amended. 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 is acceptable, and no new non-clinical or clinical safety concerns have been identified. Intravenous tranexamic acid has been in use in the UK for over 20 years, and has a well-established level of efficacy and safety. An Article 31 referral procedure concluded that the benefit-risk profile for tranexamic acid was positive. The request of the applicant for a biowaiver is acceptable and bioequivalence, between the test and reference products, has been shown through comparable physico-chemical characteristics. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in-line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The currently approved labels are listed below:

**Tranexamic Acid**

**500mg / 5ml**

100mg/ml Solution for injection. For IV use.  
PL 31745/0028

Batch Number      Expiry

**Tranexamic Acid**

**1g / 10ml**

100mg/ml Solution for injection.  
For IV use  
PL 31745/0028

Batch Number      Expiry

**Tranexamic Acid**  
100mg/ml Solution for injection

**500mg / 5ml**

**bourned bisqus**

For intravenous use  
5 ampoules

Tranexamic Acid 100mg/ml Solution for injection

**500mg / 5ml**

5 ampoules

Tranexamic Acid 100mg/ml Solution for injection

**500mg / 5ml**

5 ampoules

Each 5ml ampoule contains 500mg Tranexamic acid.  
Each 1ml contains 100mg Tranexamic acid.  
Also contains water for injections,  
sodium hydroxide, hydrochloric acid.  
For single use only.  
Once opened use immediately.  
Discard any unused contents.  
Read the package leaflet  
before use.  
Keep out of the sight and  
reach of children.  
Do not refrigerate or freeze.

**bourned bisqus**

Spots for dispensing label

Distributed by:  
Bourned Bisqus Ltd  
Chirk, Wrexham  
UK, LL14 5NS  
PL 31745/0028

MA Holder:  
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## Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report  
(Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached Y/N (version)