PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrTRANEXAMIC ACID INJECTION BP

Tranexamic Acid Injection

Solution for Injection, 100 mg / mL, Intravenous

BP

Antifibrinolytic Agent

SteriMax Inc.
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Oakville, ON
L6H 6R4

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	09/2022
4 DOSAGE AND ADMINISTRATION, 4.4 Administration	09/2022
7 WARNINGS AND PRECAUTIONS	09/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Tranexamic Acid Injection BP (tranexamic acid) is indicated for:

- Increased local fibrinolysis when the diagnosis is indicative of hyperfibrinolysis, as with dental extraction in patients with coagulopathies (in conjunction with antihaemophilic factor).

1.1 Pediatrics

No data are available to Health Canada for tranexamic acid for intravenous administration; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Clinical studies of tranexamic acid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

2 CONTRAINDICATIONS

- Intrathecal and epidural administration of tranexamic acid is contraindicated.

- Patients with a history or risk of thrombosis should not be given Tranexamic Acid Injection BP (tranexamic acid), unless at the same time it is possible to give treatment with anticoagulants. The preparation should not be given to patients with acquired disturbances of colour vision. If disturbances of vision arise during the course of treatment the administration of the preparation should be discontinued.

- Patients with active thromboembolic disease, such as deep vein thrombosis, pulmonary embolism, and cerebral thrombosis.

- Patients with subarachnoid haemorrhage: the limited clinical experience shows that a reduced risk for re-bleeding is offset by an increase in the rate of cerebral ischaemia.

- Heamaturia (see 7 WARNINGS and PRECAUTIONS).

- Tranexamic Acid Injection BP is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Tranexamic Acid Injection BP is intended for intravenous injection or infusion only.
- Erroneous administration of Tranexamic Acid Injection BP via intrathecal and epidural routes has resulted in serious harm, including death (see 7 WARNINGS AND PRECAUTIONS)
- Tranexamic acid blood levels are increased in patients with renal insufficiency. Dose modifications are required in patients with renal insufficiency (see 4.2 Recommended dose and Dosage Adjustment)
- Hypotension may occur after fast injection.
- The risk for thromboembolic events may be increased in patients using hormonal contraceptives. If Tranexamic Acid Injection BP has to be used in these patients, advise them to use an effective alternative (nonhormonal) contraceptive method. (see 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

- Dental Surgery in Patients with Coagulopathies: 2 hours before the operation, Factor VIII and Factor IX should be given as well as Tranexamic Acid Injection BP, 10 mg intravenously per kg body weight. After the operation, 25 mg/kg tranexamic acid is given orally 3-4 times a day for 6-8 days. After the operation the patient does not generally require further substitution therapy.
- Patients with Impaired Renal Function: In patients with serum creatine concentrations of 120 to 250 µmol/L, 10 mg intravenously tranexamic acid per kg body weight twice daily. At serum creatine levels of 250 to 500 µmol/L the dosage should be 10 mg intravenously per kg body weight at 24-hourly intervals, and at serum creatine levels of 500 µmol/L or more, the same dose should be given at intervals of 48 hours between doses.

4.3 Reconstitution

Parenteral Products:

For intravenous infusion Tranexamic Acid Injection BP injection may be mixed with:

- electrolyte solutions (e.g. 0.9% NaCl solution, Ringer's solution),
- carbohydrate solutions (e.g. 5% glucose solution),
- amino acid solutions and
- dextran solutions (e.g. dextran 40, dextran 70).

Heparin may be added to Tranexamic Acid Injection BP. Tranexamic Acid Injection BP should not be mixed with blood and infusion solutions containing penicillin.

The required volume of Tranexamic Acid Injection BP may be added to the chosen infusion solution to achieve final concentrations of 1 or 2 g in 100 mL (10 or 20 mg/mL, 1% or 2%). A solution with a 100 mL final volume would be prepared as shown in the table 1:

Table 1 – Reconstitution

Ampoules Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
5 mL	qsp 100 mL	100 mL	Solution 0.5 % (5 mg / mL)
10 mL	qsp 100 mL	100 mL	Solution 1 % (10 mg / mL)
2 x 10 mL	qsp 100 mL	100 mL	Solution 2 % (20 mg / mL)

* See above for compatible diluents.

