SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRANEXEL 250 mg/2.5 mL I.V. Solution for Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Tranexamic acid 250 mg/2.5 mL

Excipients:

"For excipients, see section 6.1."

3. PHARMACEUTICAL FORM

Ampoule containing solution for injection. Colorless, odorless, clean, clear liquid

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Tranexamic acid is indicated for hemorrhages due to local or generalized primary hyperfibrinolysis and subsequent haemorrhages in tissues that are rich in plasminogen activators or under endocrine effects, or where there is a risk of secondary hemorrhage.

Usage in gynecology:

Bleeding after uterine or vaginal surgery, including primary menorrhagia, intrauterine device (IUD) administration, or bleeding during pregnancy and cervical conization.

Otorhinolaryngology:

Epistakis and other local bleeding, post-operative (eg, tonsilectomy) bleeding.

Use in urology:

Bleeding during or after prostatectomy and other urogenital surgeries, hematuria due to prostate hypertrophy, prostate cancer and hemorrhagic cystitis (secondary to radiotherapy).

Surgical use:

Hyperfibrinolytic hemorrhages in thoracic-cardiovascular surgery, orthopedic surgery and gastric surgery.

Use in internal diseases:

In addition to treatment of erosive bleeding in the stomach and duodenum, bleeding in liver cirrhosis and cancers, hemoptysis in destructive lung diseases, long-term prophylaxis in patients with hereditary angioneurotic edema, bleeding complications in patients with hemophilia and thrombolytic therapy.

Use in ophthalmology:

Traumatic hyphema.

Use in dentistry:

Tooth extractions (especially in patients with hemophilia).

Other:

Tranexamic acid may also be prepared according to the invention; Streptokinase may be used as an antidote in all cases of excessive fibrinolysis that may result from urokinase or tissue plasminogen activator (tPA) therapy. It can be used in cases of disseminated intravascular coagulation dominated by fibrinolytic system activity (see section 4.4).

4.2. Posology and method of administration

Posology/administrationfrequency and duration

Adults: Depending on the clinical situation, it is generally recommended to administer 5-10 mL (500-1000 mg) by slow intravenous injection 3-4 times in a day.

When administered as intravenous infusion, it may be administered at a dose of 25-50 mg/kg/day after reconstitution with a suitable diluent (See section 4.5).

The duration of treatment is usually 3-5 days. Only hereditary angioneurotic edema requires long-term treatment. In cases where the treatment period exceeds 3 days, oral administration is recommended.

Epistaxis due to hyperfibrinolysis: Local treatment is applied with nasal tampon soaked in tranexamic acid ampoule content. For unstoppable or residual bleeding, 500-1000 mg is used 3 times a day.

Gastrointestinal bleeding: 1000 mg 3 times a day orally or parenterally for a week.

Bleeding due to hypermenorrhea and IUD: As soon as bleeding starts; 500-1000 mg on the first day, 500-1000 mg on the second day, 500-1000 mg on the second day, 500-1000 mg on the third day and 500-1000 mg on the fourth day. In some cases, 500-1000 mg may be administered.

Cervical conization surgery: 500-1000 mg is recommended 3 times a day during the first 1-2 weeks postoperatively.

Prostatectomy: 1-2 ampoules are administered intravenously 2-3 times a day for three days (first dose during operation). Oral administration is then initiated and 500-1000 mg is administered 2-3 times a day until macroscopic hematuria is resolved.

Tonsilectomy: 1-2 ampoules are administered intravenously 2-3 times a day for three days (first dose during operation). Oral administration is then initiated and 500-1000 mg is administered 2-3 times a day until bleeding stops.

Traumatic hyphema: 1000-1500 mg 3 times a day is recommended.

Hereditary angioneurotic edema: Intermittent episodes of exacerbation or treatment for the first time 3 times a day at a 1000 mg dose is administered continuously.

The administration of a single dose of 10 mL (1 gram) in disseminated intravascular coagulation, dominated by fibrinolytic system, controls bleeding.

