

PRODUCT MONOGRAPH

^{Pr}CYKLOKAPRON®

500 mg Tranexamic acid tablets House Std. and
100 mg/ml Tranexamic acid injection House Std.

Antifibrinolytic agent

Pfizer Canada Inc
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Kirkland, Quebec, H9J 2M5

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PRODUCT MONOGRAPH

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**Tranexamic acid tablets House Std. and
Tranexamic acid injection House Std.**

THERAPEUTIC CLASSIFICATION

Antifibrinolytic agent

ACTION

CYKLOKAPRON (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).

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

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.

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.

Possible routes of biotransformation are acetylation or deamination followed by oxidation or reduction. After oral administration approximately 50% of the parent compound, 2% of the deaminated dicarboxylic acid, and 0.5% of the acetylated product are excreted.

Tranexamic acid is eliminated by glomerular filtration, excretion being about 30% at one hour, 55% at three hours and 90% at 24 hours after intravenous administration of 10 mg per kg body weight. After oral administration of 10-15 mg per kg body weight, excretion was 1% at one hour, 7% at three hours and 39% at 24 hours.

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.

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 the tissues investigated, and up to 7-8 hours in the serum (Andersson et al, 1968).

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.

After both oral and intravenous administration tranexamic acid passes into the semen and inhibits its fibrinolytic activity, but without affecting the motility of the spermatozoa (Liedholm, 1973). 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.

Three hours after a single oral dose of 25 mg per kg body weight, the peak serum level was 15.4 mg per L and the aqueous humour level was 1.6 mg per L.

INDICATIONS AND CLINICAL USE

Hereditary angioneurotic oedema.

Increased local fibrinolysis when the diagnosis is indicative of hyperfibrinolysis, as with conization of the cervix, dental extraction in patients with coagulopathies (in conjunction with antihæmophilic factor) epistaxis, hyphaema, and menorrhagia (hypermenorrhæa).

CONTRAINDICATIONS

Patients with a history or risk of thrombosis should not be given **CYKLOKAPRON** (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 hæmorrhage: the limited clinical experience shows that a reduced risk for re-bleeding is offset by an increase in the rate of cerebral ischaemia.

Haematuria (see WARNINGS and PRECAUTIONS)

Hypersensitivity to tranexamic acid or any of the ingredients.

WARNINGS

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.

Patients with irregular menstrual bleeding should not use CYKLOKAPRON 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 CYKLOKAPRON, an alternative treatment should be considered.

Venous and arterial thrombosis or thromboembolism has been reported in patients treated with CYKLOKAPRON. Patients with a high risk for thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should use CYKLOKAPRON only if there is a strong medical indication and under strict medical supervision.

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

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.

Convulsions have been reported in association with tranexamic acid treatment.

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.

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 CYKLOKAPRON is an antifibrinolytic, concomitant use of hormonal contraception and CYKLOKAPRON may further exacerbate this increased thrombotic risk. Women using hormonal contraception should use CYKLOKAPRON only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event (see DRUG INTERACTIONS).

Patients taking anticoagulants (see DOSAGE and ADMINISTRATION)

Use in pregnancy: The safety of CYKLOKAPRON (tranexamic acid) during pregnancy has not yet been established. No harmful effects have been reported.

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.

Tranexamic acid crosses over to the fetus (Kullander and Nilsson, 1970). After an I.V. injection of 10 mg per kg the concentration can reach a level of about 30 µg per mL fetal serum.

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.

PRECAUTIONS

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 DOSAGE and ADMINISTRATION).

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

Nursing Mothers:

Tranexamic acid is secreted in the mother's milk at a concentration only a hundredth of the corresponding serum levels (Eriksson et al, 1971). The investigators are of the opinion that tranexamic acid can be given during lactation without risk to the child.

Children:

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

Driving/Operating Machinery:

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

Drug Interactions:

No studies of interactions between CYKLOKAPRON 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.

Potential drug-drug interactions leading to myocardial infarction after coadministration with hormonal contraceptives, hydrochlorothiazide, desmopressin, sulbactam-ampicillin, carbazochrome, ranitidine, or nitroglycerin.