NB: **1 g of tranexamic acid** is obtained from 1 vial of 10 mL or 2 vials of 5 mL;
2g of tranexamic acid are obtained from 2 vials of 10 mL or 4 vials of 5 mL.

An example of preparation and administration of a solution for intravenous infusion is summarized in the table 2:

Table 2: Infusion rates for undiluted and diluted tranexamic acid solutions

	Weight (kg)	Bolus (50 mg/min)		
		Undiluted solution (100 mg/mL)	Diluted Solution	
			1% (10 mg/mL)	2% (20 mg/mL)
Infusion rate	-	0.5 mL/min	5 mL/min	2.5 mL/min
Example of a patient dosed at 10 mg/kg	70	7 mL (14 mins)	70 mL (14 mins)	35 mL (14 mins)

The mixture should be used immediately after preparation. If storage is necessary, the mixture should be stored at 15-30°C for a maximum of 24 hours. Mixture not used within 24 hours of preparation, should be discarded.

The vials of Tranexamic Acid Injection BP are sterile. Tranexamic Acid Injection BP injection is intended for single use. Unused product must be discarded. As with all parenteral drug products, Tranexamic Acid Injection BP should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration, whenever solution and container permit.

4.4 Administration

Tranexamic Acid Injection BP is intended for intravenous injection or infusion only.

Erroneous administration of Tranexamic Acid Injection BP via intrathecal and epidural routes has resulted in serious harm, including death (See WARNINGS AND PRECAUTIONS).

Tranexamic Acid Injection BP is intended for intravenous administration (intravenous injection and infusion). Tranexamic Acid Injection BP should be administered intravenously by slow injection over a period of at least 5 minutes. The recommended rate of bolus infusion is 50 mg/min. To administer 50 mg/min to the patient directly via intravenous injection, 0.5 mL/min of undiluted Tranexamic Acid Injection BP (100 mg/mL) should be administered by slow intravenous injection. To administer 50 mg/min as an infusion, solutions diluted to 1% tranexamic acid (i.e. 1 g in 100 mL or 10 mg/mL), may be administered at 5 mL/min or solutions diluted to 2% tranexamic acid, may be administered at 2.5 mL/min.

5 OVERDOSAGE

There is no known case of overdosage of tranexamic acid in humans. Symptoms may include nausea, diarrhoea, dizziness, headache, convulsions, vomiting orthostatic symptoms and hypotension. Treatment of overdosage would consist of initiating vomiting, institution of gastric lavage, charcoal therapy, and symptomatic treatment. Maintain adequate diuresis.

It has been seen that 37 g of tranexamic acid caused mild intoxication in a seventeen-year-old after gastric lavage.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTH, COMPOSITION AND PACKAGING

Table 3 Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution / 100 mg / mL / tranexamic acid	Water for Injection

Packaging

Solution for injection: Vials containing 100 mg Tranexamic acid per mL.

Packages of 10 x 5 mL, 10 x 10 mL and 1 x 50 mL vials

The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized parenteral admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for the preparation of admixtures only. Dispensing from a Pharmacy Bulk Vial should be completed as soon as possible after initial entry.

7 WARNINGS AND PRECAUTIONS

General

The erroneous administration of tranexamic acid via intrathecal or epidural routes has been reported, resulting in serious adverse reactions including death.

Care should be exercised to confirm the correct route of administration, when other injectable medications are to be administered during the same procedure with Tranexamic Acid Injection BP.

Cardiovascular

Venous and arterial thrombosis or thromboembolism has been reported in patients treated with tranexamic acid. Patients with a high risk for thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should use Tranexamic Acid Injection BP only if there is a

strong medical indication and under strict medical supervision.

Patients with disseminated intravascular coagulation (DIC), who require treatment with Tranexamic Acid Injection BP, must be under the strict supervision of a physician experienced in treating this disorder.

Driving and Operating Machinery

Tranexamic acid may cause dizziness and therefore may influence the ability to drive or use machines.

