

Tranexamic Acid Injection I.P.

CYKLOKAPRON[®]



1. GENERIC NAME

Tranexamic Acid Injection I.P 100.000 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

Hemorrhage or risk of hemorrhage 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

In renal insufficiency leading to a risk of accumulation, the use of tranexamic acid is contraindicated in patient with severe renal impairment (see section 4.3).

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

<i>Serum creatinine (micromol/l)</i>	mg/10 mL	<i>Intravenous dose</i>	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).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 2.0.
- 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).
- Severe renal impairment (risk of accumulation).
- History of convulsions.
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions).

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 should not be administered by the intramuscular route.

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 urethral obstruction.

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 hemostaseology and under strict medical supervision (see section 4.3). Tranexamic acid should be administered with care in patients receiving oral contraceptives 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 theoretical risk of increased thrombus-formation as with oestrogens. 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.

Pregnancy

There are no or limited amount of data from the use of tranexamic acid in pregnant women. Although studies in animals do not indicate teratogenic effects, tranexamic acid is therefore not recommended during the first trimester of pregnancy as precaution for use.

Based on the limited clinical data on the use of tranexamic acid in different clinical haemorrhagic settings during the second and third trimesters, it was determined that there were no deleterious effects for the foetus. Tranexamic acid should be used during pregnancy only if the expected benefit justifies the potential risk.

Breast-feeding

Tranexamic acid is excreted in human milk. Therefore, breast-feeding is not recommended.

Fertility

There are no clinical data on the effects of tranexamic acid on fertility.

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.

System organ class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Frequency not known (cannot be estimated from the available data)
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.

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

5.2 Pharmacodynamic properties

No specific dose-effect study or PK study has been conducted in children.

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.

No specific pharmacokinetic study has been conducted in children.

6 NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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

Because of the absence of interaction studies, simultaneous treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field.

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

Tranexamic Acid Injection I.P 100.000 mg/ml is added by slow intravenous injection at a rate of 1 ml/minute.

Tranexamic Acid Injection I.P 100.000 mg/ml is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

9 Details of manufacturer

M/s. Pfizer Manufacturing Belgium NV Rijksweg 12, B-2870 Puurs, NA (Belgium)

10 Details of import license number with date

FF-362-7589 dated 24 March 2017

11 Date of revision

March 2020