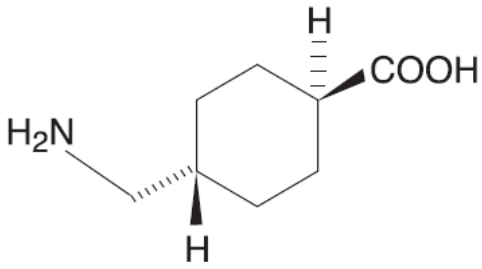
For the Use of a Specialist Only

XAMIC INJECTION
(Tranexamic Acid Injection 100 mg/ml)

COMPOSITION
XAMIC INJECTION
Each 5 ml injection contains;
Tranexamic Acid I.P. 500 mg.

PROPERTIES
Tranexamic acid is trans-4-(aminomethyl)cyclohexane carboxylic acid. It is white crystalline powder, freely soluble in water and in glacial acetic acid, practically insoluble in alcohol and in acetone. The empirical formula is $C_8H_{15}NO_2$ and its structure is:



CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Tranexamic acid produces an antifibrinolytic effect by competitively inhibiting the activation of plasminogen to plasmin. It is also a weak noncompetitive inhibitor of plasmin. These properties make possible its clinical use as an antifibrinolytic in the treatment of both general and local fibrinolytic hemorrhages. It has a mechanism of action similar to, but about 10 times more potent than epsilon aminocaproic acid (EACA). Tranexamic acid binds considerably more strongly than EACA to both the strong and weak sites in the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds. The pharmacological significance of the binding to these different sites has not yet been evaluated. Tranexamic acid in concentrations up to 10 mg per mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. On the other hand, tranexamic acid in concentrations of 10 mg and 1 mg per mL blood prolongs the thrombin time.

PHARMACOKINETICS
Absorption from the human gastrointestinal tract is not complete (40%). Tranexamic acid does not bind to serum albumin. The plasma protein binding which seems to be fully accounted for by its binding to plasminogen, appears to be negligible at therapeutic plasma levels of 5 to 10 mg/L. Possible routes of biotransformation are acetylation or deamination followed by oxidation or reduction. After oral administration approximately 50% of the parent compound, 2% of the deaminated dicarboxylic acid and 0.5% of the acetylated product are excreted. Tranexamic acid is eliminated by glomerular filtration, excretion being about 30% at 1 hour, 55% at 3 hours and

90% at 24 hours after I.V. administration of 10 mg/kg. After oral administration of 10 to 15 mg/kg, excretion was 1% at 1 hour, 7% at 3 hours and 39% at 24 hours. I.V. administration of 10 mg/kg gave plasma concentrations of 18.3 μg, 9.6 μg and 5 μg/ ml respectively; 1, 3 and 5 hours after the injection. When administered 36 to 48 hours before surgery in 4 doses of 10 to 20 mg/kg an antifibrinolytically active concentration (10 μg/ml) of tranexamic acid remained up to 17 hours in the tissues investigated and up to 7 to 8 hours in the serum. Tranexamic acid crosses the placenta. After an I.V. Injection of 10 mg/kg the concentration of tranexamic acid can rise to about 30 μg/ml of fetal serum. Tranexamic acid also passes over into the breast milk during lactation in concentration 1/100 of the corresponding serum levels. After both oral and I.V. administration tranexamic acid passes into the semen and inhibits its fibrinolytic activity, but without affecting the motility of the spermatozoa. The ability of tranexamic acid to cross the blood-brain barrier has been demonstrated when administered to patients with ruptured intracranial aneurysms. Tranexamic acid diffuses rapidly to the joint fluid and to the synovial membrane. The biological half-life in the joint fluid was about 3 hours. Three hours after a single oral dose of 25 mg/kg, the peak serum level was 15.4 mg/L and the aqueous humour levels were 1.6 mg/L. After an intravenous dose of 1 g, the plasma concentration time curve shows a tri exponential 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 the unchanged drug.