Endocrine and Metabolism

Hormonal Contraceptives: Combination hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Because Tranexamic Acid Injection BP is an antifibrinolytic, concomitant use of hormonal contraception and Tranexamic Acid Injection BP may further exacerbate this increased thrombotic risk. Women using hormonal contraception should use Tranexamic Acid Injection BP only if there is a strong medical need and the benefit of treatment will outweigh the potential risk of a thrombotic event. The risk for thromboembolic events may be increased in patients using hormonal contraceptives. If Tranexamic Acid Injection BP has to be used in these patients, advise them to use an effective alternative (nonhormonal) contraceptive method. (see 9 DRUG INTERATIONS).

The following patients should consult their doctor prior to initiating treatment with Tranexamic Acid Injection BP: obese and diabetic, with polycystic ovary syndrome or a history of endometrial cancer in a first-degreerelative, women receiving unopposed oestrogen or tamoxifen.

Hematologic

Avoid concomitant use of Tranexamic Acid Injection BP with medical products that are prothrombotic because concomitant use can further increase the risk of thromboembolic adverse reactions associated with tranexamic acid.

Patients with irregular menstrual bleeding should not use Tranexamic Acid Injection BP until the cause of the irregularity has been established.

Patients should consult their doctor if menstrual bleeding is not reduced after three menstrual cycles. If menstrual bleeding is not adequately reduced by Tranexamic Acid Injection BP, an alternative treatment should be considered.

Patients taking anticoagulants (see 4.2 Recommended Dose and Dosage Adjustment).

Neurologic

Convulsions have been reported in association with tranexamic acid treatment.

Ophthalmologic

Visual disturbances including visual impairment, vision blurred, impaired color vision have been reported with tranexamic acid. For patients who are to be treated for several weeks with tranexamic

acid, an ophthalmic check-up is advisable (sharpness of vision, colour vision, fundus, field of vision, etc.) if possible, before treatment is initiated and regularly during treatments.

Renal

Tranexamic acid therapy is not indicated in haematuria caused by diseases of the renal parenchyma. Intravascular precipitation of fibrin frequently occurs in these conditions and may aggravate the disease. In addition, in cases of massive renal hemorrhage of any cause, antifibrinolytic therapy carries the risk of clot retention in the renal pelvis.

Care should be taken in cases of renal insufficiency due to the risk of accumulation, and where there is pronounced haematuria from the upper urinary tract, since in isolated cases obstacles to passage have been observed in the tract (see 4.2 Recommended Dose and Dosage Adjustment).

Reproductive Health: Female and Male Potential

- **Fertility**

There are limited clinical data regarding the impact of tranexamic acid on fertility.

Tranexamic acid passes into the semen and inhibits its fibrinolytic activity, but without affecting the motility of the spermatozoa.

Sensitivity/Resistance

Cases of allergic reaction with use of intravenous tranexamic acid, including anaphylaxis or anaphylactoid reaction have been reported that are suggestive of a causal relationship. Patients should be closely monitored for the possibility of a severe allergic reaction occurring following its administration.

7.1 Special Populations

7.1.1 Pregnant Women

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.

Fibrinolytic activity is very high in neonates. It is not known for certain whether a reduction of this activity during the first hours of life is harmful. Kullander and Nilsson who have wide experience with tranexamic acid in connection with childbirth have observed no negative effect on the infants.

For decisions regarding the use of tranexamic acid during pregnancy, the potential risk of tranexamic acid administration on the fetus 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.

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 fetal outcomes. There are cases of fetal

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 actual risk of major birth defects with use of tranexamic acid during pregnancy is not clear.

There were 13 clinical studies that described fetal 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 fetuses and infants exposed to tranexamic acid in utero.

A woman with fibrinolytic bleeding in the fourth month of pregnancy was treated with tranexamic acid for a total of 64 days. The total dose was 256 g. The delivery occurred spontaneously in the 30th week of pregnancy and was normal in all other respects. The infant was healthy.

