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

XAMIC INJECTION

1. **Generic Name**
   Tranexamic Acid Injection I.P.

2. **Qualitative and quantitative composition**
   Each 5 ml injection contains; Tranexamic Acid I.P. 500 mg
   Water for injection I.P. …q.s.

3. **Dosage form and strength**
   Dosage Form: Injection
   Strength: 500 mg/5 ml

4. **Clinical particulars**

4.1 Therapeutic indication

Xamic injection is used for the treatment of Haemorrhage or risk of haemorrhage in increased fibrinolysis of hereditary angioneurotic oedema.

4.2 Posology and method of administration

Xamic Injection is for intravenous use only.

Do not use the injection if the contents are not clear or show particulate matter.

Use in patients with impaired renal function

In the case of patients with moderate to severe impaired renal function, the dosages need to be reduced. Depending on the serum creatinine levels the recommended dosage is as follows:

SERUM CREATINE (µ mol/L)	DOSAGE
120 to 250 (1.36 to 2.83mg/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 5mg/kg every 24 hours

For intravenous infusion, Xamic Injection may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and Dextran solutions. The mixture should be prepared the same day the solution is to be used. Heparin may be added to Xamic Injection. Xamic Injection should NOT be mixed with blood. The drug is a synthetic amino acid, and should NOT be mixed with solutions containing penicillin.

Local Fibrinolysis: The recommended standard dose is 5-10ml (500-1000mg) 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 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 wt/day.

Children: According to body weight (10mg/kg body wt/ 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 10ml (1g) is sufficient to control bleeding.

2) Neutralisation of thrombolytic therapy; 10mg/kg body wt by slow intravenous injection.

4.3 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).

4.4 Special warnings and precautions for use

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

• Intravenous injections or infusions should be given very slowly (maximum 1 mL per minute)

• 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 (IV.) 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, 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 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 should only be administered if there is a strong medical indication after consulting a physician experienced in haemostaseology 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 Drugs interactions

As per reported data, 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 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Women of childbearing potential

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

Pregnancy

There are no or limited amount of data from the use of tranexamic acid in pregnant women. As a result, although reported studies in animals do not indicate teratogenic effects, as precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy.

Limited reported 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, 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

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.

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/Seizures particularly in case of misuse (see 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 side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

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 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..

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics, Antifibrinolytics, Amin oacids
ATC code: B02AA02

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

Reported *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 (CPB) where 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 a patient weight with a dose of 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.

5.3 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. As per reported data, following administration of an intravenous injection of 10 mg/kg to 12 pregnant women, the concentration of tranexamic acid in serum ranged 10-53 microgram/mL while that in cord blood ranged 4-31 microgram/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. Elimination half-life of tranexamic acid is approximately 3 hours.

Other special populations
Plasma concentrations increase in patients with renal failure.

No specific pharmacokinetic study has been conducted in children.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology
Reported non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Epileptogenic activity has been observed in animals with intrathecal use of tranexamic acid.

7. Description
Clear, colourless solution filled in clear glass ampoules.

8. Pharmaceutical particulars

8.1 Incompatibilities
This medicinal product should not be mixed with blood for transfusion or with solutions containing penicillin.

8.2 Shelf-life
2 years

8.3 Packaging information
It is available as clear, colorless solution filled in 5 ml clear, colorless glass ampoules.

8.4 Storage and handing instructions
Keep in a cool place. Keep out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet:

9.1 What Xamic Injection is and what it is used for

Xamic Injection contains tranexamic acid which belongs to a group of medicines called antihaemorragics; antifibrinolitics, aminoacids.

Xamic Injection is used for the treatment of excessive bleeding in patients with:

Local Fibrinolysis: For short term use in prophylaxis and treatment in patients at high risk of pre and post-operative haemorrhage following:
a) Prostatectomy
b) Conisation of the cervix

General Fibrinolysis:

a) Haemorrhagic complications in association with thrombolytic therapy.

