Tranexamic acid

Hemanex®

500 mg Capsule

Anti-Fibrinolytic

FORMULATION
Each capsule contains:

Tranexamic acid……500 mg

PRODUCT DESCRIPTION
Tranexamic acid (Hemanex®) 500 mg is a size #0 hard gelatin capsule with bright orange opaque cap and buff opaque body.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS

Tranexamic acid is an anti-fibrinolytic agent. It is a competitive inhibitor of plasminogen activation and at much higher concentrations is a noncompetitive inhibitor of plasmin.

Human plasminogen contains lysine binding sites that are important for interactions not only with synthetic antifibrinolytic amino acid derivatives but also with $\cdot_2$-antiplasmin and fibrin. One of these binding sites has a high affinity for tranexamic acid; the others have low affinity.

Tranexamic acid almost completely blocks the interaction of plasminogen and the heavy chain of plasmin with the lysine binding site of plasminogen. Saturation of this site with tranexamic acid prevents binding of plasminogen to the surface of fibrin. This process retards fibrinolysis because, although plasmin is still formed, it is unable to bind to fibrinogen or fibrin monomer. Conversely, when tranexamic acid blocks the binding site of plasmin, inactivation by $\cdot_2$-antiplasmin is impossible.

In vitro, tranexamic acid 1 mg per mL does not aggregate platelets. Tranexamic acid in concentrations up to 10 mg per mL blood has no influence on platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. In contrast, tranexamic acid in concentrations of 10 mg and 1 mg per mL blood prolongs thrombin time.

PHARMACOKINETICS
Tranexamic acid is rapidly absorbed from the gastrointestinal tract. Peak plasma levels after oral administration of 1 or 2 g are 8 or 15 mg/L, both obtained three hours after dosing. Bioavailability is about 30 to 50%. Food intake does not influence absorption.

Tranexamic acid is widely distributed in the body and has very low protein binding, i.e., about 3% at therapeutic plasma levels and is accounted for by binding to plasminogen. It does not bind to serum albumin. Tranexamic acid's antifibrinolytically active concentration (10 µg/mL) remains in different tissues for about 17 hours and in the serum for up to 7 or 8 hours when administered 36 to 48 hours before surgery in four doses of 10 to 20 mg/kg body weight.

Tranexamic acid crosses the placenta but secretion in breast milk is low. No data are available concerning the concentration in gastric juice, but the clinical effect of tranexamic acid on gastrointestinal hemorrhage has been clearly demonstrated.

Acetylation or deamination followed by oxidation or reduction are possible routes of biotransformation. 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 excreted in the urine by glomerular filtration mainly as unchanged drug. The total amount of metabolites excreted in urine within 72 hours is less than 5%. After administration of a 10 to 15 mg/kg oral dose, the urinary excretion at 24 and 48 hours is 39 and 41%, respectively. Tranexamic acid's plasma half-life is approximately two hours.

INDICATIONS
For the treatment and control of excessive bleeding in various surgical and medical conditions including:

- **Surgical**
  - General surgical cases
  - Prostatectomy
- **Obstetric and gynecologic**
  - Menorrhagia/menometrorrhagia
  - Postpartum hemorrhage
  - Abortion
  - Conisation of the cervix
- **Medical**
  - Epistaxis
  - Hemoptysis
  - Peptic ulcer disease with hemorrhage
  - Hematuria
  - Blood dyscrasias with hemorrhage (e.g., hemophilia)
  - Hereditary angioneurotic edema
- **Dental**
  - Following tooth extraction and dental surgery

