1. NAME OF THE MEDICINAL PRODUCT

CYKLOKAPRON TABLETS
CYKLOKAPRON INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: tranexamic acid

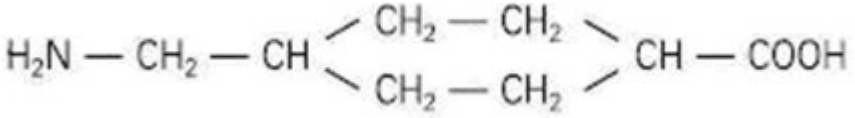
Dosage Form	**Strength**
Film-coated tablets	500 mg
Injection	100 mg/mL

3. PHARMACEUTICAL FORM

Film-coated tablets
Injection

Chemical name: trans-4-(aminomethyl) cyclohexanecarboxylic acid.

Structural formula:



Empirical formula: $C_8H_{15}NO_2$ Molecular weight: 157.2

Tranexamic acid is a white crystalline powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis.

  Local fibrinolysis may occur in the following conditions: Menorrhagia, prostatectomy and bladder surgery, haematuria, gastrointestinal haemorrhage, epistaxis, ulcerative colitis, conisation of the cervix, and dental extraction in patients with coagulopathies.

  General fibrinolysis may occur in the following conditions and situations: Prostatic and pancreatic cancer, after thoracic and other major surgery, in obstetrical complications such as ablatio placentae and postpartum haemorrhage, leukemia, liver diseases, in connection with thrombolytic therapy with streptokinase.

- Hereditary angioneurotic oedema.

4.2. Posology and method of administration

TRANEXAMIC ACID MUST NOT BE USED FOR INTRATHECAL OR EPIDURAL ADMINISTRATION.

The recommended standard dose is 5 mL to 10 mL by slow intravenous injection at a rate of 1 mL/minute or 2 to 3 tablets of 0.5 g 2 to 3 times daily.

For the indications listed below, the following doses are recommended:

General fibrinolysis: 1.0 g (2 ampoules of 5 mL) by slow intravenous injection every 6 to 8 hours.

Prostatectomy: 0.5 g to 1.0 g (1 to 2 ampoules of 5 mL) by slow intravenous injection every 6 to 8 hours (the first injection being given during the operation) for the first 3 days after surgery, thereafter 1 g to 1.5 g orally (2 to 3 tablets) 2 to 3 times daily until macroscopic haematuria is no longer present.

Haematuria: 1 g to 1.5 g orally (2 to 3 tablets) 2 to 3 times daily until macroscopic haematuria is no longer present.

Epistaxis: 1.5 g orally (3 tablets) 3 times a day should be administered for 4 to 10 days. Cyklokapron solution for injection may be applied topically to the nasal mucosa of patients suffering from epistaxis. This can be done by soaking a gauze strip in the solution, and then packing the nasal cavity.

Menorrhagia: 1 g to 1.5 g orally (2 to 3 tablets) 3 to 4 times daily for 3 to 4 days. Cyklokapron therapy is initiated when bleeding has become profuse.

Conisation of the cervix: 1.5 g orally (3 tablets) 3 times a day for 12 to 14 days postoperatively.

Dental extraction in patients with coagulopathies: Immediately before surgery, Cyklokapron 10 mg/kg body weight should be given intravenously. After surgery, 25 mg/kg body weight is given orally 3 to 4 times daily for 6 to 8 days. Coagulation factor concentrate might be necessary to administrate. This decision should be taken after consulting specialists on coagulation.

Hereditary angioneurotic oedema: 1 g to 1.5 g orally (2 to 3 tablets) 2 to 3 times daily as intermittent or continuous treatment, depending on whether the patient has prodromal symptoms or not.

For patients with moderate to severe impaired renal function, the following dosages are recommended:

Serum Creatinine (µmol/L)	**Oral Dose**	**Intravenous Dose**
120-249	15 mg/kg body weight twice daily	10 mg/kg body weight twice daily
250-500	15 mg/kg body weight daily	10 mg/kg body weight daily
>500	7.5 mg/kg body weight daily	5 mg/kg body weight daily

4.3. Contraindications

Intrathecal and epidural administration of tranexamic acid is contraindicated.

Active thromboembolic disease, such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis.

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.

Hypersensitivity to tranexamic acid or any of the ingredients.

4.4. Special warnings and precautions for use

Patients with irregular menstrual bleeding should not use Cyklokapron until the cause of the irregularity has been established. If menstrual bleeding is not adequately reduced by Cyklokapron, an alternative treatment should be considered.

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. The risk for thromboembolic events may be increased in patients using hormonal contraceptives. If Cyklokapron has to be used in these patients, advise them to use an effective alternative (nonhormonal) contraceptive method.

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.

The blood levels are increased in patients with renal insufficiency. Therefore a dose reduction is recommended (see section 4.2 Posology and method of administration).

In haematuria from the upper urinary tract, blood clots can, in a few cases, lead to ureteric obstruction.

Clinical experience with Cyklokapron in menorrhagic children under 15 years of age is not available.

Convulsions have been reported in association with tranexamic acid treatment. Serious events including death were reported in patients erroneously treated with tranexamic acid via intrathecal or epidural injection (see section 4.3 Contraindications).

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies 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.