Because CYKLOKAPRON is an antifibrinolytic, concomitant use of hormonal contraception and CYKLOKAPRON may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives (see WARNINGS).

ADVERSE REACTIONS

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

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

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

Eye Disorders: To be observed by reason of experimental findings in animals: In the dog, retina changes have been observed after long-term administration of large doses of tranexamic acid and

in the cat, after intravenous injection of 250 mg per kg body weight per day for 14 days. Such changes have not been obtained in the rat, where the maximum tolerated dose has been administered.

No retinal changes have been reported or observed at ophthalmic check-ups of patients treated with CYKLOKAPRON for several weeks or months.

Post-market Surveillance: Rare cases of adverse events have been reported with the use of tranexamic acid.

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.

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

Nervous System Disorders: dizziness and seizures

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no known case of overdosage of CYKLOKAPRON in humans. Symptoms may be 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

DOSAGE AND ADMINISTRATION

Conization of the cervix: 2-3 tablets every 8-12 hours, 12 days post-operatively

Epistaxis: 2-3 tablets every 8-12 hours for 10 days

Hyphaema: 2-3 tablets every 8-12 hours for 7 days

Dental Surgery in Patients with Coagulopathies: 2 hours before the operation, Factor VIII and Factor IX should be given as well as CYKLOKAPRON, 25 mg orally or 10 mg intravenously per kg body weight. After the operation, 25 mg/kg CYKLOKAPRON is given orally 3-4 times a day for 6-8 days. After the operation the patient does not generally require further substitution therapy.

Administration

CYKLOKAPRON solution for injection is intended for intravenous administration (intravenous injection and infusion). CYKLOKAPRON solution for injection 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 CYKLOKAPRON solution for injection (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.

For intravenous infusion CYKLOKAPRON 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 CYKLOKAPRON solution for injection. CYKLOKAPRON solution for injection should not be mixed with blood and infusion solutions containing penicillin.

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

| Preparation of infusion solutions | Solution 1% (10 mg/mL) | Solution 2% (20 mg/mL) |
|-----------------------------------|------------------------|------------------------|
| Tranexamic acid (g) | 1g | 2g |
| Compatible diluents* | qsp 100 mL | qsp 100 mL |

* See above for compatible diluents.

NB:

1g 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 below:

| Infusion rates for undiluted and diluted tranexamic acid solutions | | | | |
|--|-------------|--------------------------------|------------------|-----------------|
| | Weight (kg) | Bolus (50 mg/min) | | |
| | | Undiluted solution (100 mg/mL) | Diluted solution | |
| | | | 1% (10mg/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 | 7mL (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 2 – 8°C for a maximum of 24 hours. Mixture not used within 24 hours of preparation, should be discarded.

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

Menorrhagia (hypermenorrhea): 2-3 tablets, 3-4 times a day for several days. CYKLOKAPRON treatment should only be started when copious bleeding has begun.

Hereditary angioneurotic oedema: Some patients can sense the onset of attacks and are best treated intermittently with 2-3 tablets, 2-3 times a day for several days. Others should be treated continuously with this dose.

Children: Dosage should be calculated according to body weight at 25 mg/kg, 2-3 times a day. Clinical experience with CYKLOKAPRON in menorrhagic (hypermenorrhea) children under 18 years of age is not available.

Patients with Impaired Renal Function: In patients with serum creatine concentrations of 120 to 250 µmol/L, 15 mg orally or 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 15 mg orally or 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.

Missed Dose:

If you forget to take your tablets you should take your next dose as usual. Do not take extra tablets to make up for the missed dose.

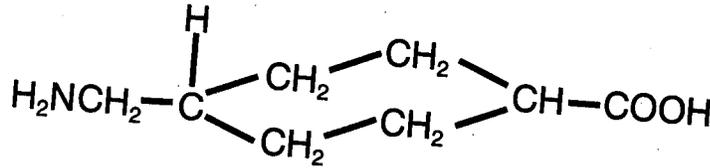
PHARMACEUTICAL INFORMATION

Drug Substance: Tranexamic acid

INN Name: Tranexamic acid

Chemical Name: trans-4 (aminomethyl) cyclohexanecarboxylic acid

Structural Formula:



Molecular Formula: C₈H₁₅NO₂

Molecular Weight: 157.2

Physical Form: A white crystalline powder odourless or almost odourless.