DOSAGE AND ADMINISTRATION

INDICATIONS		RECOMMENDED TRANEXAMIC ACID ADULT DOSE
SURGICAL	General Surgical Cases	0.5 to 1 g (10 to 15 mg/kg body weight) IV every 8 to 12 hours, immediately after surgery, then, **orally, 1 to 1.5 g every 6 to 8 hours**
	Prostatectomy	0.5 to 1 g IV every 8 hours (the first injection given during the operation) for the first three days after surgery, then, **orally, 1 to 1.5 g every 6 to 8 hours until macroscopic hematuria is no longer present**
OBSTETRIC & GYNECOLOGIC	Menorrhagia/ Menometrorrhagia	**Orally, 1 to1.5 g every 6 to 8 hours** for 3 to 4 days
	Postpartum hemorrhage	1 g IV (taking 1 minute to administer); If bleeding continues, repeat 1 g after 30 minutes, then, **orally, 1 to 1.5 g (25 mg/kg body weight) every 6 to 8 hours**
	Conisation of the Cervix	~~After surgery:~~ **Orally, 1.5 g every 8 hours** for 12 to 14 days
MEDICAL	Epistaxis	**Orally, 1.5 g every 8 hours** for 4 to 10 days
	Gastrointestinal hemorrhage	1 g IV every 4 hours for a maximum of 3 days, then, **orally, 1.5 g, every 6 hours** for a maximum of 4 days
	Hematuria	**Orally, 1 to 1.5 g every 8 to 12 hours** daily until macroscopic hematuria is no longer present
	Hereditary angioneurotic edema	**Orally, 1 to 1.5 g every 8 to 12 hours** as intermittent or continuous treatment depending on the prodromal symptoms of the patient
DENTAL	Dental surgery in patients with coagulopathies	Immediately before surgery: **10 mg/kg body weight IV** ~~After surgery:~~ **Orally, 1 to 1.5 g (25 mg/kg body weight) every 6 to 8 hours** for 6 to 8 days
Or, as prescribed by a physician		

Dosage in children: 25 mg/kg body weight per dose, two or three times daily, depending on the indication

Dosage in Renal Insufficiency:

Serum Creatinine (mg/dL)	Tranexamic Acid Dosage
1.36 to 2.83	15 mg/kg body weight twice a day
2.83 to 5.66	15 mg/kg body weight twice a day
>5.66	15 mg/kg body weight every 48 hours or 7.5 mg/kg body weight every 24 hours

CONTRAINDICATIONS
- Hypersensitivity to tranexamic acid or any component of the product
- Active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis)
- History of thrombosis or thromboembolism (e.g., retinal vein or artery occlusion) or intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, hypercoagulopathy), unless at the same time it is possible to give treatments with anticoagulants
- Patients receiving thrombin because of increased risk of thrombosis
- Patients with acquired disturbances of color vision. If disturbances of color vision arise during the course of treatment, discontinue the drug
- Patients with subarachnoid hemorrhage since cerebral edema and cerebral infarction may be caused by tranexamic acid in such cases

WARNINGS AND PRECAUTIONS

• For patients on prolonged treatment with tranexamic acid, perform an ophthalmological examination (including visual acuity, color vision, eyeground, and visual field) before and at regular intervals during treatment, since visual abnormalities are the most frequently reported adverse reactions in some postmarketing studies. Discontinue tranexamic acid if changes are found.

• In clinical trials, no retinal changes have been reported in patients treated with tranexamic acid for weeks and months. However, focal areas of retinal degeneration have developed in cats, dogs, rabbits, and rats following oral or IV tranexamic acid at doses between 126 and 1600 mg/kg/day (3 to 40 times the recommended human dose) from six days to one year.

• Reduce dose in patients with renal insufficiency because of the risk of drug accumulation.

• Treatment with tranexamic acid is not indicated in hematuria caused by diseases of the renal parenchyma. Intravascular precipitation of fibrin frequently occurs and may aggravate the disease. Furthermore, antifibrinolytic treatment carries the risk of clot retention in the renal pelvis in cases of massive renal hemorrhage of any cause.

• Urinary tract obstruction due to clot formation in patients with severe bleeding from the upper urinary tract has been reported in patients taking tranexamic acid.

• Patients with a high risk for thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should use tranexamic acid only if there is a strong medical indication and under strict medical supervision.

• Although clinical evidence shows no significant increase in thrombosis, the possible risk of thrombosis cannot be ruled out. Venous and arterial thrombosis or thromboembolism have been reported in patients given tranexamic acid. Also, cases of central retinal artery and central retinal vein obstruction have been observed. A few patients have developed intracranial thrombosis with tranexamic acid but further observation is needed to assess the significance of this potential hazard.

• Combination hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Since tranexamic acid is antifibrinolytic, the concomitant use of hormonal contraception and tranexamic acid may further exacerbate this increased thrombotic risk. There are no data on the risk of thrombotic events with the concomitant use of tranexamic acid with hormonal contraceptives. Thus, women using hormonal contraception should use tranexamic acid only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event.

• Patients with disseminated intravascular coagulation who require treatment with tranexamic acid must be under the strict supervision of a physician experienced in treating this disorder.

• Patients with irregular menstrual bleeding should not use tranexamic acid until the cause of irregular bleeding has been established. Consider an alternative treatment if menstrual bleeding is not adequately reduced by tranexamic acid.

