

# Tranexamic Acid Injection I.P.

## CYKLOKAPRON<sup>®</sup>



### 1. GENERIC NAME

Tranexamic Acid Injection I.P 100 mg/mL

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 100 mg tranexamic acid.

#### List of excipients

Water for Injection

### 3. DOSAGE FORM AND STRENGTH

Solution for injection/infusion.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis.

#### 4.2 Posology and method of administration

##### Posology

##### *Adults*

Unless otherwise prescribed, the following doses are recommended:

##### 1. Standard treatment of local fibrinolysis:

0.5 g (1 ampoule of 5 mL) to 1 g (1 ampoule of 10 mL or 2 ampoules of 5 mL) tranexamic acid by slow intravenous injection or infusion (= 1 mL/minute) two to three times daily

## 2. Standard treatment of general fibrinolysis:

1 g (1 ampoule of 10 mL or 2 ampoules of 5 mL) tranexamic acid by slow intravenous injection or infusion (= 1 mL/minute) every 6 to 8 hours, equivalent to 15 mg/kg body weight (BW)

### *Renal impairment*

For patients with renal impairment, the dosage of tranexamic acid should be reduced according to the serum creatinine level:

Serum creatinine (micromol/L)	Serum creatinine mg/dL	Intravenous dose	Administration
120 to 249	1.35 to 2.82	10 mg/kg body weight	Every 12 hours
250 to 500	2.82 to 5.65	10 mg/kg body weight	Every 24 hours
>500	>5.65	5 mg/kg body weight	Every 24 hours

### *Hepatic impairment*

No dose adjustment is required in patients with hepatic impairment.

### *Elderly*

No reduction in dosage is necessary unless there is evidence of renal failure.

### Mode of administration

The administration is strictly limited to slow intravenous injection or infusion of a maximum of 1 mL per minute (see section 8.4).

**TRANEXAMIC ACID SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY and should not be administered intrathecally or epidural** (see sections 4.3 and 4.4).

IN ORDER TO REDUCE THE RISK OF FATAL MEDICATION ERRORS DUE TO INCORRECT ROUTE OF ADMINISTRATION OF TRANEXAMIC ACID, IT IS STRONGLY RECOMMENDED TO LABEL THE SYRINGES CONTAINING TRANEXAMIC ACID (see sections 4.3, 4.4 and 8.4).

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 2.
- Acute venous or arterial thrombosis (see section 4.4).
- Fibrinolytic conditions following consumption coagulopathy except in patients with predominant activation of the fibrinolytic system with acute severe bleeding (see section 4.4).
- History of convulsions.
- Intrathecal, epidural, intraventricular injection and intracerebral application (risk of cerebral oedema, convulsions and death).

#### 4.4 Special warnings and precautions for use

The indications and method of administration indicated above should be followed strictly:

- Intravenous injections or infusions should be given very slowly (max. 1 mL per minute).
- Tranexamic acid must not be administered by the intramuscular route.

##### Risk of medication errors due to incorrect route of administration

Tranexamic Acid Injection I.P 100 mg/mL is for intravenous use only. Intrathecal, epidural, intraventricular and intracerebral use of Tranexamic Acid Injection I.P 100 mg/mL is contraindicated (see section 4.3). Serious adverse reactions including fatal events have been reported when tranexamic acid was inadvertently administered intrathecally. These events have included severe back, gluteal and lower limb pain, myoclonus and generalised seizures, and cardiac arrhythmias.

Care should be exercised to ensure the correct route of administration of Tranexamic Acid Injection I.P 100 mg/mL. Healthcare professionals should be aware of the potential for confusion of Tranexamic Acid Injection I.P 100 mg/mL with other injectables which could result in inadvertent intrathecal administration of Tranexamic Acid Injection I.P 100 mg/mL. This includes in particular intrathecally administered injectables that may be used during the same procedure as tranexamic acid.

Syringes containing Tranexamic Acid Injection I.P 100 mg/mL should be clearly labelled with the intravenous route of administration.

##### Convulsions

Cases of convulsions have been reported in association with tranexamic acid treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following intravenous (IV.) injection of tranexamic acid in high doses. With the use of the recommended lower doses of tranexamic acid, the incidence of post-operative seizures was the same as that in untreated patients.

##### Visual disturbances

Attention should be paid to possible visual disturbances including visual impairment, vision blurred, impaired colour vision and if necessary, the treatment should be discontinued. With continuous long-term use of tranexamic acid, regular ophthalmologic examinations (eye examinations including visual acuity, colour vision, fundus, visual field etc.) are indicated. With pathological ophthalmic changes, particularly with diseases of the retina, the physician must decide after consulting a specialist on the necessity for the long-term use of tranexamic acid in each individual case.

## Haematuria

In case of haematuria from the upper urinary tract, there is a risk of urinary obstruction at the lower levels of the tract.

If left untreated, urinary obstruction may lead to serious consequences such as renal insufficiency, urinary tract infection, hydronephrosis, and anuria. Therefore, close monitoring is recommended for those patients with haematuria or risk of haematuria from the upper urinary tract.