In a case of threatened placental abruption that was prevented by giving tranexamic acid, the patient had already lost two children in connection with placental abruption. In the 26th week of her third pregnancy bleeding occurred, indicating abruption. Pathological proteolysis with predominant activation of the fibrinolytic system was established. Between the 26th and 33rd week of pregnancy about 250 g of tranexamic acid were given, both intravenously and orally. The bleeding was arrested, and a healthy child was delivered by Caesarean section.

The estimated background risk for major birth defects and miscarriage for the indicated human population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

7.1.2 Breast Feeding

Tranexamic acid is secreted in the mother's milk at a concentration of only a hundredth of the corresponding serum levels.

Published literature reports the presence of tranexamic acid in human milk. There are no data on the effects of tranexamic acid on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tranexamic acid and any potential adverse effects on the breastfed child from tranexamic acid or from the underlying maternal condition.

7.1.3 Pediatrics

No data are available to Health Canada for tranexaminc acid for intravenous administration; therefore, Health Canada has not authorized Tranexamic Acid Injection BP for this indication for pediatric use.

See 1.1 Pediatrics.

7.1.4 Geriatrics

Clinical Studies of tranexamic acid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. See 1.2 Geriatrics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Gastrointestinal Disorders: Gastrointestinal symptoms (nausea, vomiting, diarrhea) occur but disappear when the dose is reduced.

Immune System Disorders: allergic dermatitis has been reported less commonly.

Nervous System Disorders: Isolated cases of dizziness or reduced blood pressure have been reported

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Eye Disorders: No retinal changes have been reported or observed at ophthalmic check-ups of patients treated with tranexamic acid for several weeks or months. This is despite experimental findings in animals (dog and cat) where retina changes have been observed after long-term administration of large doses of tranexamic acid.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Additional data is not available for the pediatric population that is any different from the adult population (see section 8.1).

8.3 Less Common Clinical Trial Adverse Reactions

See section 8.1.

8.3.1 Less Common Clinical Trial Adverse Reactions - Pediatrics

Additional data is not available for the pediatric population that is any different from the adult population (see section 8.1).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

No data is available regarding abnormal laboratory findings and tranexamic acid therapy.

8.5 Post-Market Adverse Reactions

Rare cases of adverse events have been reported with the use of tranexamic acid.

Eye Disorders: impaired vision, blurred vision or colour vision impairment (chromatopsia)

Immune System Disorders: Cases of allergic reaction with use of intravenous tranexamic acid, including anaphylaxis or anaphylactoid reaction have been reported that are suggestive of a causal relationship.

Nervous System Disorders: dizziness and seizures

Vascular Disorders: thromboembolic events (acute myocardial infarction, thrombosis, arterial thrombosis limb, carotid artery thrombosis, cerebral infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction). Hypotension may occur after fast injection.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No studies of interactions between tranexamic acid and other drugs have been conducted. 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.

9.4 Drug-Drug Interactions

Because Tranexamic Acid Injection BP is an antifibrinolytic, avoid concomitant use of Tranexamic Acid Injection BP with medicalproducts that are prothrombotic because concomitant use can further increase the risk of thromboembolic adverse reactions associated with tranexamic acid.

Potential drug-drug interactions may lead to myocardial infarction after coadministration with hormonal contraceptives, hydrochlorothiazide, desmopressin, sulbactam-ampicillin, carbazochrome, ranitidine, or nitroglycerin. Concomitant use of hormonal contraception and Tranexamic Acid Injection BP may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives (see 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tranexamic acid produces an antifibrinolytic effect by competitively inhibiting the activation of plasminogen to plasmin. It is also a weak non-competitive inhibitor of plasmin. These properties make possible its clinical use as an antifibrinolytic in the treatment of both general and local fibrinolytic hemorrhages. It has an action mechanism similar to, but about 10 times more potent in vitro, than that of E amino caproic acid (EACA).

Tranexamic acid binds considerably more strongly than EACA to both the strong and weak sites in the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds. The pharmacological significance of the binding to these different sites has not yet been evaluated.

