SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

Trenaxa (Tranexamic Acid Injection 500mg/5mL)(100mg/ml)

2. Qualitative and Quantitative Composition

Each 5ml contains:

Tranexamic acid Ph.Eur..... 500 mg

For full list of Excipients, see section 6.1

3. Pharmaceutical Form

Injection

Product Description: Clear colorless solution**.**

4. Clinical Particulars

4.1 Therapeutic indications

It is indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.

4.2 Posology and method of administration

Immediately before tooth extraction in patients with hemophilia, administer 10 mg per kg body weight of tranexamic acid intravenously together with replacement therapy. Following tooth extraction, intravenous therapy, at a dose of 10 mg per kg body weight three to four times daily, may be used for 2 to 8 days. ***Note:*** For patients with moderate to severe impaired renal function, the following dosages are recommended:

Serum Creatinine (µmol/L)	**Tranexamic Acid I.V.Dosage**
120 to 250 (1.36 to 2.83 mg/dL)	10 mg/kg BID
250 to 500 (2.83 to 5.66 mg/dL)	10 mg/kg daily

> 500 (> 5.66 mg/dL)	10 mg/kg every 48 hours or 5 mg/kg every 24 hours

For intravenous infusion, Injection may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and Dextran solutions. Heparin may be added to Injection. Tranexamic Injection should NOT be mixed with blood. The drug is a synthetic amino acid, and should NOT be mixed with solutions containing penicillin.

4.3 Contraindications

- In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity.
- In patients with subarachnoid hemorrhage. Anecdotal experience indicates that cerebral edema and cerebral infarction may be caused by Tranexamic Injection in such patients.
- In patients with active intravascular clotting.
- In patients with hypersensitivity to tranexamic acid or any of the ingredients.

4.2 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 Tranexamic acid, 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 Tranexamic acid 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 the physician must decide after consulting a specialist on the necessity for the long-term use of Tranexamic acid 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 Tranexamic acid, 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 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.

Pediatric Use

The drug has had limited use in pediatric patients, principally in connection with tooth extraction. The limited data suggest that dosing instructions for adults can be used for pediatric patients needing tranexamic acid therapy.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

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 Pregnancy and Lactation

Pregnancy: Category B

There are no adequate and well-controlled studies in pregnant women. However, Tranexamic acid passes the placenta and appears in cord blood at concentrations approx. equal to maternal concentrations. Therefore, it should be used only if clearly needed.

Lactation:

Tranexamic acid is present in breast milk at about a hundredth of corresponding serum levels. Therefore, caution should be exercised while administering the drug to nursing women.

4.7 Effects on ability to drive and use machines

Tranexamic Acid has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

System organ class	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Frequency not known (cannot be estimated from the available data)**
Immune system disorders			- Hypersensitivity reactions including anaphylaxis
Nervous system disorders			- Convulsions particularly in case of misuse (refer to sections 4.3 and 4.4)
Eye disorders			- Visual disturbances including impaired colour vision

Vascular disorders			- 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	- Diarrhoea - Vomiting - Nausea		
Skin and subcutaneous tissue disorders		- Dermatitis allergic	

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Cases of overdosage have been reported. Based on these reports, symptoms of overdosage may be gastrointestinal, e.g., nausea, vomiting, diarrhea; hypotensive, e.g., orthostatic symptoms; thromboembolic, e.g., arterial, venous, embolic; visual impairment; mental status changes; myoclonus, and rash.

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 per mL does not aggregate platelets in vitro.

5.2 Pharmacokinetic properties

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

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.

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

Tranexamic acid passes through the placenta. Tranexamic acid diffuses rapidly into 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 three hours.

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

An increased incidence of leukemia in male mice receiving tranexamic acid in food at a concentration of 4.8% (equivalent to doses as high as 5 g/kg/day) may have been related to treatment. Female mice were not included in this experiment. Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long-term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic / neoplastic changes in the liver. No mutagenic activity has been demonstrated in several *in vitro* and in vivo test systems.

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

6. Pharmaceutical Particulars

6.1 List of Excipients

Water for Injection

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Store below 30°C, in a dry place protected from light.

6.5 Nature and contents of container

Ampoule containing 5 ml injection. Such 5 amopules are packed in a carton along with pack insert.

6.6 Special Precaution for disposal

None.

7. Supplier

Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade, Marol Church Road, Andheri (East), Mumbai- 400 059,
India
Phone: +91-22-66762800
Fax: +91-22-2821 6599
E-mail: exports@macleodspharma.com

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