SUMMARY OF PRODUCT CHARACTERISTICS

PAUSE INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Tranexamic Acid BP 500 mg in 5 ml for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains Tranexamic Acid BP 500mg.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Local fibrinolysis

For short term use in prophylaxis and treatment in patients at high risk of per- and post-operative haemorrhage following:

a) Prostatectomy

b) Conisation of the cervix

c) Surgical procedures and dental extractions in haemophiliacs

General fibrinolysis

a) Hemorrhagic complications in association with thrombolytic therapy.

b) Haemorrhage associated with disseminated intravascular coagulation (DIC) with predominant activation of the fibrinolytic system.

4.2 Posology and method of administration

Route of administration:

Administration of the injection is strictly limited to slow intravenous use.

Local fibrinolysis: The recommended standard dose is 5-10 ml (500-1000 mg) by slow intravenous injection (1 ml/min), three times daily. If treatment continues for more than three days, consideration should be given to the use of tranexamic acid tablets.

Alternatively, following an initial intravenous injection, subsequent treatment may proceed by intravenous infusion. Following addition to a suitable diluent, tranexamic acid may be administered at a rate of 25-50 mg/kg body weight/day.

Children: According to body weight (1Omg/kg body weight/ 2-3 times daily).

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

General fibrinolysis

1. In disseminated intravascular coagulation with predominant activation of the fibrinolytic system, usually a single dose of 10 ml (1 g) is sufficient to control bleeding.

2. Neutralization of thrombolytic therapy: 1Omg/kg body weight by slow intravenous injection.

Renal impairment:

In patients with renal insufficiency because of the risk of accumulation, the dose should be reduced according to the following table:

Serum Creatinine	Dose by IV Route	Dose Frequency
120-250 micromol /1 (1.36 to 2.83 mg/dL)	10 mg/kg	Twice daily
250-500 micromol/1 (2.83 to 5.66 mg/dL)	10 mg/kg	Every 24th hour
> 500 micromol /1 (>5.66 mg/dL)	5 mg/kg	Every 24th hour

4.3 Contraindications

- Hypersensitivity to the active substance or to any of its excipients listed in section 6.1.
- Acute venous or arterial thrombosis (see section 4.4).
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding (see section 4.4).
- 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 long-term 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 (see section 4.3).

Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis (see section 4.5).

Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with tranexamic acid (see section 4.3). 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 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 tranexamic acid in DIC should be considered only when appropriate haematological 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 haemostasis 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 is 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 precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy.

Limited clinical data of 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.

Breast-feeding

Tranexamic acid is excreted in human milk. Therefore, breast-feeding is not recommended.

Fertility

There are no clinical data on the effects of tranexamic acid on 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

The ADRs reported from clinical studies and post-marketing experience are listed below according to system organ class.

Tabulated list of adverse reactions

Adverse reactions reported are presented in table below. Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Undesirable Effects
Immune system disorders	Not known	- Hypersensitivity reactions including anaphylaxis
Nervous system disorders	Not known	- Convulsions particularly in case of misuse (refer to sections 4.3 and 4.4)
Eye disorders	Not known	- Visual disturbances including impaired colour vision
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 embolism at any sites
Gastrointestinal disorders	Common	- Diarrhoea - Vomiting - Nausea
Skin and subcutaneous tissue disorders	Uncommon	- Dermatitis allergic

4.9 Overdose

No case of overdose has been reported.

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 of overdose should be supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, Antifibrinolytics, Aminoacids

ATC code: B02AA02

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.

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 litres.

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 µg/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.

Excretion

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. Elimination half-life of tranexamic acid is approximately 3 hours.

Special populations

Plasma concentrations increase in patients with renal failure.

No specific PK study has been conducted in children.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Water for injection.

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the active Ingredient.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry and dark place, below 25°C.

6.5 Nature and contents of container

Pause Injection, 500mgl5mL is supplied in USP Type- I glass ampoules, 5 such ampoules are placed in a plastic tray which is packed in printed carton along with a pack Insert.

6.6 Special precautions for disposal and other handling

Store in a dry and dark place, below 25°C. Keep Away from Reach of Children

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Limited

8. MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT