**Tranxameic acid**

**Use: Labeled Indications**

1. **Menstrual bleeding, heavy (oral**): Treatment of cyclic heavy menstrual bleeding.
2. **Tooth extraction in patients with hemostatic defects** (injection, oral ) : Short-term use in hemophilia patients to reduce or prevent hemorrhage and reduce need for replacement therapy during and following tooth extraction

**Use: Off-Label: Adult**

1. **Dental procedures in patients on oral anticoagulant therapyLevel** of Evidence [G]
2. **Hemoptysis (nonmassive**), treatmentLevel of Evidence [C]
3. **Hereditary angioedema, long-term prophylaxisLevel** of Evidence [G]
4. **Hereditary hemorrhagic telangiectasia, epistaxis or other bleeding** sitesLevel of Evidence [B]
5. **Intracranial hemorrhage associated with thrombolytic treatment**Level of Evidence [G]
6. **Perioperative prevention of blood loss and transfusion, cardiac surgery**Level of Evidence [A]
7. **Perioperative prevention of blood loss and transfusion, orthopedic surgery (hip or knee arthroplasty**)Level of Evidence [A, G]
8. **Perioperative prevention of blood loss and transfusion, spinal surgery**Level of Evidence [B]
9. **Postpartum hemorrhage**, preventionLevel of Evidence [G]
10. **Postpartum hemorrhage**, treatmentLevel of Evidence [A, G]
11. **Subarachnoid hemorrhage, prevention of early aneurysmal rebleeding**Level of Evidence [C, G]
12. **Trauma-associated hemorrhage or traumatic brain** injuryLevel of Evidence [A

**Administration: IV**

May be administered by direct IV injection at a maximum rate of 100 mg/minute , faster rates may cause hypotension.

Administration: Injectable Detail

pH: 6.5 to 8 (intact vial/ampule).

**Administration: Oral**

Administer without regard to meals. Swallow tablet whole; do not break, chew, or crush.

**Administration: Inhalation**

Inhalation via nebulization (off-label use/route): Administer over 15 minutes via jet nebulizer

**Contraindications**

**Hypersensitivity to tranexamic acid or any component of the formulation**

**Injection: Active intravascular clotting; subarachnoid hemorrhage**. Note: Although subarachnoid hemorrhage (SAH) is listed in the manufacturer’s labeling as a contraindication due to risk of cerebral edema and cerebral infarction, use has been described in the literature for aneurysmal SAH. When definitive treatment of the aneurysm is unavoidably delayed and no other contraindications exist, short-term use (<72 hours) of tranexamic acid is a reasonable treatment option to reduce the risk of early rebleeding without an increased risk of vasospasm and delayed ischemia; however, clinical trial data regarding improved outcomes are not conclusive at this time and an increased risk of deep venous thrombosis has been reported

**Oral:** **Active thromboembolic disease (eg, cerebral thrombosis, DVT, or PE); history of thrombosis or thromboembolism, including retinal vein or retinal artery occlusion; intrinsic risk of thrombosis or thromboembolism** (eg, hypercoagulopathy, thrombogenic cardiac rhythm disease, thrombogenic valvular disease); concurrent use of combination hormonal contraception

Canadian labeling: Additional contraindications (not in the US labeling): Injection, oral: History or risk of thrombosis (unless concurrent anticoagulation therapy is possible); hematuria

Warnings/Precautions

**Concerns related to adverse effects:**

**• CNS effects**: May cause dizziness, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

**• Hypersensitivity reactions:** Severe hypersensitivity reactions, including anaphylaxis or anaphylactoid reaction have been reported. Discontinue use if serious reactions occur; do not reinitiate treatment.

• **Ocular effects:** Visual defects (eg, color vision change, visual loss) and retinal venous and arterial occlusions have been reported; discontinue treatment if ocular changes occur; prompt ophthalmic examination should be performed by an ophthalmologist. Ligneous conjunctivitis has been reported with the oral formulation but resolved upon discontinuation of therapy. Consider ophthalmic monitoring at regular intervals in patients on long-term therapy (>3 months).

• **Seizure**

• **Thrombotic events:** Venous and arterial thrombosis or thromboembolism, including central retinal artery/vein obstruction, has been reported. Use the injection with caution in patients with thromboembolic disease; oral formulation is contraindicated in patients with a history of or active thromboembolic disease or with an intrinsic risk of thromboembolic events (eg, thrombogenic valvular disease, thrombogenic cardiac rhythm disease, hypercoagulopathy). Concomitant use with certain procoagulant agents (eg, anti-inhibitor coagulant complex/factor IX complex concentrates, oral tretinoin, hormonal contraceptives) may further increase the risk of thrombosis; concurrent use with either the oral or injectable formulation may be contraindicated, not recommended, or to be used with caution.