Solubility: Tranexamic acid is freely soluble in water.

COMPOSITION

Tablets (500 mg)

Tranexamic acid House Std., 500 mg/tablet

Nonmedicinal Ingredients: Cellulose microcrystalline, Colloidal silica anhydrous, Hydroxypropylcel, Magnesium Stearate, Povidone, Talcum. The tablets are coated with Eudragit E, Magnesium Stearate, PEG 8000, Talcum, Titanium Dioxide and Vanillin.

Injection (100 mg/mL)

Tranexamic acid House Std. 100 mg/mL

Nonmedicinal Ingredient: Water for injection to 1.0 mL

pH: CYKLOKAPRON injection has pH 6.5-8.

Storage: Store all dosage forms at room temperature (15 - 30°C).

AVAILABILITY

Tablets (white, film-coated, capsule-shaped with CY engraved in arcs, 8 x 18 mm) in bottles of 100. Each tablet contains 500 mg Tranexamic acid.

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

Packages of 10 x 5mL and 10 x 10mL ampoules.

PHARMACOLOGY

The therapeutic plasma concentration of CYKLOKAPRON (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.

Antifibrinolytic Effect *In Vivo*:

Thirty minutes after hyperfibrinolytic states have been produced by injection of streptokinase in rabbits, fibrinolysis was immediately terminated by an intravenous dose of 30 mg/kg of Tranexamic acid, compared to a 3-10 times higher dose of 100-300 mg/kg E amino caproic acid (EACA) necessary to obtain comparable effects.

Dogs show an immediate 40% decrease in urinary urokinase excretion at an oral dose of 55 mg/kg Tranexamic acid in the feed.

An intravenous dose of 50 mg/kg of tranexamic acid decreases pulmonary fibrinolysis in the rat. Maximum inhibition occurred 5-15 minutes after injection of 600 mg/kg and the effect lasted for 8 hours.

Influence on Other Enzyme Mechanisms:

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 (e.g. Dubber et al, 1965). 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) Andersson et al, 1965. Tranexamic acid (7×10^{-2} M) added to blood 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 on glass bead adhesiveness for 24 hours after the administration (Jong, 1974).

The activity of chymotrypsin is not impaired by synthetic antifibrinolytics and an inhibition of the action of 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.

Interaction with the Cardiovascular System:

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 in arterial blood pressure, respiration or ECG (Marmo et al, 1973).

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.

TOXICITY

Acute Toxicity:

The acute toxicity of Tranexamic acid was studied over 24 hours and 7 days in mice and rats and 24 hours, 48 hours and 7 days in rabbits, following intravenous, intraperitoneal, subcutaneous and oral administration. In a fourth study mortality was examined 72 hours after intravenous oral and subcutaneous administration. The lethal oral doses exceed 5-10 g/kg body weight in all studied species and the LD₅₀ values after intravenous injection were about 1-1.5 g/kg body weight in mice, rats and dogs.

Subacute Toxicity:

In six subacute toxicity studies, daily doses of Tranexamic acid were administered: orally to rats (1 to 5 g/kg for 10 weeks) and dogs (100 to 500 mg/kg for 4 months); intravenously to dogs (20-500 mg/kg for 1 month and 1 g/kg for 3 days) and to rabbits (60-180 mg/kg for 13 days); and intraperitoneally to rats (0-1000 mg/kg for 2 weeks). Dose-related emesis, loose stools or diarrhea, and decreased body weight gain were the only observed drug induced findings in the oral and intraperitoneal studies.

In intravenous administration to rabbits the only clinical finding was dose-related tachypnea.

In the intravenous short-term (3-day) study, one dog vomited frequently during the first infusion and at the end of the infusion convulsed and died. At necropsy, this dog had a small hemorrhage in the heart and histological examination showed heart petechiae.

In the 1 month intravenous study in dogs given 20, 100 or 500 mg/kg/day (Balazs & Porpora, 1969, Ohtake & Kepenis, 1969) emesis and salivation occurred at the two highest dose levels. Microscopically, pulmonary thromboembolism was found in one 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.

