

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212020Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **TRANEXAMIC ACID IN SODIUM CHLORIDE INJECTION** safely and effectively. See full prescribing information for **TRANEXAMIC ACID IN SODIUM CHLORIDE INJECTION**.

TRANEXAMIC ACID IN SODIUM CHLORIDE injection, for intravenous use
Initial U.S. Approval: 1986

INDICATIONS AND USAGE

Tranexamic Acid in Sodium Chloride Injection is an antifibrinolytic indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction (1).

DOSAGE AND ADMINISTRATION

- Before Extraction: Administer 10 mg/kg actual body weight of Tranexamic Acid in Sodium Chloride Injection intravenously with replacement therapy.
- After Extraction: Administer 10 mg/kg actual body weight 3-4 times daily for 2 to 8 days. Infuse no more than 10 mL/minute to avoid hypotension (2.1).
- Reduce the dosage for patients with renal impairment (2.2, 8.6).

DOSAGE FORMS AND STRENGTHS

Injection: 1,000 mg of tranexamic acid in 100 mL (10 mg/mL) sterile, unpreserved, colorless solution in a single-dose bag for intravenous use (3).

CONTRAINDICATIONS

- In patients with subarachnoid hemorrhage, due to risk of cerebral edema and cerebral infarction (4).
- In patients with active intravascular clotting (4).
- In patients with severe hypersensitivity reactions to tranexamic acid or any of the ingredients (4).

WARNINGS AND PRECAUTIONS

- Risk of Thrombosis with concomitant use of Factor IX: Avoid concomitant use (5.1).
- Seizures: Inadvertent injection into neuraxial system may result in seizures (5.2).
- Hypersensitivity Reactions: In case of severe reaction, discontinue use seek immediate medical attention (5.3).
- Visual Disturbances: Visual or ocular adverse effects may occur. Discontinue use if visual or ocular symptoms occur (5.4).
- Dizziness may occur. Advise patients not to drive if dizziness occurs (5.5).

ADVERSE REACTIONS

Most common adverse reactions are nausea, vomiting, diarrhea, allergic dermatitis, giddiness, hypotension, and thromboembolic events (6).

To report **SUSPECTED ADVERSE REACTIONS**, contact **Exela Pharma Sciences, LLC at 1-888-451-4321 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.

DRUG INTERACTIONS

- Prothrombotic Medical Products: Avoid concomitant use, can further increase the risk of thromboembolic adverse reactions associated with tranexamic acid (5.1, 7.1, 8.3).
- Chlorpromazine: May result in increased risk of bleeding (7.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tranexamic Acid in Sodium Chloride Injection is indicated in patients with hemophilia for short-term use (two to eight days) to reduce the risk of hemorrhage during and following tooth extraction.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of Tranexamic Acid in Sodium Chloride Injection is 10 mg/kg actual body weight intravenously administered as a single dose, immediately before tooth extractions. Infuse no more than 10 mL/minute to avoid hypotension. Following tooth extraction, Tranexamic Acid in Sodium Chloride Injection may be administered for 2 to 8 days at a dose of 10 mg/kg actual body weight three to four times daily, intravenously.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use Tranexamic Acid in Sodium Chloride Injection if particulate matter or coloration is seen.

Tranexamic Acid in Sodium Chloride Injection should NOT be mixed with blood. The drug is a synthetic amino acid and should NOT be mixed with solutions containing penicillin.

The premix flexible plastic container bag contains no preservative; discard any unused portion.

2.2 Recommended Dosage for Patients with Varying Degrees of Renal Impairment

The recommended dosage of Tranexamic Acid in Sodium Chloride Injection in patients with varying degrees of renal impairment is described in Table 1 [see Use in Specific Populations (8.6)].

Table 1. Recommended Dosage in Patients with Varying Degrees of Renal Impairment*

<u>Serum Creatinine (mg/dL)</u>	<u>Tranexamic Acid in Sodium Chloride Injection Intravenous Dosage</u>
1.36 to 2.83 (120 to 250 micromol/L)	10 mg/kg twice daily
2.83 to 5.66 (250 to 500 micromol/L)	10 mg/kg daily
>5.66 (>500 micromol/L)	10 mg/kg every 48 hours or 5 mg/kg every 24 hours

*Dose reduction is recommended for all doses, both before and after tooth extraction.

