SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

EMXAMIC INJECTION (Tranexamic Acid Injection BP 500mg/5ml)

2. Qualitative and Quantitative Composition Composition:

Each 5 ml contains:

Tranexamic Acid BP 500 mg Water for Injection BP q.s.

For the full list of excipients see section 6.1.

3. Pharmaceutical Form

Solution for Injection

4. Clinical Particulars

4.1 Therapeutic Indications

Prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year.

Specific indications include:

- Haemorrhage caused by general or local fibrinolysis such as:
- Menorrhagia and metrorrhagia,
- Gastrointestinal bleeding,
- Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract
- Ear Nose Throat surgery (adenoidectomy, tonsillectomy, dental extractions),
- Gynaecological surgery or disorders of obstetric origin,
- Thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery,
- Management of hemorrhage due to the administration of a fibrinolytic agent.

4.2 Posology and Method of Administration

Posology

Adults

Unless otherwise prescribed, the following doses are recommended:

1) Standard treatment of local fibrinolysis:

0.5 g (1 ampoule of 5 ml) to 1 g (1 ampoule of 10 ml or 2 ampoules of 5 ml) tranexamic acid by slow intravenous injection (=1 ml/minute) two to three times daily.

2) Standard treatment of general fibrinolysis:

1 g (1 ampoule of 10 ml or 2 ampoules of 5 ml) tranexamic acid by slow intravenous injection (= 1 ml/minute) every 6 to 8 hours, equivalent to 15 mg/kg BW.

Renal impairment

In renal insufficiency leading to a risk of accumulation, the use of tranexamic acid is contraindicated in patient with severe renal impairment. For patient with mild to moderate renal impairment, the dosage of tranexamic acid should be reduced according to the serum creatinine level:

Serum Creatine		Dose IV	Administration
µ mol/l	mg/10ml		
120 to 249	1.35 to 2.82	10mg/kg BW	Every 12 hours
250 to 500	2.82 to 5.65	10mg/kg BW	Every 24 hours
> 500	> 5.65	5 mg/kg BW	Every 24 hours

Hepatic impairment

No dose adjustment is required in patient with hepatic impairment.

Paediatric Population:

In children from 1 year, for current approved indications, the dosage is in the region of 20 mg/kg/day. However, data on efficacy, posology and safety for these indications are limited. The efficacy, posology and safety of tranexamic acid in children undergoing cardiac surgery have not been fully established. Currently available data are limited.

Elderly:

No reduction in dosage is necessary unless there is evidence of renal failure.

Method of administration

The administration is strictly limited to slow intravenous injection.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding

- Severe renal impairment (risk of accumulation)
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)

4.4 Special Warnings and Precautions for Use

The indications and method of administration indicated above should be followed strictly:

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

Convulsions

Cases of convulsions have been reported in association with tranexamic acid treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following intravenous (i.v.) injection of tranexamic acid in high doses. With the use of the recommended lower doses of TXA, the incidence of post-operative seizures was the same as that in untreated patients.

Visual disturbances

Attention should be paid to possible visual disturbances including visual impairment, vision blurred, impaired colour vision and if necessary, the treatment should be discontinued. With continuous long-term use of TXA solution for injection, regular ophthalmologic examinations (eye examinations including visual acuity, colour vision, fundus, visual field etc.) are indicated. With pathological ophthalmic changes, particularly with diseases of the retina, the physician must decide after consulting a specialist on the necessity for the longterm use of TXA solution for injection in each individual case.

Haematuria

In case of haematuria from the upper urinary tract, there is a risk for urethral obstruction.

Thromboembolic events

Before use of TXA, risk factors of thromboembolic disease should be considered. In patients with a history of thromboembolic diseases or in those with increased incidence of thromboembolic events in their family history (patients with a high risk of thrombophilia), Tranexamic acid solution for injection should only be administered if there is a strong medical indication after consulting a physician experienced in hemostaseology and under strict medical supervision.

Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis. Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with tranexamic acid. If tranexamic acid is given it must be restricted to those in whom there is predominant activation of the fibrinolytic system with acute severe bleeding. Characteristically, the hematological 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 1g tranexamic acid is frequently sufficient to control bleeding. Administration of Tranexamic acid in DIC should be considered only when appropriate hematological laboratory facilities and expertise are available.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

No interaction studies have been performed. Simultaneous treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field. Medicinal products that act on hemostasis should be given with caution to patients treated with tranexamic acid. There is a theoretical risk of increased thrombus-formation potential, such as with oestrogens. Alternatively, the antifibrinolytic action of the drug may be antagonised with thrombolytic drugs.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy

There are insufficient clinical data on the use of tranexamic acid in pregnant women. As a result, although studies in animals do not indicate teratogenic effects, as a precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy. Limited clinical data on the use of tranexamic acid in different clinical haemorrhagic settings during the second

and third trimesters did not identify deleterious effect for the foetus. Tranexamic acid should be used throughout pregnancy only if the expected benefit justifies the potential risk.