Disease-related concerns:

• Disseminated intravascular coagulation: Use with extreme caution in patients with disseminated intravascular coagulation requiring antifibrinolytic therapy; patients should be under strict supervision of a health care provider experienced in treating this disorder.

• Renal impairment: Use with caution in patients with renal impairment; dosage modification necessary.

• Subarachnoid hemorrhage: Use with caution in patients with subarachnoid hemorrhage (SAH); cerebral edema and infarction may occur. According to the manufacturer's labeling, use of the injection is contraindicated in patients with SAH; however, use has been described in the literature for aneurysmal SAH and is considered a reasonable treatment option in select patients

• Vascular disease: Use with caution in patients with uncorrected cardiovascular or cerebrovascular disease due to the complications of thrombosis.

**Concurrent drug therapy issues:**

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information

**Reproductive Considerations**

Tranexamic acid is an alternative agent for the treatment of heavy menstrual bleeding and one option for females who desire future fertility . The manufacturer recommends non-hormonal contraception during treatment, as hormonal contraceptives may increase the risk of thromboembolic events. However, tranexamic acid in combination with oral contraceptives may be considered for the treatment of heavy menstrual bleeding when monotherapy is ineffective and other treatment options have failed

**Pregnancy Considerations**

* Tranexamic acid crosses the placenta; concentrations within cord blood are similar to maternal serum.
* Oral tranexamic acid is used off label for the long-term prophylaxis of hereditary angioedema (HAE) and use for this indication in pregnant females has been reported. Tranexamic acid may be considered for long-term prophylaxis of HAE during pregnancy when preferred treatment is not available
* IV tranexamic acid is used off label for the treatment of postpartum hemorrhage A significant reduction in risk of death due to bleeding was observed when treatment was started within 3 hours of vaginal birth or cesarean section (WOMAN Trial Collaborators 2017). Tranexamic acid is recommended for the treatment of obstetric hemorrhage when initial therapy fails (ACOG 183 2017; WHO 2017).
* IV tranexamic acid has also been studied for prophylaxis of postpartum hemorrhage in females prior to vaginal or cesarean delivery (Novikova 2015; Saccone 2019; Sentilhes 2018; Simonazzi 2016; Xia 2020). Tranexamic acid may be considered as adjunctive therapy in women at high risk for postpartum hemorrhage. However, available data related to prophylactic use is insufficient and use for routine prophylaxis against postpartum hemorrhage is not currently recommended outside of the context of clinical research

**Breast-Feeding Considerations**

* Tranexamic acid is present in breast milk.
* Although other agents are preferred, breastfeeding is considered acceptable during use of tranexamic acid for prophylaxis of hereditary angioedema

**Drug Interactions: Avoid Concomitant Use**

* Avoid concomitant use of Tranexamic Acid with any of the following: Anti-inhibitor Coagulant Complex (Human); Estrogen Derivatives (Contraceptive); Factor IX Complex (Human) [(Factors II, IX, X)]; Progestins (Contraceptive); Prothrombin Complex Concentrate (Human) [(Factors II, VII, IX, X), Protein C, and Protein S]
* Drug Interactions: Decreased Effect
* There are no known significant interactions involving a decrease in effect.
* Drug Interactions: Increased Effect/Toxicity

**Tranexamic Acid may increase the levels/effects of: Anti-inhibitor Coagulant Complex (Human); Factor IX Complex (Human) [(Factors II, IX, X)]; Prothrombin Complex Concentrate (Human) [(Factors II, VII, IX, X), Protein C, and Protein S]**

**The levels/effects of Tranexamic Acid may be increased by: Estrogen Derivatives (Contraceptive); Progestins (Contraceptive); Tretinoin (Systemic)**

**Monitoring Parameters**

**Ophthalmic examination (visual acuity, optical coherence tomography) at regular intervals if on long-term therapy (>3 months); signs/symptoms of hypersensitivity reactions, seizures, and thrombotic events**

**Dosing: Adult**

**The adult dosing recommendations are based upon the best available evidence and clinical expertise.**

**Note: Safety: Higher total IV doses (eg, ≥50 mg/kg), such as those given perioperatively, may be associated with an increased risk of seizures; lower doses (eg, 1 or 2 g given in the first 8 hours of trauma) do not appear to increase the risk of seizure or venous thromboembolism**

**Hemoptysis (nonmassive), treatment (off-label use):**

**Inhalation for nebulization**: 500 mg (using injectable solution) 3 times daily for up to 5 days

**Hereditary angioedema, long-term prophylaxis (alternative agent) (off-label use):**

Note: May be used when other agents (eg, C1-inhibitor, androgens) are not available or contraindicated The recommended dosage range is based on use of 500 mg tablets available internationally, but not in the United States.