4.6. Fertility, pregnancy and lactation

Pregnancy

Available data from published studies, case series and case reports with tranexamic acid use in pregnant women in the second and third trimester and at the time of delivery have not clarified whether there is a drug-associated risk of miscarriage or adverse maternal or 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 risk of major birth defects with use of tranexamic acid during pregnancy is not clear.

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

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.

It is not known whether tranexamic acid use in pregnant women may cause a drug-associated risk of miscarriage or adverse maternal or fetal outcomes. 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.

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

There were 13 clinical studies that described 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*.

Lactation

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.

Fertility

There are no clinical data in humans supporting the impact of tranexamic acid on fertility.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Gastrointestinal disturbances occur in more than 30% of the patients at an oral administration of 6 g/day. The disturbances disappear when the dose is reduced.

Giddiness, nausea and hypotension occur when the intravenous injection is too fast.

Allergic skin reactions have been reported as an uncommon undesirable effect.

Common (>1/100):	**Gastrointestinal Disorders:** nausea, vomiting, diarrhoea
Uncommon (≥1/1000 to <1/100):	**Immune System Disorders:** dermatitis allergic

Post-marketing Surveillance

The following adverse events have been reported in association with tranexamic acid therapy.

Immune System Disorders: hypersensitivity including anaphylactic reaction
Nervous System Disorders: convulsion, dizziness
Eye Disorders: chromatopsia, visual impairment
Vascular Disorders: embolism, hypotension (after fast injection)

4.9. Overdose

Symptoms

Nausea, diarrhoea, dizziness, headache, and convulsions. Orthostatic symptoms and hypotension may occur.
Risk of thrombosis in predisposed individuals.

Treatment of Overdosage

If justified, initiate vomiting, then gastric lavage, charcoal therapy and symptomatic treatment. Maintain adequate diuresis.

Toxicity

37 g of tranexamic acid caused mild intoxication in a 17-year-old after gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Tranexamic acid is a competitive inhibitor of plasminogen activation, and at much higher concentrations, a noncompetitive inhibitor of plasmin, i.e., actions similar to aminocaproic acid. Tranexamic acid is about 10 times more potent *in vitro* than aminocaproic acid.

Tranexamic acid binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds. Tranexamic acid in a concentration of 1 mg/mL does not aggregate platelets *in vitro*.

Tranexamic acid in concentrations up to 10 mg/mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. However, tranexamic acid in concentrations as low as 1 mg/mL can prolong the thrombin time.

5.2. Pharmacokinetic properties

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.

After an intravenous dose of 1 g, the plasma concentration time curve shows a triexponential decay with a half-life of about 2 hours for the terminal elimination phase. The initial volume of distribution is about 9 L to 12 L. Urinary excretion via glomerular filtration is the main route of elimination. Overall renal clearance is equal to overall plasma clearance (110 mL/min to 116 mL/min) and more than 95% of the dose is excreted in the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg body weight.

An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to 7 or 8 hours.

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

The concentration of tranexamic acid in a number of other tissues is lower than in blood. In breast milk the concentration of tranexamic acid is about one-hundredth of the serum peak concentration. The concentration of tranexamic acid in cerebrospinal fluid is about one-tenth of that of the plasma. The drug passes into the aqueous humour, the concentration being about one-tenth of the plasma concentration.

Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.

5.3. Preclinical safety data

<u>Carcinogenesis, Mutagenesis, Impairment of Fertility</u>

No evidence of carcinogenicity or mutagenicity was observed in conventional studies of tranexamic acid. In a fertility and early embryonic development study, tranexamic acid had no effect on fertility or reproductive function of male or female rats at clinically relevant doses.

Reproductive Toxicity

In reproductive toxicity studies, tranexamic acid had no adverse effect on reproductive parameters of mice, rats and rabbits at clinically relevant doses (see section 4.6 Fertility, pregnancy and lactation).

Animal Toxicology and/or Pharmacology

Nonclinical studies have shown a retinal toxicity associated with tranexamic acid. Toxicity is characterised 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 relevant doses, effects in dogs are only observed at multiples of the clinical dose. Studies suggest that the underlying mechanism may be related to a transient retinal ischaemia at higher dose exposures, linked to the known sympathomimetic effect of high plasma levels of tranexamic acid. The clinical relevance of these findings is unknown.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cyklokapron Tablets

Cellulose microcrystalline (E460), hydroxypropyl cellulose L-HPC (E463), talc (E553b), magnesium stearate (E572), silicone anhydrous, colloidal povidone (E1201)

Cyklokapron Injection

One 5 mL ampoule contains 500 mg tranexamic acid in water for injections.

6.2. Incompatibilities

For intravenous infusion, Cyklokapron for injection may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions. The solution should be prepared the same day the solution is to be used.

Cyklokapron injection may be mixed with heparin.

Cyklokapron injection should NOT be added to blood for transfusion or to injections containing penicillin.

Cyklokapron solution for injection has pH 6.5–8.

6.3. Shelf life

Please refer to carton for shelf life.

6.4. Special precautions for storage

Tablets: Do not store above 25°C.
Injection: Do not store above 25°C. Protect from freezing.

6.5. Nature and contents of container

Cyklokapron Tablets

Pack sizes of 20, 50 or 100 tablets in plastic bottles.

Cyklokapron Injection

Each box of Cyklokapron Injection contains ten ampoules.

6.6. Instructions for use/handling

Not applicable.

7. PRODUCT OWNER

Pfizer Inc.
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