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

9.2 What you need to know before you use Xamic Injection.

❖ **Do not take Xamic Injection if:**

- You are allergic to tranexamic acid or any of the other ingredients of this medicine
- You have currently a disease leading to blood clots
- You have a condition called ‘consumption coagulopathy’ where blood in the whole body starts to clot.
- You have kidney problems
- You have a history of convulsions

Due to the risk of cerebral oedema and convulsions, intrathecal and intraventricular injection and intracerebral application are not recommended.

If you think any of these apply to you, or if you are in any doubt at all, tell your doctor before taking Xamic Injection.

Warnings and precautions

Talk to your doctor or nurse if any of these apply to you to help him or her decide if Xamic Injection is suitable for you:

- If you have had blood in your urine, it may lead to urinary tract obstruction.
- If you have a risk of having blood clots.
- If you have excessive clotting or bleeding throughout your body (disseminated intravascular coagulation), Xamic Injection may not be right for you, except if you have acute severe bleeding and blood test have shown the process that inhibits blood clotting called fibrinolysis is activated.
- If you have had convulsions, Xamic Injection should not be administered. Your doctor must use the minimal dose possible to avoid convulsions following treatment with Xamic Injection.
- If you are on a long-term treatment with Xamic Injection, attention should be paid to possible disturbances of colour vision and if necessary the treatment should be discontinued. With continuous long-term use of Xamic 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, your doctor must take a decision after consulting a specialist on the necessity for the long-term use of Xamic Injection in your case.

Other medicines and Xamic Injection

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

You should specifically tell them if you take:

• other medicines that help blood to clot called antifibrinolytic medicines
• medicines that prevent blood clotting, called thrombolytic medicines
• oral contraceptives

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Tranexamic acid is excreted in human milk. Therefore, the use of Xamic Injection during breast-feeding is not recommended.

Driving and using machines

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

9.3 How to use Xamic Injection

Xamic Injection will be given to you by slow injection or infusion into a vein.

Your doctor will decide the correct dose for you and how long you should take it.

Use in children

If Xamic Injection is given to a child from one year, the dose will be based on the child's weight. Your doctor will decide the correct dose for the child and how long he/she should take it.

Use in elderly

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

Use in patients with kidney problem

If you have a kidney problem, your dose of tranexamic acid will be reduced according to a test performed on your blood (serum creatinine level).

Use in patients with hepatic impairment

No reduction in dosage is necessary.

Method of administration
Xamic Injection should only be administered slowly into a vein.
Xamic Injection must not be injected into a muscle.

If you are given more Xamic Injection **than the recommended dose**
If you are given more Xamic Injection than the recommended dose you may experience a transitory blood pressure lowering. Talk to a doctor or pharmacist immediately.

9.4 Possible Side Effects
Like all medicines Xamic injection can cause side effects, although not everybody gets them.

Side effects reported with Xamic Injection **are:**

The following side effects have been observed with Xamic Injection

Common: may affect up to 1 in 10 people
• effects on the stomach and intestines: nausea, vomiting, diarrhoea

Uncommon: may affect up to 1 in 100 people
• effects on the skin problems: rash

Not known: frequency cannot be estimated from the available data
• malaise with hypotension (low blood pressure), with or without loss of consciousness, especially if the injection is given too quickly
• blood clots
• effects on the nervous system: convulsions
• effects on the eyes: vision disturbances including impaired colour vision
• effects on the immune system: allergic reactions

- **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5 How to store Xamic Injection
Keep out of the sight and reach of children. Do not take this medicine after the expiry date shown on the carton. The expiry date refers to the last day of that month. Do not use the injection if the contents are not clear or show particulate matter. Store in a cool place. Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

9.6 Contents of the pack and other information

What Xamic Injection contains:

The active substance in this product is Tranexamic Acid.

10. Details of manufacturer
Manufactured by:
Torrent Pharmaceuticals Ltd.
Indrad-382 721, Dist.Mehsana INDIA
At.Plot No., J-174, J-168, J-168/1,MIDC,Tarapur,
Dist.Thane-401 506

11. Details of permission or licence number with date
Mfg.Lic.No-KD-2035-A dated 19.05.14

12. **Date of revision**
Aug 2019

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/XAMIC Injection 500mg/Aug-2019/03/PI