3 DOSAGE FORMS AND STRENGTHS

Injection: 1,000 mg of tranexamic acid in 100 mL (10 mg/mL), colorless solution in a single-dose bag for intravenous use

4 CONTRAINDICATIONS

Tranexamic Acid in Sodium Chloride Injection is contraindicated:

- In patients with subarachnoid hemorrhage. Anecdotal experience indicates that cerebral edema and cerebral infarction may be caused by tranexamic acid in such patients.
- In patients with active intravascular clotting [*see Warnings and Precautions (5.1)*].
- In patients with history of hypersensitivity to tranexamic acid or any of the ingredients [*see Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Risk

Tranexamic Acid in Sodium Chloride Injection is contraindicated in patients with active intravascular clotting.

Tranexamic acid is an antifibrinolytic and may increase the risk of thromboembolic events. Venous and arterial thrombosis or thromboembolism has been reported in patients treated with tranexamic acid. Avoid concomitant use of Tranexamic Acid in Sodium Chloride Injection and medical products that are pro-thrombotic, as the risk of thrombosis may be increased. These medications include, but are not limited to, Factor IX Complex concentrates, Anti-inhibitor Coagulant concentrates, and hormonal contraceptives [*see Drug Interactions (7.1) and Use in Specific Populations (8.3)*].

5.2 Seizures

Tranexamic acid may cause seizures, including focal and generalized seizures. The most common setting for tranexamic acid-induced seizures has been during cardiovascular surgery (a setting in which Tranexamic Acid in Sodium Chloride Injection is not FDA approved and which uses doses of up to ten-fold higher than the recommended human dose and in patients inadvertently given tranexamic acid into the neuraxial system). Tranexamic Acid in Sodium Chloride Injection is not approved and not recommended for neuraxial administration. Consider dose reduction during surgery and dose adjustments for patients with clinical conditions such as renal dysfunction. Closely monitor the patient during surgery. Consider EEG monitoring for patients with history of seizures or who experience myoclonic movements, twitching, or show evidence of focal seizures. Discontinue Tranexamic Acid in Sodium Chloride Injection if seizures occur.

5.3 Hypersensitivity Reactions

Cases of hypersensitivity reactions, including anaphylactic reactions, have occurred with use of intravenous tranexamic acid. Discontinue treatment with Tranexamic Acid in Sodium Chloride Injection if serious reaction occurs, provide appropriate medical management, and do not restart treatment. Tranexamic Acid in Sodium Chloride Injection is contraindicated in patients with a history of hypersensitivity to tranexamic acid.

5.4 Visual Disturbances

Although not seen in humans, focal areas of retinal degeneration have been observed 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. No retinal changes have been observed in eye examinations of patients treated with tranexamic acid for up to 8 years. Patients expected to be treated for greater than 3 months may consider ophthalmic monitoring including visual acuity and optical coherence tomography at regular intervals. Discontinue Tranexamic Acid in Sodium Chloride Injection if changes in ophthalmological examination occurs.

5.5 Dizziness

Tranexamic acid may cause dizziness. Concomitant use of other drugs that may also cause dizziness may worsen this effect. Advise patients to avoid driving or using machines until they know how Tranexamic Acid in Sodium Chloride Injection affects them.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Thromboembolic Risk *[see Warnings and Precautions (5.1)]*
- Seizures *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Visual Disturbances *[see Warnings and Precautions (5.4)]*
- Dizziness *[see Warnings and Precautions (5.5)]*

6.1 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of tranexamic acid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disturbances (nausea, vomiting, diarrhea) may occur and may resolve with dose-reduction. Allergic dermatitis and giddiness have been reported. Hypotension has been reported when intravenous injection is too rapid.

Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery, vein obstruction and cases associated with concomitant use of combination hormonal contraceptives) 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.

Anaphylaxis or anaphylactoid reactions have been reported that are suggestive of a causal relationship.