The therapeutic plasma concentration of Tranexamic Acid Injection BP (tranexamic acid) is 5-15 mg/L. The functional interaction between plasminogen and tissue activator, located mainly on fibrin, is prevented by dissociation of the complex between fibrin and specific substrate binding sites on plasminogen. A potentiating effect on natural inhibitors also appears to contribute to the clinical effect during antifibrinolytic therapy.

10.2 Pharmacodynamics

When administered 36-48 hours before surgery in four doses of 10-20 mg per kg body weight, an antifibrinolytically active concentration (10 µg/mL) of tranexamic acid remained up to 17 hours in thetissues investigated, and up to 7-8 hours in the serum.

Tranexamic acid (5×10^{-2}M) competitively inhibits the activation of trypsinogen by enterokinase and non-competitively inhibits the proteolytic activity of trypsin at 4-fold greater concentration. While aminocaproic acid moderately inhibits trypsin (40%), urinary kallikrein (30%) and pancreatic kallikrein(60%), Tranexamic acid has little effect (less than 10%) on any of these enzymes.

A still weaker effect is exerted on thrombin (7×10^{-3}M, 100 mg/L). Tranexamic acid (7×10^{-2}M) added toblood has no influence on the platelet count, coagulation time, one-stage prothrombin time or recalcification time. The plasma levels of AHF, Factor IX, prothrombin, Factor VII, Factor V and fibrinogen also remain unchanged *in vitro*.

Tranexamic acid (7×10^{-3}M, 1 g/L) does not aggregate human platelets *in vitro*. On the contrary *in vivo* (dogs) a dose of 30 mg/kg I.V. showed a decreased ADP-induced aggregability and a stabilizing effect onglass bead adhesiveness for 24 hours after the administration.

The activity of chymotrypsin is not impaired by synthetic antifibrinolytics and an inhibition of the actionof pepsin is observed only in high concentrations, 6×10^{-3}M. The degradation of bradykinin in human plasma is not significantly inhibited at 10^{-2}M.

Tranexamic acid administered by I.V. infusion in the anaesthetized cat in doses of 0.4-2 mg/kg/min for 60 minutes and i.m. in the rabbit, cat and dog in doses of 170 mg/kg do not cause significant changes inarterial blood pressure, respiration of ECG.

The mechanism of the cardiovascular effect of Tranexamic acid is less clear than that of E-amino caproic acid, which appears to produce an indirect sympathomimetic effect. In relation to its therapeutic effect Tranexamic acid has about 10 times less potent effect than EACA on blood pressure. Threshold doses to produce increase in the blood pressure and heart rate are 50-100

mg/kg for Tranexamic acid and 30-50 mg/kg for EACA in anaesthetized cats, corresponding to a human equivalentdose of 160-320 mg/kg for tranexamic acid and 96-160 mg/kg for EACA.

10.3 Pharmacokinetics

Absorption

Absorption from the human gastrointestinal tract is not complete (40%).

Distribution

Tranexamic acid does not bind to serum albumin. The plasma protein binding seems to be fully accounted for by its binding to plasminogen and appears to be negligible at therapeutic plasma levels of 5-10 mg/L.

Intravenous administration of 10 mg per kg body weight gave plasma concentrations of 18.3 µg, 9.6 µg and 5 µg per mL one, three and five hours after the injection.

The ability of tranexamic acid to cross the blood brain barrier has been demonstrated when administered to patients with ruptured intracranial aneurysms.

Tranexamic acid diffuses rapidly to the joint fluid and to the synovial membrane. In the joint fluid the same concentration was obtained as in the serum. The biological half-life in the joint fluid was about 3 hours.

Metabolism

Possible routes of biotransformation are acetylation or deamination followed by oxidation or reduction.

Elimination

Tranexamic acid is eliminated by glomerular filtration, excretion being about 30% at one hour, 55% atthree hours and 90% at 24 hours after intravenous administration of 10 mg per kg body weight.

Special Populations and Conditions

- **Pediatrics**

Clinical experience with tranexamic acid in menorrhagic children under 18 years of age is not available.

- **Pregnancy and Breast-feeding**

Tranexamic acid crosses the placenta. After an intravenous injection of 10 mg per kg the concentration can rise to about 30 µg per mL of fetal serum.