It is administered as 10 mg/kg slow intravenous injection to neutralize thrombolytic therapy.

Method of administration:

TRANEXEL can be administered as slow i.v. injection or continuous infusion.

There are also oral forms of tranexamic acid. Tranexamic acid can be used independently from foods.

Additional information for special populations:

Renal/Hepatic impairment:

Renal failure: In renal failure, if intravenous administration will be performed, the dose can be changed according to plasma creatinine values or creatinine clearance as follows. Similar arrangements are valid for oral administration.

Serum creatinine	Creatinine clearance	Tranexamic acid dose (I.V.)
120-250 mcmol/L (1.36-2.83 mg/dL)	75-30 mL/min	10 mg/kg at 12-hour intervals
250-500 mcmol/L) (2.83-5.66 mg/dl)	30-15 mL/min	10 mg/kg at 24-hour intervals
>500 mcmol/L (>5.66 mg/dL)	<15 mL/min	10 mg/kg at 48-hour intervals or 5 mg/kg at 24-hour intervals

Hepatic failure: No dosage adjustment is required in patient with epatic impairment.

Pediatric population:

There are some studies about use of tranexamic acid in pediatric patients present. In children, recommended dose is usually 10-20 mg/kg 3-4 times in a day.

Geriatric population:

No special dosage adjustment is required since there are no symptoms for hepatic impairment.

4.3. Contraindications

TRANEXEL contraindicated in;

- hypersensitivity to the drug substance (tranexamic acid) or to any other components;
- in patients with acquired color vision impairment in patients with subarachnoid hemorrhage and coagulation system active intravascular coagulation and in patients with thromboembolic disease (see section 4.4),
- history of convulsions
- intrathecal and intraventricular injection, intracerebral administration (risk of cerebral oedema and convulsions).
- severe renal impairment due to the risk of accumulation.

4.4. Special warnings and special precautions for use

Intravenous injections should be given very slowly. Tranexamic acid should not be administered by the intramuscular route.

Subarachnoid hemorrhage: TRANEXEL is not used in patients with subarachnoid hemorrhage as there is a risk of cerebral edema and cerebral infection (See section 4.3).

Because of the risk of cerebral edema and convulsions, intrathecal or intraventicular injection and intracerebral administration are contraindicated. Tranexamic acid should not be administered in patients with a history of convulsions.

Tranexamic acid should be performed under the supervision of the patients with disseminated intravascular coagulation (DIC) with definite diagnosis by clotting time measurements. Due to the suppression of fibrinolysis by the effect of tranexamic acid, the thrombi may undesirably stabilize in the manifest hypercoagulability. For this reason, intravascular coagulation with heparin should be stopped before TRANEXEL is administered, and DIC should be prevented by replacing the decreased fibrinogen as a result of excessive consumption. In the treatment of DIC, acute severe bleeding should be limited to the presence of fibrinolytic system activation. Use of TRANEXEL in the treatment of DIC should be performed only where appropriate hematological laboratory facilities are available and under the supervision of experts. The coagulation system should not be applied in cases where DIC is dominant.

Characteristically, the haematological profile approximates to the following: reduced euglobulin clot lysis time; prolonged prothrombin time; reduced plasma levels of fibrinogen, factors V and VIII, plasminogen fibrinolysin and alpha-2 macroglobulin; normal plasma levels of P and P

complex; i.e. factors II (prothrombin), VIII and X; increased plasma levels of fibrinogen degradation products; a normal platelet count. The foregoing presumes that the underlying disease state does not of itself modify the various elements in this profile. In such acute cases a single dose of 1 g tranexamic acid is frequently sufficient to control bleeding. Administration of TRANEXEL in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available.

Ureteral obstruction has been reported in patients with massive upper urinary tract bleeding (especially hemophilia) treated with tranexamic acid.

There is a risk of mechanical anuria due to ureteral plug formation in the case of renal-induced hemorrhage.

It should be considered that the risk of venous or arterial thrombosis may increase in patients with a history of thromboembolism.