7 DRUG INTERACTIONS

7.1 Prothrombotic Medical Products

Avoid concomitant use of Tranexamic Acid in Sodium Chloride Injection with medical products that are prothrombotic because concomitant use can further increase the risk of thromboembolic adverse reactions associated with tranexamic acid *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)]*.

7.2 Chlorpromazine

Concurrent use of chlorpromazine and Tranexamic Acid in Sodium Chloride Injection may result in increased risk of bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published studies, case series and case reports with tranexamic acid use in pregnant women in the second and third trimester and at the time of delivery have not identified a drug-associated risk of miscarriage or adverse maternal or fetal outcomes. There are no reports regarding the use of tranexamic acid during the first trimester of

pregnancy; therefore, there are no data regarding the risk of major birth defects with use of tranexamic acid during pregnancy. However, tranexamic acid is known to pass the placenta and appears in cord blood at concentrations approximately equal to maternal concentration (*see Data*). Reproduction studies performed in mice, rats, and rabbits have not revealed any adverse effects on the fetus due to tranexamic acid.

The estimated background risk for major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2-4% and 15–20%, respectively.

Data

Human Data

Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg/kg to pregnant women is about 30 mg/liter, as high as in the maternal blood.

8.2 Lactation

Risk Summary

Published literature reports the presence of tranexamic acid in human milk. There are no data on the effects of tranexamic acid on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tranexamic Acid in Sodium Chloride Injection and any potential adverse effects on the breastfed child from Tranexamic Acid in Sodium Chloride Injection or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Concomitant use of Tranexamic Acid in Sodium Chloride Injection, which is an antifibrinolytic, with hormonal contraceptives may increase the risk for thromboembolic adverse reactions. Advise patients to use an effective alternative (nonhormonal) contraceptive method [*see Warnings and Precautions (5.5) and Drug Interactions (7.1)*].

8.4 Pediatric Use

There are limited data concerning the use of tranexamic acid in pediatric patients with hemophilia who are undergoing tooth extraction. The limited data suggest that there are no significant pharmacokinetic differences between adult and pediatric patients.

8.5 Geriatric Use

Clinical studies of tranexamic acid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

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 [*Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

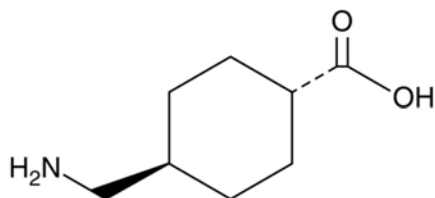
Reduce the dosage of Tranexamic Acid in Sodium Chloride Injection in patients with renal impairment, based on the patient's serum creatinine [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Cases of overdosage of tranexamic acid have been reported. Based on these reports, symptoms of overdosage may be gastrointestinal, e.g, nausea, vomiting, diarrhea; hypotensive, e.g, orthostatic symptoms; thromboembolic; e.g, arterial, venous, embolic; visual impairment; mental status changes; myoclonus and rash. Tranexamic acid is not dialyzable.

11 DESCRIPTION

Tranexamic acid is trans-4-(aminomethyl)cyclohexanecarboxylic acid, an antifibrinolytic agent. Tranexamic acid is a white crystalline powder. The structural formula is



Empirical Formula: $C_8H_{15}NO_2$ Molecular Weight: 157.2

Tranexamic Acid in Sodium Chloride Injection is a clear to colorless sterile, nonpyrogenic injectable solution for intravenous administration. Each IV bag contains 1000 mg tranexamic acid, USP, 700 mg of sodium chloride, USP and Water for Injection, USP. The aqueous solution has a pH of 6.5 to 8.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tranexamic acid is a synthetic lysine amino acid derivative, which diminishes the dissolution of hemostatic fibrin by plasmin. In the presence of tranexamic acid, the lysine receptor binding sites of plasmin for fibrin are occupied, preventing binding to fibrin monomers, thus preserving and stabilizing fibrin's matrix structure.

The antifibrinolytic effects of tranexamic acid are mediated by reversible interactions at multiple binding sites within plasminogen. Native human plasminogen contains 4 to 5 lysine binding sites with low affinity for tranexamic acid ($K_d = 750 \mu\text{mol/l}$) and 1 with high affinity ($K_d = 1.1 \mu\text{mol/L}$). The high affinity lysine site of plasminogen is involved in its binding to fibrin. Saturation of the high affinity binding site with tranexamic acid displaces plasminogen from the surface of fibrin. Although plasmin may be formed by conformational changes in plasminogen, binding to and dissolution of the fibrin matrix is inhibited.