• Indissoluble clots may develop in body cavities such as pleural space and joint spaces due to extravascular clots which may be resistant to physiological fibrinolysis.

• A case of severe allergic reaction to tranexamic acid was reported in a clinical trial, involving a subject who experienced dyspnea, tightening of throat, and facial flushing that required emergency medical treatment. A case of anaphylactic shock has also been reported involving a patient who received an intravenous bolus of tranexamic acid.

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

• Cerebral edema and cerebral infarction may be caused by tranexamic acid use in women with subarachnoid hemorrhage.

• 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.

• Convulsions have been reported in association with tranexamic acid treatment.

INTERACTION WITH OTHER MEDICAMENTS

- ***Batroxobin:*** May cause thromboembolism.
- ***Coagulation factor agents (e.g., Eptacog-alfa):*** Coagulation may be further activated at sites with enhanced local fibrinolysis such as the oral cavity.
- ***Hemocoagulase:*** Coadministration at high doses may cause thrombosis.
- ***Others:***
  - Simultaneous treatment with anticoagulants should be under the strict supervision of an expert physician
  - Tranexamic acid may counteract the thrombolytic effect of fibrinolytic preparations
  - Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both tranexamic acid and tissue plasminogen activators. Thus, exercise caution if a woman taking tranexamic acid requires tissue plasminogen activators.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: *Pregnancy Category B.* There are no adequate and well controlled studies in pregnant women. However, tranexamic acid crosses the placenta and appears in cord blood. Use in pregnancy only if clearly needed.

Lactation: Tranexamic acid is present in breast milk at 1% of the corresponding serum levels. Use in breastfeeding women only if clearly needed.

Children: Tranexamic acid has had limited use in children, principally in tooth extraction.

Elderly: Since elderly patients often have reduced physiological function, careful supervision and dosage reduction are recommended.

UNDESIRABLE EFFECTS

Gastrointestinal: Nausea, vomiting, diarrhea, anorexia, heartburn, abdominal pain, abdominal tenderness and discomfort

Hypersensitivity: Anaphylactic shock, anaphylactoid reactions

Musculoskeletal: Back pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, arthralgia, muscle cramps and spasms, fatigue

Nervous: Giddiness, convulsion, dizziness, drowsiness, headache, migraine

Respiratory: Nasal and sinus symptoms including respiratory tract and sinus congestion, sinusitis, acute sinusitis, sinus headache, allergic sinusitis, sinus pain, multiple allergies, seasonal allergies

Skin: Allergic skin reaction, rash, itching

Others: Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, central retinal artery and vein obstruction), chromatopsia, impaired color vision and other visual disturbances, hypotension, anemia, shock

OVERDOSE AND TREATMENT

There are limited data on tranexamic acid overdosage. Symptoms may include dizziness, headache, nausea, vomiting, diarrhea, hypotension, or orthostatic hypotension.

There is no known antidote for tranexamic acid overdose. In cases of overdose, discontinue treatment and institute symptomatic and supportive measures as required. Activated charcoal may decrease absorption if given within one or two hours after ingestion. Administer activated charcoal via a nasogastric tube once the airway is protected in patients who are not fully conscious or have impaired gag reflex.

Monitor vital signs to detect a possible hypotensive episode. In patients with severe vomiting or diarrhea, monitor fluid and electrolyte levels and administer intravenous fluids and replace electrolytes as necessary. Monitor urine output and maintain adequate diuresis. Monitor for clinical evidence of thromboembolic complications (e.g., chest pain, shortness of breath, flank pain, extremity pain). Because there is a risk of thrombosis in predisposed individuals, anticoagulant therapy should be considered in these patients.

In symptomatic patients, support cardiac and respiratory function. Monitor blood count, renal function, pulse oximetry and/or blood gases and obtain a chest x-ray. Obtain an ECG and institute continuous cardiac monitoring.

STORAGE CONDITION

• Store at temperatures not exceeding 30°C
• Keep the product out of reach and sight of children

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Tranexamic acid (Hemanex®) 500 mg Capsule, in blister pack x 10's (box of 100's)

Manufactured by: AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines

Distributed by: UNILAB, Inc.
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Under authority by: BIOFEMME, INC.
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

DATE OF REVISION OF THE PACKAGE INSERT: January 2018

Trusted Quality Healthcare

Reg. IPOPHIL