For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Tranexamic Acid Injection IP
Tensinic®

Composition:
Each 5ml contains:
Tranexamic Acid IP..... 500 mg
Water for Injections IP..... q.s.

DOSAGE FORM
Solution for injection

THERAPEUTIC INDICATIONS
- Abnormal bleeding in which local hyperfibrinolysis is considered to be involved (pulmonary, haemorrhage, epistaxis, renal bleeding abnormal bleeding during or after prostate surgery).
- Haemorrhage or risk of haemorrhage in increased fibrinolysis of hereditatory angioneurotic oedema.
- Treatment of excessive bleeding in patients with hemophilia during & following tooth extraction.

POSOLOGY AND METHOD OF ADMINISTRATION
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 contra-indicated 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 creatinine		Dose IV	Administration
µ mol/l	Mg/10 ml		
120 to 249	1.35 to 2.82	10 mg/kg BW	Every 12 hours
250 to 500	2.82 to 5.65	10 mg/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 and are described in section 'Pharmacodynamic properties.'
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.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- 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)

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,
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 1g 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.

DRUG 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.

USE IN SPECIFIC POPULATIONS
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.

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: 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	- Dizziness, convulsions particularly in case of misuse
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 thrombosis at any sites
Gastrointestinal disorders	Common	- Diarrhoea - Vomiting - Nausea
Skin and subcutaneous tissues disorders	Uncommon	- Dermatitis allergic

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

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.

CLINICAL PHARMACOLOGY
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic effects
Pharmacotherapeutic group: Antihemorrhagics, Antifibrinolytics, Amino acids
ATC code: B02A A02
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.

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 µ g/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.

Paediatric population
No specific PK study has been conducted in children.

NONCLINICAL TOXICOLOGY
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.

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

STORAGE AND HANDLING INSTRUCTIONS:
Store protected from light at temperature not exceeding 30ºC.

PACKAGING INFORMATION:
Ampoule of 5ml

Marketed by & ® Regd. Trade Mark of:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai - 400 030, India.

Note: This prescribing information is applicable for India Market only

DATE
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