## Thromboembolic events

Before use of tranexamic acid, risk factors of thromboembolic disease should be considered. In patients with a history of thromboembolic diseases or in those with increased incidence of thromboembolic events in their family history (patients with a high risk of thrombophilia), tranexamic acid should only be administered if there is a strong medical indication after consulting a physician experienced in haemostaseology and under strict medical supervision (see section 4.3). Tranexamic acid should be administered with care in patients using hormonal contraception because of the increased risk of thrombosis (see section 4.5).

## Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with tranexamic acid (see section 4.3). If tranexamic acid is given it must be restricted to those in whom there is predominant activation of the fibrinolytic system with acute severe bleeding.

Characteristically, the haematological profile approximates to the following: reduced euglobulin clot lysis time; prolonged prothrombin time; reduced plasma levels of fibrinogen, factors V and VIII, plasminogen, fibrinolysin and alpha-2 macroglobulin; normal plasma levels of P and P complex; i.e. factors II (prothrombin), VIII and X; increased plasma levels of fibrinogen degradation products; a normal platelet count. The foregoing presumes that the underlying disease state does not of itself modify the various elements in this profile. In such acute cases a single dose of 1 g tranexamic acid is frequently sufficient to control bleeding. Administration of tranexamic acid in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available.

## **4.5 Drug interactions**

No interaction studies have been performed. Simultaneous treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field.

Medicinal products that act on haemostasis should be given with caution to patients treated with tranexamic acid. There is a risk of increased thrombus-formation potential during,

concomitant use with hormonal contraception. Alternatively, the antifibrinolytic action of the drug may be antagonised with thrombolytic drugs.

#### 4.6 Use in special populations

##### Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment (see sections 4.4 and 4.5).

##### Pregnancy

Available data from published studies, case series and case reports with tranexamic acid use in pregnant women in the second and third trimester and at the time of delivery have not clarified whether there is a drug-associated risk of miscarriage or adverse maternal or foetal outcomes. There are cases of foetal structural abnormalities that resulted in death of the newborn following administration of tranexamic acid to the mother during conception or the first trimester of pregnancy; however, due to other confounding factors the risk of major birth defects with use of tranexamic acid during pregnancy is not clear.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg/kg to pregnant women is about 30 mg/L, as high as in the maternal blood.

There were 13 clinical studies that described foetal and/or neonatal functional issues such as low Apgar score, neonatal sepsis, cephalohematoma and 9 clinical studies that discussed alterations to growth including low birth weight and preterm birth at 22-36 weeks of gestation in foetuses and infants exposed to tranexamic acid *in-utero*.

For decisions regarding the use of tranexamic acid during pregnancy, the potential risk of tranexamic acid administration on the foetus should always be considered along with the mother's clinical need for tranexamic acid; an accurate risk-benefit evaluation should drive the treating physician's decision.

##### Breast-feeding

Published literature reports the presence of tranexamic acid in human milk. There are limited data on the effects of tranexamic acid on the breast-fed child or the effects on milk production. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for tranexamic acid and any potential adverse effects on the breast-fed child from tranexamic acid or from the underlying maternal condition.

Due to limited data, no final assessment can be established on the use of tranexamic acid during breast-feeding.

### Fertility

There are no clinical data on the effects of tranexamic acid on fertility. In animal studies, tranexamic acid did not affect male or female fertility at clinically relevant doses (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

No studies have been performed on the ability to drive and use machines.

### **4.8 Undesirable effects**

The adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

#### Tabulated list of adverse reactions

Adverse reactions reported are presented in table below. Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

<b>System organ class</b>	<b>Common ≥1/100 to &lt;1/10</b>	<b>Uncommon ≥1/1,000 to &lt;1/100</b>	<b>Frequency not known (cannot be estimated from the available data)</b>
Immune system disorders			- Hypersensitivity reactions including anaphylaxis
Nervous system disorders			- Convulsions particularly in case of misuse (see sections 4.3 and 4.4)
Eye disorders			- Visual disturbances including impaired colour vision
Vascular disorders			- Malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration) - Arterial or venous thrombosis at any sites
Gastrointestinal disorders	- Diarrhoea - Vomiting - Nausea		
Skin and subcutaneous tissue disorders		- Dermatitis allergic	

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

### **4.9 Overdose**

No case of overdose has been reported.

Signs and symptoms may include dizziness, headache, hypotension, and convulsions. It has been shown that convulsions tend to occur at higher frequency with increasing dose.

Supportive care should be provided in case of overdose.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Mechanism of action**

Pharmacotherapeutic group: Antihemorrhagics, Antifibrinolytics, Amino acids; ATC code: B02AA02.

Tranexamic acid exerts an antihemorrhagic activity by inhibiting the fibrinolytic properties of plasmin.

A complex involving tranexamic acid and plasminogen is constituted, with the tranexamic acid linked to plasminogen when transformed into plasmin.

The activity of the tranexamic acid-plasmin complex on the activity on fibrin is lower than the activity of free plasmin alone.

### **5.2 Pharmacodynamic properties**

*In vitro* studies showed that high tranexamic dosages decreased the activity of complement.

