MODULE-1 (ADMINISTRATIVE & PRPDUCT INFORMATION)
TRANEXAMIC ACID INJECTION BP 100MG/ML

1.3 Product Information

1.3.1 Summary of product characteristics

1. Name of the Medicinal Product
Tranexamic Acid Injection BP 100mg/ml

2. Qualitative and Quantitative Composition
Each ml contains:
Tranexamic Acid BP 100mg
Water for Injection BP q.s.

Filling : 5ml Ampoule

Batch Size : 100 LITRES/ 19608 AMPOULES

S.No.	Ingredients	Claim (mg/ml)	Function	Std. Qty. /Batch	O.A.	Qty. (mg/Amp)	Qty. with O.A.
Active							
1.	Tranexamic Acid BP	100.00	Anti-Fibrinolytics	10.00 Kg	---	500.00 mg	10.00 Kg
Inactive							
1.	Disodium EDTA BP	---	Chelating agent	0.100 Kg	---	5.00 mg	0.100 Kg
2.	Sodium Chloride BP	---	Buffer	1.900 Kg	---	45.00 mg	1.900 Kg
3.	Water for Injection BP	---	Solvent	q.s.	---	q.s.	q.s.

***The quantity calculated based on target fill volume 5.1 ml**
 # Quantity is based on 100% W/V assay & 0% LOD

Abbreviation:
USP : United States Pharmacopoeia.
BP : British Pharmacopoeia.
O.A. : Overages
Std. Qty. : Standard Quantity

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Batch Calculation for Tranexamic Acid BP:

Batch Size : 100 Litres (100000ml)

Filling : 5ml Ampoule

Each ml contains:

Tranexamic Acid	BP	100mg
Water for Injection	BP	q.s.

Actual Quantity required **:** $\frac{\text{Label Claim x 100 x 100 x Factor x Batch Size}}{\text{Assay x (100 - LOD) x 100}}$

: $\frac{\text{100 x 100 x 100 x Factor x 100000}}{\text{100 x 100}}$

: **10000000mg (**10000g)

: **10.00 Kg of Tranexamic Acid BP**

3. Pharmaceutical Form

Solution for Injection **"**A clear colourless solution filled in 5ml clear glass red ring ampoule on constriction.**"**

4. Clinical Particulars

4.1 Therapeutic Indication

Adults

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 haemorrhage due to the administration of a fibrinolytic agent.

4.2 Posology and method of administration

Unless otherwise prescribed, the following doses are recommended:
1. Standard treatment of local fibrinolysis:
0.5 g to 1 g tranexamic acid by slow intravenous injection (= 1 ml/minute) two to three times daily
2. Standard treatment of general fibrinolysis:
1 g 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 patients 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**
µmol/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, 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.

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 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 retina, 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 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.

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

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.

Breast-feeding

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

None known.

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: Common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), not known (can not 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 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 nausea, vomiting, 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.

Maintain a high fluid intake to promote renal excretion. Anticoagulant treatment should be considered. There is a risk of thrombosis in predisposed individuals.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, Antifibrinolytics, Aminoacids
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.

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 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.

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.

5.3 Preclinical safety data

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

6. Pharmaceutical Particulars

6.1 List of excipients

Di Sodium EDTA BP
Sodium Chloride BP
Water for Injection BP

6.2 Incompatibilities

Tranexamic Acid Solution for Injection should not be added to blood for transfusion, or to injections containing penicillin.

6.3 Shelf Life

2 YEARS

6.4 Special precautions for storage

Store in a cool & dark place.

6.5 Nature and contents of container

5ml clear glass red ring ampoule on constriction

6.6 Special precautions for disposal and other handling

None.

7. Marketing authorisation holder

Indus Pharma Pvt. Ltd.
Manufacturing site (Works):
A-181, RIICO Industrial Area
Ghiloth, Alwar Rajasthan

8. Marketing authorisation Number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text