Tranexamic acid also passes over into the breast milk during lactation in concentrations 1/100 of the corresponding serum levels.

- **Renal Insufficiency**

See 4.2 Recommended Dose and Dosage Adjustment.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 - 30°C).

Keep out of reach and sight of children.

Once the product is reconstituted, the mixture should be used immediately after preparation. If storage is necessary, the mixture should be stored at 15 – 30°C for a maximum of 24 hours. Mixture not used within 24 hours of preparation, should be discarded.

The vials of Tranexamic Acid Injection BP are sterile. Tranexamic Acid Injection BP is intended for single use. Unused product must be discarded. As with all parenteral drug products, Tranexamic Acid Injection BP should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration, whenever solution and container permit.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

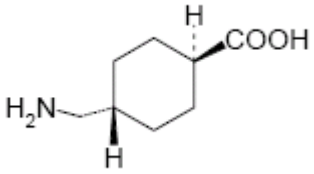
Drug Substance

Proper name: Tranexamic acid

Chemical name: trans-4 (aminomethyl) cyclohexanecarboxylic acid

Molecular formula and molecular mass: $C_8H_{15}NO_2$ and 157.21 g / mol

Structural formula:



Physiochemical properties: A white crystalline powder.

Product Characteristics:

Solubility: Tranexamic acid is freely soluble in water and glacial acetic acid, partially insoluble in acetone and alcohol.

pH: Tranexamic Acid Injection BP has pH 6.5-8.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

- The data is not available.

14.2 Comparative Bioavailability Studies

- The data is not available.

14.3 Immunogenicity

- The data is not available.

14.4 Clinical Trials – Reference Biologic Drug

- The data is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Nonclinical studies have shown a retinal toxicity associated with tranexamic acid. Toxicity is characterized by retinal atrophy commencing with changes to the retinal pigmented epithelium and progressing to retinal detachment in cats. The toxicity appears to be dose related, and changes are partially reversible at lower doses. Effects (some fully reversible) are seen in cats at clinically relevantdoses. In the dog, effects were only observed at extremely high dose levels of 2 x 400 mg/kg/day andpeak plasma levels of about 200 mg per litre. By comparison, in humans peak plasma levels are in therange of 10-20 mg per litre after a therapeutic oral dose of about 30 mg/kg body weight.

Studies suggest that the underlying mechanism for retinal toxicity may be related to a transient retinal ischemia at higher dose exposures, linked to the known sympathomimetic effect of high plasma levelsof tranexamic acid. The clinical relevance of these findings is unknown.

In subacute toxicity studies, daily doses of Tranexamic acid administered orally to rats (1 to 5 g/kg for 10 weeks) and dogs (100 to 500 mg/kg for 4 months) and intraperitoneally to rats (0 to 1000 mg/kg for2 weeks) resulted in dose-related emesis, loose stools or diarrhea, and decreased body weight gain.

Intravenous administration of tranexamic acid to rabbits (60 to 180 mg/kg for 13 days) resulted indose-related tachypnea.

In the 1-month intravenous study in dogs given 20, 100 or 500 mg/kg/day emesis and salivation occurred at the two highest dose levels. Microscopically, pulmonary thromboembolism was found inone dog receiving the intermediate dose and one from the high dose group. The latter dog also had two thrombophletitides in the urinary bladder. No cardiac hemorrhages were found.

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

No other significant observations have been made in general toxicology studies.

Carcinogenicity

In one of the carcinogenicity studies in which rats were given tranexamic acid in high doses, biliary hyperplasia, cholangioma and adenocarcinoma of the liver were found.

These findings have not been reproduced in a number of subsequent carcinogenicity studies. An increased incidence of leukemia (although not statistically significant) occurred in one study in mice given 4.8 percent Tranexamic acid for 20 months. In other studies, the frequency and histologic appearance of the observed tumors were similar in the test groups and in the untreated animals.

Reproductive and Development Toxicology:

In reproductive toxicity studies, tranexamic acid had no adverse effect on reproductive parameters of mice, rats, and rabbits at clinically relevant doses.