12.2 Pharmacodynamics

Tranexamic acid in concentrations of 1 mg/mL and 10 mg/mL prolongs the thrombin time. An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to seven or eight hours.

Tranexamic acid in concentrations up to 10 mg/mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from healthy subjects.

12.3 Pharmacokinetics

Distribution

The initial volume of distribution is about 9 to 12 liters. 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.

Elimination

After an intravenous dose of 1 g, the plasma concentration time curve shows a triexponential decay with a half-life of about 2 hours for the terminal elimination phase.

Excretion

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. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg/kg body weight.

Specific Populations

Renal Impairment

The effect of renal impairment on the disposition of Tranexamic Acid in Sodium Chloride Injection has not been evaluated. Urinary excretion following a single intravenous injection of tranexamic acid declines as renal function decreases. Following a single 10 mg/kg intravenous injection of tranexamic acid, the 24-hour urinary fractions of tranexamic acid with serum creatinine concentrations 1.4 – 2.8, 2.8 – 5.7, and greater than 5.7 mg/dL were 51, 39, and 19%, respectively. The 24-hour tranexamic acid plasma concentrations for these patients demonstrated a direct relationship to the degree of renal impairment. Therefore, dose adjustment is needed in patients with renal impairment [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.6)*].

Drug Interaction Studies

No studies of interactions between Tranexamic Acid in Sodium Chloride Injection and other drugs have been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

An increased incidence of leukemia in male mice receiving tranexamic acid in food at a concentration of 4.8% (equivalent to doses as high as 5 g/kg/day) may have been related to treatment. Female mice were not included in this experiment.

Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long-term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic/neoplastic changes in the liver. No mutagenic activity has been demonstrated in several *in vitro* and *in vivo* test systems.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tranexamic Acid in Sodium Chloride Injection is supplied as a sterile, unpreserved, colorless solution in a single-dose polymeric bag containing 1000 mg tranexamic acid in 100 mL of solution (10 mg/mL) sealed with a Twist Off port and oversealed in an aluminum pouch (NDC 51754-0108-1).

Discard any unused portion.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Thromboembolic Risk

- Inform patients that Tranexamic Acid in Sodium Chloride Injection may cause venous and arterial thrombosis or thromboembolism and to contact their healthcare provider for any signs or symptoms suggestive of thromboembolism.
- Advise patients using hormonal contraception that combined use with Tranexamic Acid in Sodium Chloride Injection may increase the risk for thromboembolic adverse reactions and to use effective alternative (nonhormonal) contraception during therapy with Tranexamic Acid in Sodium Chloride Injection [see *Warnings and Precautions* (5.1), *Drug Interactions* (7.1) and *Use in Specific Populations* (8.3)].

Seizures

Inform patients that Tranexamic Acid in Sodium Chloride Injection may cause seizures and to contact their healthcare provider for any signs or symptoms suggestive of seizures [see *Warnings and Precautions* (5.2)].

Hypersensitivity Reactions

Inform patients that Tranexamic Acid in Sodium Chloride Injection may cause hypersensitivity reactions and to contact their healthcare provider for any signs or symptoms of hypersensitivity reactions [see *Warnings and Precautions* (5.3)].

Visual Disturbances

Inform patients that Tranexamic Acid in Sodium Chloride Injection can cause visual disturbance and that they should report any eye symptoms or change in their vision to their healthcare provider and to follow-up with an ophthalmologist for a complete ophthalmologic evaluation, including dilated retinal examination of the retina [see *Warnings and Precautions* (5.4)].

Risk of Driving and Operating Machinery

Inform patients that Tranexamic Acid in Sodium Chloride Injection may cause dizziness, and that the patient should be cautioned about driving, operating machinery, or performing hazardous tasks while taking Tranexamic Acid in Sodium Chloride Injection [see *Warnings and Precautions* (5.5)].

Manufactured and Distributed by:



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/s/

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