Oral: Initial: 1 to 1.5 g two to three times daily; reduce to 500 mg once or twice daily when frequency of attacks decreases (Gompels 2005; Levy 2010); maximum total daily dose: 4 to 6 g/day

**Hereditary hemorrhagic telangiectasia, epistaxis or other bleeding sites (alternative agent) (off-label use):**

Note: May be used in carefully selected patients in whom local therapy and other management options are insufficient. The recommended dosage range is based on use of 500 mg tablets available internationally, but not in the United States.

Oral: Initial: 1.5 g twice daily or 1 g three times daily for 4 to 10 days; adjust dose as needed based on response and tolerability to a usual daily dose of 2 to 4.5 g in 2 or 3 divided doses

**Menstrual bleeding, heavy (alternative agent):**

Note: Consider for use in women who decline or should not use hormonal therapy. Start once heavy menstrual bleeding has begun.

**Oral:**

**Lysteda: 1.3 g three times daily for up to 5 days during monthly menstruation.**

**Cyklokapron [Canadian product]: 1 to 1.5 g three to four times daily for several days during menstruation.**

**Tooth extraction in patients with hemostatic defects** (eg, hemophilia, von Willebrand disease, other factor deficiencies associated with bleeding) (adjunctive therapy):

* Note: Generally used in conjunction with (and not as a substitute for) replacement of the appropriate clotting factor, especially in individuals with hemophilia. Do not give simultaneously with an activated prothrombin complex concentrate, as this can increase the risk of thromboembolism; if used concurrently, they should be separated by ≥12 hours (WFH Consultation with a hemophilia treatment center is advised.
* IV: 10 mg/kg using actual body weight (usual dose range: 500 mg to 1 g) administered ~2 hours before procedure at a rate not to exceed 100 mg/minute (generally over 10 to 20 minutes), then 10 mg/kg 3 to 4 times daily for 2 to 8 days. Alternatively, 10 mg/kg as a single dose ~2 hours prior to procedure; following procedure, transition to oral tranexamic acid depending on individual patient characteristics, type of procedure, other therapies, and degree of bleeding (Berube 2020; Cyklokapron Canadian product monograph; van Galen 2019).
* Oral: 25 mg/kg (usual dose range: 1 to 1.5 g) given 2 hours prior to procedure, then 25 mg/kg (usual dose range: 1 to 1.5 g) 3 to 4 times daily for up to 7 to 10 days (Berube 2020; Cyklokapron Canadian product monograph; Hoots 2019; van Galen 2019). The recommended oral dosage range is based on use of 500 mg tablets available internationally, but not in the United States.

**Mechanism of Action**

Forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis; it also inhibits the proteolytic activity of plasmin

With reduction in plasmin activity, tranexamic acid also reduces activation of complement and consumption of C1 esterase inhibitor (C1-INH), thereby decreasing inflammation associated with hereditary angioedema.

**Adverse Reactions**

10%:

1. **Gastrointestinal: Abdominal pain** (oral: 20%)
2. **Nervous system: Headache** (oral: 50%)
3. **Neuromuscular & skeletal: Back pain (oral: 21%), musculoskeletal pain** (oral: 11%)
4. **Respiratory: Nasal signs and symptoms** (oral: 25%; including sinus symptoms)

1% to 10%:

1. **Hematologic & oncologic: Anemia** (oral: 6%)
2. **Nervous system: Fatigue** (oral: 5%)
3. **Neuromuscular & skeletal: Arthralgia (oral: 7%), muscle cramps (oral: ≤7%), muscle spasm (oral: ≤7%)**
4. **Postmarketing:**
5. **Cardiovascular: Cerebral thrombosis, deep vein thrombosis, hypotension (with rapid IV injection), pulmonary embolism**
6. **Dermatologic: Allergic dermatitis, allergic skin reaction**
7. **Gastrointestinal: Diarrhea, nausea, vomiting**
8. **Genitourinary: Ureteral obstruction**
9. **Hypersensitivity: Anaphylactic shock, anaphylaxis, hypersensitivity reaction, nonimmune anaphylaxis, severe hypersensitivity reaction**
10. **Nervous system: Dizziness, seizure**
11. **Ophthalmic: Chromatopsia, conjunctivitis (ligneous), retinal artery occlusion, retinal vein occlusion, visual disturbance**
12. **Renal: Renal cortical necrosis**

**Menorrhagia: Recommended dosage is 2 tablets 3 times daily as long as needed for up to 4 days. If very heavy menstrual bleeding, dosage may be increased. A total dose of 4g daily (8 tablets) should not be exceeded. Treatment with Tranexamic acid should not be initiated until menstrual bleeding has started.(1 tablet =500 mg)**