17 SUPPORTING PRODUCT MONOGRAPHS

1. CYKLOKAPRON®, Solution for Injection, 100 mg / ml, Submission Control No. 254356, Product Monograph, Pfizer Canada ULC. NOV 25, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Tranexamic Acid Injection BP

(Tranexamic acid injection)

Read this carefully before you start taking **Tranexamic Acid Injection BP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Tranexamic Acid Injection BP**.

What is Tranexamic Acid Injection BP used for?
Tranexamic Acid Injection BP is used in adults:

- to prevent or reduce bleeding from tooth extraction

How does Tranexamic Acid Injection BP work?
Tranexamic Acid Injection BP belongs to one of a group of medicines called antifibrinolytic agents. It works by blocking the breakdown of blood clots, which helps to prevent or reduce bleeding.

What are the ingredients in Tranexamic Acid Injection BP?

Medicinal ingredient: Tranexamic Acid

Nonmedicinal ingredients: Water for injection

Tranexamic Acid Injection BP comes in the following dosage form:

Solution for Injection: 100 mg / mL of tranexamic acid.

Do not use Tranexamic Acid Injection BP if:

- you have a history or are at a higher risk for thrombosis (blood clots in the veins or arteries). This includes diseases where a blood clot breaks loose and blocks another blood vessel (e.g., deep vein thrombosis, pulmonary embolism, and cerebral thrombosis).
- you are allergic to tranexamic acid or to any other ingredients in CYKLOKAPRON.
- you have a colour vision problem that is not genetic.
- you have blood in the urine.
- you have bleeding in the space between your brain and the surrounding membrane (subarachnoid haemorrhage).

The Tranexamic Acid Injection BP (solution for injection) is only for intravenous use. Do not administer Tranexamic Acid Injection BP using other routes of administration as this can cause serious adverse events including death.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Tranexamic Acid Injection BP. Talk about any health conditions or problems you may have, including if you:

- have kidney problems.
- have irregular menstrual bleeding where the cause is not known.
- are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed. Tranexamic Acid Injection BP can pass into breast milk and affect your unborn baby.
- are taking any of the following:
    - anticoagulants (used to prevent blood clots and thin the blood);
    - hormonal birth control methods (e.g., "the pill"); or
    - tamoxifen (used to treat breast cancer).
- have a condition known as disseminated intravascular coagulation (DIC; excessive blood clotting). Tranexamic Acid Injection BP will only be given if your healthcare professional has done blood tests to check you are suitable, otherwise other anti-clotting medicines may be a better option for you.
- are obese.
- have diabetes.
- have polycystic ovary syndrome (a condition that produces high levels of a male hormone called androgen causing irregular or no periods).
- have a history of cancer of the uterine (endometrial cancer) in a close relative.
- are on estrogen therapy.
- are over the age of 65 years old.
- are at a higher risk for blood clots in the veins or arteries (e.g., a history of blood clots or a family history of blood clotting conditions).

Other warnings you should know about:

Taking Tranexamic Acid Injection BP can cause the following:

- **Allergic reaction:** This can occur when Tranexamic Acid Injection BP is given intravenously (directly into your bloodstream). Your healthcare professional will closely monitor you after Tranexamic Acid Injection BP administration.
- **Seizures** (fits)
- **Thromboembolism** (blood clot in a vein or artery)
- **Vision problems**: This can include blurred vision, loss of vision, and impaired colour vision. If you are prescribed to take Tranexamic Acid Injection BP for several weeks, you should get an eye check-up before you start taking Tranexamic Acid Injection BP and at regular intervals. These check-ups will assess thesharpness of your vision, colour vision, and field of vision. If you notice any change in your vision, especially in your colour vision, tell your healthcare professional right away.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Pregnancy:

- Tranexamic Acid Injection BP can pass through the placenta and harm your unborn baby. If you are able to get pregnant, plan to become pregnant, are pregnant, or are taking hormonal birth control methods, there are specific risks that you must first discuss with your healthcare professional.
- Tranexamic Acid Injection BP can affect hormonal birth control methods such as “the pill” and can cause unwanted serious effects. Therefore, you should use a non-hormonal birth control methodwhile you are taking Tranexamic Acid Injection BP. If you have any questions about this, talk to your healthcare professional.
- If you become pregnant or think you are pregnant while taking Tranexamic Acid Injection BP, tell yourhealthcare professional right away.