In long-term treatment with tranexamic acid, visual and color separation controls, fundus and visual field examinations should be performed. If visual failure occurs during treatment, the drug should be discontinued.

Eye tests (e.g. visual acuity, slit lamp, intraocular pressure, visual field) and liver function tests should be performed regularly in patients requiring long-term tranexamic acid treatment, such as hereditary angioneurotic edema.

Renal failure: In the case of severe renal impairment, the dose should be reduced according to creatinine clearance or serum creatinine values (See section 4.2).

In patients with irregular menstrual bleeding, tranexamic acid should not be used until the cause of irregular bleeding is understood.

Because of the increased risk of thrombosis, tranexamic acid should be used with caution in patients using oral contraceptives.

There is no clinical experience with menorrhagic children under 15 years of age.

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

Pharmacological interactions may occur as a result of combination of tranexamic acid with fibrinolytic drugs. When administered simultaneously with heparin, coumarin derivatives, salicylates or antiaggregants, the effect of tranexamic acid may be reduced as with other antifibrinolytics.

Laboratory Test Interactions: There is no significant change in prothrombin test (Quick test) in people using tranexamic acid.

TRANEXEL injection solution can be mixed with isotonic sodium chloride, isotonic glucose, 20% fructose, dextran 40, dextran 70 and ringer solution.

It should be used immediately after opening. After reconstitution, it is stable for 24 hours at 2-8°C.

Tranexamic acid should be used with caution in patients with smoking, obese, and over 35 years of age who use oral contraceptives due to increased risk of thrombosis.

See section 6.2 for drug incompatibilities.

Additional information for special populations:

No interaction studies have been performed.

Pediatric population:

No interaction studies have been performed.

4.6. Pregnancy and lactation

General advice

Pregnancy category is B.

Women with child-bearing potential/Contraception

There is no warning for women of childbearing potential, caution should be exercised when administering to this population.

Since use of tranexamic acid increases the risk of thromboembolism in women who use hormonal birth control, combined administration is contraindicated.

Pregnancy

Since there are no sufficient and well-controlled studies with pregnant women, tranexamic acid should be used only if it is clearly necessary, especially in the early stages of pregnancy.

Studies in animals have shown that there are direct or indirect harmful effects in relation to pregnancy/embryonal/fatal development/birth or postnatal development.

The potential risk for humans is unknown.

Precautions should be given to pregnant women.

Lactation

Since tranexamic acid is excreted in breast milk at 1/100 of the concentration in maternal blood, it is not expected to have an antifibrinolytic effect in the infant.

Fertility

There is no information on this topic.

4.7. Effects on ability to drive and use machines

Tranexamic acid has no effect on drive and use machines or its effect can be neglected.

4.8. Undesirable effects

Tranexamic acid is generally well tolerated.

Undesirable reactions to tranexamic acid are listed below by body systems and frequency.

Frequencies are defined as: very common (> 1/10); common (> 1/100 to <1/10); uncommon (>1/ 1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000), unknown (cannot be estimated from the available data).

Nervous system diseases

Unknown: Dizziness; convulsions, especially in case of misuse (see section 4.4 “Special warnings and precautions for use”)

Immune system diseases

Unknown: Anaphylactic reaction, anaphylactic shock, immune hypersensitivity reactions

Eye disease

Rare: Color vision disorders

Cardiac diseases

Rare: Thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, central retinal artery and vein thrombosis)

Unknown: Hypotension and dizziness may rarely be seen in patients undergoing treatment by fast i.v. administration. Intravenous administration should not be less than 1 mL/min. Hypotension by oral administration has not been reported.

Gastrointestinal diseases

Rare: Gastrointestinal side effects such as nausea, vomiting, diarrhea may occur and may be eliminated by reducing dose.

Skin and subcutaneous tissues disorders

Rare: Allergic skin reactions

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Overdose with tranexamic acid has not been reported up to date.