INDICATIONS

Xamic injection is used for the treatment of excessive bleeding in patients with hemophilia during and following tooth extraction. 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.

DOSAGE AND ADMINISTRATION

Immediately before dental extraction in patients with hemophilia, administer 10 mg per kg body weight of Xamic intravenously together with replacement therapy.

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)	**I.V. 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 5 mg/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 or syrup. 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.

DIRECTIONS FOR USE
- For intravenous use only.
- Do not use the injection if the contents are not clear or show particulate matter.

CONTRAINDICATIONS
Tranexamic acid is contraindicated in following conditions:
1) In patients with active intravascular clotting.
2) In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity.
3) In patients with subarachnoid hemorrhage, anecedotal experience indicates that cerebral edema and cerebral infarction may be caused by Tranexamic acid.
4) Thromboembolic Risk when using combination hormonal contraception

WARNINGS
Focal areas of retinal degeneration have developed in cats, dogs and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. The incidence of such lesions has varied from 25 % to 100 % of animals treated and was dose-related. At lower doses some lesions have appeared to be reversible. Limited data in cats and rabbits showed retinal changes in some animals with doses as low as 126 mg/kg/day (only about 3 times the recommended human doses) administered for several days to two weeks. No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials.

However, visual abnormalities, often poorly characterized, represent the most frequently reported post marketing adverse reaction in Sweden. For patients who are to be treated continually for longer than several days, an ophthalmological examination, including visual acuity, color vision, eye-ground and visual fields, is advised, before commencing and at regular intervals during the course of treatment. Tranexamic acid should be discontinued if changes in examination results are found. In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity. Tranexamic injection is contra-indicated in patients with a history of thromboembolic disease.

In patients with renal insufficiency, because of the risk of accumulation. The dose should be reduced as mentioned in Dosage and Administration.

In massive haematuria from the upper urinary tract (especially in haemophilia) since, in a few cases, ureteric obstruction has been reported.

In patients with disseminated intravascular coagulation (DIC) treatment 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 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. The fibrinolytic activity in the blood will be reduced for about 4 hours if renal function is normal. Anticoagulation with heparin should be instigated in order to prevent further fibrin deposition. Administration of Tranexamic Acid Injection in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available. Tranexamic Acid Injection must not be administered in DIC with predominant activation of the coagulation system.

Thromboembolic Risk

Concomitant Use of Hormonal Contraceptives

Combination hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Because Tranexamic Acid is antifibrinolytic, the risk of venous thromboembolism, as well as arterial thromboses such as stroke, may increase further when hormonal contraceptives are administered with Tranexamic Acid . This is of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age.

Women using hormonal contraception were excluded from the clinical trials supporting the safety and efficacy of Tranexamic Acid, and there are no clinical trial data on the risk of thrombotic events with the concomitant use of Tranexamic Acid with hormonal contraceptives. However, there have been ostmarketing reports of venous and arterial thrombotic events in women who have used tranexamic acid concomitantly with combination hormonal

contraceptives. For this reason, concomitant use of tranexamic acid with combination hormonal contraceptives is contraindicated.

PRECAUTIONS

General

The dose of Tranexamic acid Tablets and injection should be reduced in patients with renal insufficiency because of the risk of accumulation. Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with Tranexamic acid. Venous and arterial thrombosis or thromboembolism has been reported in patients treated with Tranexamic acid. In addition, cases of central retinal artery and central retinal vein obstruction have been reported. Patients with a previous history of thromboembolic disease may be at increased risk for venous or arterial thrombosis. Tranexamic acid should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased. Patients with disseminated intravascular coagulation (DIC), who require treatment with Tranexamic acid, must be under strict supervision of a physician experienced in treating this disorder.