Driving and using machines:
Tranexamic Acid Injection BP can cause dizziness. Before you drive or do tasks that require special attention, wait until you know how you respond to Tranexamic Acid Injection BP.

Tell your doctor or pharmacists about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Tranexamic Acid Injection BP:

- medicines used to help your blood clot;
- hormonal birth control (e.g., “the pill”);
- anticoagulants used to prevent blood clots and thin the blood;
- hydrochlorothiazide, a diuretic that is typically used to treat high blood pressure;
- desmopressin, a medicine used to treat diabetes;
- sulbactam-ampicillin, an antibiotic used to treat bacterial infections;
- carbazochrome, a medicine used to help your blood clot;
- ranitidine, a medicine used to lower the amount of stomach acid;
- nitroglycerin, a medicine used to treat or prevent chest pain.

How to take Tranexamic Acid Injection BP:

- **Solution for Injection:** Your healthcare professional will prepare and give you Tranexamic Acid Injection BP solution for injection. You will receive Tranexamic Acid Injection BP through your veins (i.e., “intravenously”or “IV”) by slow injection as a bolus IV dose over 5 minutes or as an IV drip. They will ensure that the correct route of administration (IV) is used to give your dose. Other routes of administration are **NOT** to be used as this can cause serious adverse events including death.

Usual dose:

- Your healthcare professional will decide the best dose based on weight.

Overdose:

Symptoms of an overdose with Tranexamic Acid Injection BP include:

- diarrhea;
- dizziness;
- headache;
- nausea;
- seizures;
- symptoms of low blood pressure (e.g., blurry vision, confusion, fainting, light-headedness,weakness); and
- vomiting.

If you think you, or a person you are caring for, have taken too much Tranexamic Acid Injection BP, contact a health care practitioner, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Tranexamic Acid Injection BP?

These are not all the possible side effects you may have when taking Tranexamic Adid Injection BP. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of Tranexamic Adid Injection BP may include:

- diarrhea;
- dizziness, especially if the injection is given too quickly;

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach, vomiting, hives, rash, or swelling of the face, lips, tongue, or throat.			✓

- nausea (feeling sick);
- vomiting.

Eye problems: blurred vision, changes to the sharpness of vision, loss of vision, or color vision change, changes to the field of vision, or sudden loss of eyesight in one eye.			✓
Seizures (fit): loss of consciousness with uncontrollable shaking.			✓
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light- headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, or possible irregular heartbeat.			✓
Thromboembolism (blood clot in a vein or artery, including in the brain, limbs, and heart): arm or leg pain, tenderness or swelling, skin that is red or warm, coldness, tingling, numbness, pale skin, muscle pain, muscle spasms, weakness, dizziness, numbness, weakness on one side of the body, and problems with talking, writing, or understanding language.			✓

Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing, difficulty speaking, lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking, or loss of balance.			✓
Acute renal cortical necrosis (death of the tissue in the outer part of the kidney): red or dark brown urine, blood in urine, lower back pain, fever, changes in blood pressure, or urine flow is reduced or stopped.			✓
Hypotension (low blood pressure): dizziness, fainting, light- headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up and after fast injection).		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to HealthCanada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how toreport online, by

mail or by fax; or

- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your sideeffects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store the unopened vials at room temperature (15-30°C). After dilution, the mixture should be immediately used. However, if needed, the mixture can be stored at 2°C to 8°C for up to 24 hours. If the mixture is not used within 24 hours of preparation, it should be discarded.
- Keep out of the reach and sight of children.

If you want more information about Tranexamic Adid Injection BP:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for health professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug- product-database.html); the manufacturer's website (www.sterimaxinc.com), or by calling 1-800-881-3550.

This leaflet was prepared by **Steri*Max* Inc.**
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