Chronic Toxicity:

In eight chronic toxicity studies, Tranexamic acid was administered: orally to rats (0-4000 mg/kg/day for 1 year), to dogs (200-1600 mg/kg/day and 800-1200 mg/kg/day for 1 year); in the diet to rats (0-4.8% for 22 months and 0-5% for 19 months) and to rats and mice (4.8% for 20 months); subcutaneously to mice (0.8-1.5 mg single injection observed for 1 year) and subcutaneously (0-3.5 g/kg/wk) or orally (0-10 g/kg/wk) to rats for 2 years.

At extremely high dose levels of 2 x 400 mg/kg/day and peak plasma levels of about 200 mg per litre, in chronic oral toxicity studies in dogs, atrophy in the anterior (ora ciliniaris retinae) and posterior (around the optic disc) retina have been observed.

The atrophic retinal changes are similar to those observed in senescence in dogs and man. In man, peak plasma levels are in the range of 10-20 mg per litre after a therapeutic oral dose of about 30 mg/kg body weight. Similar changes have been produced in high level daily intravenous infusion of Tranexamic acid in dogs and cats.

Eye damage was not established in the life-long feeding study (carcinogenicity study) performed in rats.

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.

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PART III: CONSUMER INFORMATION

Pr **CYKLOKAPRON[®]** (Tranexamic acid)

This leaflet is part III of a three-part "Product Monograph" published when CYKLOKAPRON was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CYKLOKAPRON. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

CYKLOKAPRON is a prescription medicine which is used to prevent or reduce bleeding in different conditions. You may have been prescribed it for one of the following:

- After minor surgery such as tooth removal in people with a hereditary blood clotting disorder (haemophilia)
- Cervical surgery (Conization of the cervix)
- Nose bleeds (Epistaxis)
- Heavy periods (menorrhagia)
- Bleeding inside the eye (hyphaema)
- A hereditary disease called angioneurotic oedema - a doctor will have told you if you have this.

What it does:

CYKLOKAPRON belongs to one of a group of medicines called antifibrinolytic agents, which are used to stop excessive bleeding after an operation or to assist with blood clotting. When you bleed your body forms clots as part of healing. In some people these clots do not stay in place long enough. This can cause too much bleeding.

When it should not be used:

Do not take CYKLOKAPRON:

- If you have a history or risk of blood clots (thromboembolism), especially in the leg, lung, brain, or tissues surrounding the brain.
- If you are allergic to tranexamic acid or any of its ingredients or similar medicines
- If you have acquired disturbances of colour vision
- If you have blood in the urine or any bleeding related to the kidney.

What the medicinal ingredient is:

Tranexamic acid

What the non-medicinal ingredients are:

Tablets: cellulose microcrystalline, colloidal silica anhydrous, eudragit E, hydroxypropylcell, magnesium stearate, PEG 8000, Povidone, talcum, titanium dioxide, vanillin.

Solution for injection: water for injection

What dosage forms it comes in:

Tablets: 500 mg

Injection: 100 mg/ ml.

WARNINGS AND PRECAUTIONS

BEFORE you use CYKLOKAPRON talk to your doctor or pharmacist if:

- you have kidney disease. The medicine can accumulate in your body. Therefore a lower dose might be given to you
- you have bleeding from the upper urinary tract. This shows as blood in your urine.
- you have ever had any uncontrollable bleeding (including irregular menstrual bleeding).
- you are pregnant or breastfeeding.
- you are taking "the pill" (hormonal contraceptives) or anticoagulants (drugs to inhibit blood from clotting as much).
- you are being treated for disseminated intravascular coagulation CYKLOKAPRON will only be given if your doctor has done blood tests to check you are suitable, otherwise other anti-clotting medicines may be a better option for you.
- you are obese, diabetic, have been told you have polycystic ovary syndrome a history of cancer of the endometrium in a close relative, are on estrogen therapy or are taking tamoxifen.

Tell your doctor or pharmacists about any prescription and non-prescription medicines you are taking, including natural or herbal remedies.