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

DRUG INTERACTIONS

Hormonal Contraceptives Because Tranexamic acid is antifibrinolytic, concomitant use of hormonal contraception and Tranexamic acid may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives. For this reason, concomitant use of Tranexamic acid with combination hormonal contraceptives is contraindicated.

Tissue Plasminogen Activators

Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both Tranexamic acid and tissue plasminogen activators. Therefore, exercise caution if a woman taking Tranexamic acid therapy requires tissue plasminogen activators.

Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates

Tranexamic acid is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased.

All-Trans Retinoic Acid (Oral Tretinoin)
Exercise caution when prescribing Tranexamic acid to women with acute promyelocytic leukemia taking all-trans retinoic acid for remission induction because of possible exacerbation of the procoagulant effect of all-trans retinoic acid.

USE IN SPECIFIC POPULATIONS

Pregnancy (Category B)
Tranexamic acid is not indicated for use in pregnant women**.** Reproduction studies have been performed in mice, rats and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to tranexamic acid. However, tranexamic acid is known to cross the placenta and appears in cord blood at concentrations approximately equal to the maternal concentration. There are no adequate and well-controlled studies in pregnant women.

An embryo-fetal developmental toxicity study in rats and a perinatal developmental toxicity study in rats were conducted using tranexamic acid. No adverse effects were observed in either study at doses up to 4 times the recommended human oral dose of 3900 mg/day based on mg/m^2 (actual animal dose 1500 mg/kg/day).

Nursing Mothers
Tranexamic acid is present in the mother's milk at a concentration of about one hundredth of the corresponding serum concentration. Tranexamic acid should be used during lactation only if clearly needed.

Pediatric Use
Tranexamic acid is indicated for women of reproductive age and is not intended for use in premenarcheal girls. Based on a pharmacokinetic study in 20 adolescent females, 12 to 16 years of age, no dose adjustment is needed in the adolescent population.

Geriatric Use
Tranexamic acid is indicated for women of reproductive age and is not intended for use by postmenopausal women.

Renal Impairment
The effect of renal impairment on the pharmacokinetics of Tranexamic acid has not been studied. Because tranexamic acid is primarily eliminated via the kidneys by glomerular filtration with more than 95% excreted as unchanged in urine, dosage adjustment in patient with renal impairment is needed.

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of Tranexamic acid has not been studied. Because only a small fraction of the drug is metabolized, dosage adjustment in patients with hepatic impairment is not needed.

ADVERSE REACTIONS
Gastrointestinal disturbances (nausea, vomiting, diarrhea) may occur but disappear when the dosage is reduced. Allergic dermatitis, giddiness, and hypotension have been reported occasionally. Hypotension has been observed when intravenous injection is too rapid. To avoid this response, the solution should not be injected more rapidly than 1 mL per minute.

Worldwide Postmarketing Reports: Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) have been rarely reported in patients receiving tranexamic acid for indications other than hemorrhage prevention in patients with hemophilia. Convulsion, chromatopsia, and visual impairment have also been reported. However, due to the spontaneous nature of the reporting of medical events and the lack of controls, the actual incidence and causal relationship of drug and event cannot be determined.

OVERDOSAGE
There are no known cases of intentional overdose with Tranexamic acid and no subjects in the clinical program took more than 2 times the prescribed amount of Tranexamic acid in a 24-hour period (>7800 mg/day). However, cases of overdose of tranexamic acid have been reported. Based on these reports, symptoms of overdose may include gastrointestinal (nausea, vomiting, diarrhea); hypotensive (e.g., orthostatic symptoms); thromboembolic (arterial, venous, embolic); visual impairment; mental status changes; myoclonus; or rash. No specific information is available on the treatment of overdose with Tranexamic acid. In the event of overdose, employ the usual supportive measures (e.g., clinical monitoring and supportive therapy) as dictated by the patient's clinical status.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Keep in a cool place. Keep out of reach of children

PRESENTATION
It is available as clear, colorless solution filled in 5 ml clear, colorless glass ampoules.

MARKETED BY

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