Headache, dizziness, nausea, vomiting, diarrhea or hypotension may occur. Symptomatic treatment (with antiemetic, antidiuretic, and antihypotensive agents) should be administered if these symptoms do not disappear by reducing dose or decreasing the injection rate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifibrinolytic drug products

ATC code: B02AA02

Tranexamic acid is an antifibronilitic drug used mainly for treatment and prophylaxis of bleeding associated with excessive fibrinolysis.

Mechanism of action: Tranexamic acid shows its hemostatic effect by inhibiting plasminogen activation and providing fibrin protective activity in cases where fibrinolysis is pathologically increased.

Tranexamic acid; It is a competitive inhibitor of plasminogen activation and a noncompetitive inhibitor of plasmin in high doses. Its effect is similar to aminocaproic acid, but it is 10 times more active. There was no effect on platelet functions, clotting time and other clotting factors in citrated and whole blood samples taken from healthy subjects up to 10 mg/mL concentrations, but it was shown to prolong thrombin time at doses of 1-10 mg/mL.

5.2 Pharmacokinetic properties

General properties

Absorption:

Since TRANEXEL solution for injection is administered intravenously, its absorption is complete. Approximately 30-50% of oral tranexamic acid is absorbed.

Distribution:

Tranexamic acid is commonly distributed in the body into interstitial and intravascular compartments.

Its distribution is almost exclusively extracellular. The initial dispersion volume is approximately 9 L.

It binds to plasma proteins at about 3%, which seems to be related to the binding of tranexamic acid to plasminogen. Tranexamic acid crosses the blood-brain barrier and passes into synovial fluid, synovial membrane, aqueous humor and semen. It crosses the placenta and excretes into breast milk. It is present in antifibronilitic concentrations in various tissues for 17 hours and in serum for 7-8 hours.

Biotransformation:

Less than 5% of the drug product is metabolized.

Elimination:

Tranexamic acid is substantially eliminated by urine and glomerular filtration in active state without change. Thus, in the case of a hyperfibrinolysis induced by urokinase or tissue plasminogen activators in the urinary tract, it may show hemostatic effect. Plasma half-life is up to 2 hours. Renal clearance is equal to plasma clearance (110-116 mL/min) and 95% of administered dose is excreted in the urine as unchanged drug.

Linearity / non-linearity:

It has linear pharmacokinetics.

Characteristics properties on patients

Pharmacokinetics in elderly patients:

Pharmacokinetic differences were not observed in elderly patients (>65 years) compared to younger patients. However, it should be considered that renal function may decrease with aging.

Pharmacokinetics in liver failure:

Since it is metabolised in very low amounts in the liver, there is no need to adjust the dose in liver failure.

Pharmacokinetics in renal failure:

Since tranexamic acid is mainly eliminated through the kidneys, it may accumulate in the body in renal failure. Therefore, dose adjustment is necessary in patients with renal insufficiency. (See section 4.2.)

5.3 Preclinical safety data

Tranexamic acid is administered to cats, dogs and rats for 6 days to 1 year at doses of 250-1600 mg/kg/day (6-40 times the recommended human dose) orally or i.v. Focal degenerations of the retina were observed. The incidence of these lesions in animals is 25-100% and dose-related. Some of the lesions observed at low doses are reversible.

Limited data are available to show changes in retina of some animals with low doses such as 126 mg/kg/day (only 3 times the recommended human dose) to cats and rabbits for several days to two weeks.

Retinal changes were not observed in patients treated with tranexamic acid for weeks / months in clinical trials.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

In the preformulation, formulation and stability studies of the drug product, no inverse interactions were observed in the triangle of active substance-excipients-inner packaging materials.

Tranexamic acid is not used with penicillin-containing solutions and blood.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature below 25 °C.

6.5 Nature and contents of container

Type I glass 2.5 mL ampoules in a carton box containing 10 ampoules.

6.6 Instructions for use and handling and disposal

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

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Date of first authorisation: 29.12.2017
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10. DATE OF REVISION OF THE TEXT