### **5.3 Pharmacokinetic properties**

#### Absorption

Peak plasma concentrations of tranexamic acid are obtained rapidly after a short intravenous infusion after which plasma concentrations decline in a multi-exponential manner.

## Distribution

The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin. The initial volume of distribution is about 9 to 12 litres.

Tranexamic acid passes through the placenta. Following administration of an intravenous injection of 10 mg/kg to 12 pregnant women, the concentration of tranexamic acid in serum ranged 10-53 micrograms/mL while that in cord blood ranged 4-31 micrograms/mL. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. Following administration of an intravenous injection of 10 mg/kg to 17 patients undergoing knee surgery, concentrations in the joint fluids were similar to those seen in corresponding serum samples. The concentration of tranexamic acid in a number of other tissues is a fraction of that observed in the blood (breast milk, one hundredth; cerebrospinal fluid, one tenth; aqueous humor, one tenth). Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.

## Elimination

Tranexamic acid is excreted mainly in the urine as unchanged drug. Urinary excretion via glomerular filtration is the main route of elimination. Renal clearance is equal to plasma clearance (110 to 116 mL/min). Excretion of tranexamic acid is about 90% within the first 24 hours after intravenous administration of 10 mg/kg body weight. The elimination half-life of tranexamic acid is approximately 3 hours.

## Other special populations

Plasma concentrations increase in patients with renal failure.

## **6. NONCLINICAL PROPERTIES**

### **6.1 Animal toxicology or pharmacology**

#### Carcinogenesis and mutagenesis

No evidence of carcinogenicity or mutagenicity was observed in conventional studies with tranexamic acid.

#### Reproductive toxicity

In reproductive toxicity studies (fertility and early embryonic development studies, embryo-foetal development studies, and pre-and postnatal studies), tranexamic acid had no adverse effect on reproductive parameters of mice, rats and rabbits at clinically relevant doses.



## General toxicology

Retinal toxicity has been observed in nonclinical studies with tranexamic acid. The observed toxicity was characterised by retinal atrophy commencing with changes to the retinal pigmented epithelium and progressing to retinal detachment in cats. The toxicity appeared to be dose-related, and changes were partially reversible at lower doses. Effects (some fully reversible) were seen in cats at clinically relevant doses, effects in dogs were only observed at multiples of the clinical dose. Studies suggest that the underlying mechanism may be related to a transient retinal ischemia at higher dose exposures, linked to the known sympathomimetic effect of high plasma levels of tranexamic acid. The clinical relevance of these findings is unknown.

Epileptogenic activity has been observed in animals with intrathecal use of tranexamic acid.

### **7. DESCRIPTION**

Clear, colourless solution with a pH of 6.5-8.0.  
1 mL contains 100 mg tranexamic acid.

### **8. PHARMACEUTICAL PARTICULARS**

#### **8.1 Incompatibilities**

This medicinal product should not be mixed with blood for transfusion or with solutions containing penicillin.

#### **8.2 Shelf life**

36 months.

#### **8.3 Packaging information**

Glass ampoules. Each ampoule contains 5 mL of Tranexamic Acid solution (100 mg/mL) for injection.

#### **8.4 Storage and handling instructions**

Store below 30°C. Protect from light. Do not freeze.  
Keep out of reach of children.

#### **Instructions for use/handling**

Healthcare professionals are strongly advised to label the Tranexamic Acid Injection I.P 100 mg/mL syringes during the withdrawal of the product from the ampoule for clear

identification and proper route of administration, to help prevent inadvertent medication errors during administration to the patient.

Tranexamic Acid Injection I.P 100 mg/mL may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions. Heparin may be added to Tranexamic Acid Injection I.P 100 mg/mL.

Tranexamic Acid Injection I.P 100 mg/mL is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

## 9. PATIENT COUNSELLING INFORMATION

### Hypersensitivity reactions

Inform patients that Tranexamic Acid Injection I.P 100 mg/mL may cause hypersensitivity reactions and to contact their healthcare provider for any signs or symptoms of hypersensitivity reactions.

### Seizures

Inform patients that tranexamic acid may cause seizures and to contact their healthcare provider for any signs or symptoms suggestive of seizures (see section 4.4).

### Visual disturbances

Inform patients that tranexamic acid can cause visual disturbance and that they should report any eye symptoms or change in their vision to their healthcare provider and to follow-up with an ophthalmologist for a complete ophthalmologic evaluation, including dilated retinal examination of the retina (see section 4.4).

### Thromboembolic events

Inform patients that tranexamic acid may increase the risk of venous and arterial thrombosis or thromboembolism and to contact their healthcare provider for any signs or symptoms suggestive of thromboembolism.

Advise patients using hormonal contraception that combined use with tranexamic acid may increase the risk for thromboembolic adverse reactions and to use effective alternative (nonhormonal) contraception during therapy with tranexamic acid (see sections 4.4 and 4.5).

## 10. DETAILS OF MANUFACTURER

M/s. Pfizer Manufacturing Belgium NV Rijksweg 12, B-2870 Puurs-Sint-Amunds, Belgium

**11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE**

FF-362-7589 dated 14 February 2023

**12. DATE OF REVISION**

March 2025