CYKLOKAPRON is not recommended for children under 18 years of age with abnormally heavy menstrual flow (hypermenorrhea).

CYKLOKAPRON may cause disturbance to your colour vision. If you are to be treated for several weeks with CYKLOKAPRON, it is advisable to have an eye check up (for sharpness of vision, colour vision, field of vision etc.) before you start on CYKLOKAPRON and at regular intervals. If you notice any change in your vision, especially in your colour vision, tell your doctor or pharmacist right away so that they can arrange for you to safely stop taking CYKLOKAPRON.

If you are taking CYKLOKAPRON for heavy periods, you should monitor your menstrual flow. If menstrual bleeding is not reduced after three menstrual cycles, consult with your doctor, an alternative treatment may be necessary.

If you experience (feel) dizziness, do not drive or use machinery.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any medicines you use including any prescription, over the counter or natural health products.

Drugs that may interact with CYKLOKAPRON include:

- any medicines used to help your blood clot.
- medicines that decrease blood clots (anticoagulants) . Treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field.
- birth control that contains hormones such as “The Pill”. The Pill along with CYKLOKAPRON may increase your chance of having a blood clot, stroke, or heart attack.
- hydrochlorothiazide, desmopressin, sulbactam-ampicillin, carbazochrome, ranitidine, or nitroglycerin. These medicines along with CYKLOKAPRON may lead to heart attacks.

PROPER USE OF THIS MEDICATION

Usual dose:

Take CYKLOKAPRON exactly as directed by your health care professional. Always take the number of tablets your doctor tells you.

The usual adult dose is 2-3 tablets two-three times daily.

Depending on why you have been given these tablets, your dose may be different.

The dose for children is calculated according to body weight (25 mg/kg).

Patients with kidney disease should receive lower doses.

CYKLOKAPRON solution for injection will usually be given to you by slow injection into a vein as a bolus intravenous (IV) dose over 5 minutes or as an IV drip. Your doctor will decide the best dose for you, based on your weight.

It should be inspected visually for clarity, particulate matter, precipitation, discolouration, and leakage prior to administration

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your tablets you should take your next dose as usual. Do not take extra tablets to make up for the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication may cause unwanted effects. However, check with your doctor or pharmacist promptly if any of the following persist or become troublesome:

- Nausea (feeling sick),

- vomiting (being sick) and
- diarrhoea

If the injection is given too quickly, you can feel dizzy due to reduced blood pressure.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and seek immediate emergency treatment |
|------------------|--|-------------------------------------|--------------|---|
| | | Only if severe | In all cases | |
| Uncommon | Allergic reactions (skin rash, hives, swelling of the face, lips, tongue or throat, and difficulty swallowing or breathing) | | | ✓ |
| | Central retinal artery and vein obstruction. Changes in your eyesight (such as changes to the sharpness of vision or field of vision and especially impaired color vision) | | ✓ | ✓ |
| | Dizziness | | ✓ | ✓ |
| | Seizures or fits | | ✓ | ✓ |
| | Pain in your chest or legs | | ✓ | |
| | Heart attack (chest pain) | | ✓ | ✓ |
| | Blood clots/deep vein thrombosis/arterial thrombosis limb (redness, warmth, swelling in your hands, legs, ankles or feet) | | ✓ | ✓ |

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | Talk with your doctor or pharmacist | | Stop taking drug and seek immediate emergency treatment |
|--|-------------------------------------|--------------|---|
| | Only if severe | In all cases | |
| Cerebral infarction/cerebrovascular accident/cerebral thrombosis (problems with speech, walking, sudden confusion, numbness or weakness) | | ✓ | ✓ |
| Acute renal cortical necrosis (trouble urinating) | | ✓ | ✓ |
| Low blood pressure (may occur after fast injection. Symptoms include dizziness, headache, and light headedness especially if you change positions quickly) | | ✓ | |

This is not a complete list of side effects. For any unexpected effects while taking CYKLOKAPRON, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 - 30°C).
Keep your medicine out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 Fax toll-free to 1-866-678-6789, or
 Mail to: Canada Vigilance Program
 Health Canada
 Postal Locator 1908C
 Ottawa, Ontario
 K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.pfizer.ca> or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001

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