Breastfeeding

Tranexamic acid is excreted in human milk. Therefore, breastfeeding is not recommended.

Fertility

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

4.7 Effects on Ability to Drive and Use Machines

No studies have been performed on the ability to drive and use machines.

4.8 Undesirable Effects

System Organ Class	Frequency	Undesirable Effects
Immune system disorders	Not known	Hypersensitivity reactions including anaphylaxis
Nervous system disorders	Not known	Dizziness, convulsions particularly in case of misuse
Eye disorders	Not known	Visual disturbances including impaired
Vascular disorders	Not known	Malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration) Arterial or venous thrombosis at any sites
Gastrointestinal disorders	Common	Diarrhoea Vomiting Nausea
Skin and subcutaneous tissues disorders	Uncommon	Dermatitis allergic

4.9 Overdose

No cases of overdose have been reported.

Symptoms

Signs and symptoms may include dizziness, headache, hypotension, and convulsions. It has been shown that convulsions tend to occur at higher frequency with increasing dose.

Management

Management of overdose should be supportive.

5. Pharmacological Properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antihemorrhagics, Antifibrinolytics, Amino acids

ATC CODE: B02AA02

Mechanism of Action

Tranexamic acid exerts an anti-haemorrhagic activity by inhibiting the fibrinolytic properties of plasmin.

A complex involving tranexamic acid, plasminogen is constituted; the tranexamic acid being linked to plasminogen when transformed into plasmin.

The activity of the tranexamic acid-plasmin complex on the activity on fibrin is lower than the activity of free plasmin alone.

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

Paediatric population

In children over one year old: Literature review identified 12 efficacy studies in paediatric cardiac surgery which have included 1073 children, 631 having received tranexamic acid. Most of them were controlled versus placebo. Studied population was heterogenic in terms of age, surgery types, dosing schedules. Study results with tranexamic acid suggest reduced blood loss and reduced blood product requirements in paediatric cardiac surgery under cardiopulmonary bypass when there is a high risk of haemorrhage, especially in cyanotic patients or patients undergoing repeat surgery. The most adapted dosing schedule appeared to be:

- first bolus of 10 mg/kg after induction of anaesthesia and prior to skin incision,
- continuous infusion of 10 mg/kg/h or injection into the CPB pump prime at a dose adapted on the CPB procedure, either according to patient weight with a 10 mg/kg dose, either according to CPB pump prime volume,
- last injection of 10 mg/kg at the end of CPB.

While studied in very few patients, the limited data suggest that continuous infusion is preferable, since it would maintain therapeutic plasma concentration throughout surgery.

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

5.2 Pharmacokinetic properties

Absorption

Peak plasma concentrations of tranexamic acid are obtained rapidly after a short intravenous infusion after which plasma concentrations decline in a multi-exponential manner.

Distribution

The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin. The initial volume of distribution is about 9 to 12 liters.

Tranexamic acid passes through the placenta. Following administration of an intravenous injection of 10 mg/kg to 12 pregnant women, the concentration of tranexamic acid in serum ranged 10-53 μ g/mL while that in cord blood ranged 4_31 μg/mL. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. Following administration of an intravenous injection of 10 mg/kg to 17 patients undergoing knee surgery, concentrations in the joint fluids were similar to those seen in corresponding serum samples. The concentration of tranexamic acid in a number of other tissues is a fraction of that observed in the blood (breast milk, one hundredth; cerebrospinal fluid, one tenth; aqueous humor, one tenth). Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.

Elimination

It is excreted mainly in the urine as unchanged drug. Urinary excretion via glomerular filtration is the main route of elimination. Renal clearance is equal to plasma clearance (110 to 116 mL/min). Excretion of tranexamic acid is about 90% within the first 24 hours after intravenous administration of 10 mg/kg body weight. Half-life of tranexamic acid is approximately 3 hours.

Renal impairment

Plasma concentrations increase in patients with renal failure.

Pediatric population

No specific PK study has been conducted in children.

5.3 Pre-Clinical Safety Data:

N/A

6. Pharmaceutical Particulars

6.1 List of Excipients

- Water for Injection BP

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store at a temperature not exceeding 30°C. Protect from light and moisture.

Keep medicine out of the reach of children.

6.5. Nature and Contents of Container

5 × 5ml ampoules placed in a plastic tray and such one plastic tray packed in a unit carton along with pack insert.

6.6. Special Precautions for Disposal and Other Handling

None

7. Applicant:

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