TRANEXAMIC ACID

INJECTION, 100 MG/ML IN 10-ML AMPOULE

GENERAL PRODUCT INFORMATION

Tranexamic acid is a competitive inhibitor of plasminogen activation. It can reduce bleeding by inhibiting the enzymatic breakdown of fibrinogen and fibrin clots. Tranexamic is relatively cheap in most contexts, easy to administer, and in routine clinical use for reduction of blood loss in surgery and trauma. It is listed on the WHO Essential Medicines List (EML) for the treatment of postpartum hemorrhage (PPH) and for the treatment of adult patients with trauma and significant risk of ongoing hemorrhage.

PPH is the main cause of maternal mortality worldwide. Most of the deaths occur soon after giving birth and almost all (99%) occur in low-income and middle-income countries.[1] The majority of PPH-associated deaths could be avoided by the use of prophylactic uterotonics during the third stage of labor and timely, appropriate management of PPH.

WHO recommends early use of intravenous tranexamic acid within 3 hours of birth in addition to standard care for women with clinically diagnosed PPH following vaginal birth or caesarean section. Tranexamic acid should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.[2]

Tranexamic acid should be recognized as a life-saving intervention and be made readily available at all times in the delivery and postpartum areas of health care facilities for the management of PPH, as part of the standard comprehensive PPH treatment package, including medical (uterotonics), non-surgical, and surgical interventions in accordance with the WHO guidelines.

[1] Say, L., Chou, D., Gemmill, A., Tunçalp, Ö., Moller, AB., Daniels, J., Gülmezoglu, AM., Temmerman, M., and Alkema, L. 2014. "Global causes of maternal death: a WHO systematic analysis." *Lancet Glob Health* 2: e323–33. doi: 10.1016/S2214-109X(14)70227-X.

[2] World Health Organization. 2017. WHO recommendation on tranexamic acid for the treatment of postpartum hemorrhage. Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/259374/9789241550154-eng.pdf

Tranexamic acid injection should be administered by the intravenous route only. However, obstetricians from several countries have recently reported inadvertent intrathecal administration of tranexamic acid and related serious neurological injuries. In most of the cases reported, tranexamic acid injection was erroneously administered instead of the intended intrathecal anesthetic (e.g., bupivacaine injection) for neuraxial anesthesia.[3,4] WHO and U.S. Food and Drug Administration (FDA) have issued an alert about the risk of inadvertent intrathecal (spinal) administration of tranexamic acid injection.[5,6] This potential risk of medication errors with tranexamic acid injection should be considered and addressed by health care professionals to avoid serious injury or death.

[3] Institute for Safe Medication Practices (ISMP). 2019. Dangerous wrong-route errors with tranexamic acid – A major cause for concern. Available at: https://www.ismp.org/resources/dangerous-wrong-route-errors-tranexamic-acid-major-cause-concern

[4] Patel, S., Robertson, B., McConachie, I. 2019. "Catastrophic drug errors involving tranexamic acid administered during spinal anaesthesia." *Anaesthesia* 74(7): 904-914. doi: 10.1111/anae.14662. Epub 2019 Apr 15. PMID: 30985928.

[5] WHO. 2022. Risk of medication errors with tranexamic acid injection resulting in inadvertent intrathecal injection. Available at: https://www.who.int/news/item/16-03-2022-risk-of-medication-errors-with-tranexamic-acid-injection-resulting-in-inadvertent-intrathecal-injection

[6] The U.S. Food and Drug Administration. 2020. FDA alerts healthcare professionals about the risk of medication errors with tranexamic acid injection resulting in inadvertent intrathecal (spinal) injection. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-healthcare-professionals-about-risk-medication-errors-tranexamic-acid-injection-resulting

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.

2. Procurers need to focus on product quality to ensure the product is sterile and safe for patient use as tranexamic acid is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product specification

Tranexamic acid injection products must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

The container-closure system (ampoule) must be sufficient to preserve sterility during the shelf life of the product.

Procurement of 100 mg/mL in 10-mL ampoule presentation is recommended, as per the WHO EML.

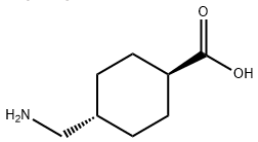
Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Tranexamic acid must be stored safely to ensure that ampoules do not break or leak, which would compromise their sterility. Products are stable at room temperature and do not need to be maintained in the cold chain.

In clinical facilities, tranexamic acid is frequently stored in close proximity with other medicines, including injectable local anesthetics indicated for spinal analgesia (e.g., for caesarean section). The presentation of some of the local anesthetics is similar to the tranexamic acid injection presentation (transparent ampoule containing transparent solution). As a result, tranexamic acid injection can erroneously be administered by intrathecal route, resulting in serious life-threatening injuries, including seizures, cardiac arrhythmias, paraplegia, permanent neurological injury, and death. Health care professionals should therefore consider the following steps as recommended by the US FDA to prevent tranexamic acid injection medication errors:

- Store tranexamic acid injection separately from other drugs, in a way that makes the labels visible to avoid reliance on identifying drugs by the packaging appearance.
- Add an auxiliary warning label to note that it contains tranexamic acid and to be administered by intravenous administration on all tranexamic acid container labels.
- Check the container label to ensure the correct product is selected and administered.
- Use barcode scanning when stocking medication cabinets and preparing or administering the product.

Name of the Medicinal Product	Tranexamic acid injection
Chemical Name	Tranexamic acid (trans-4-(Aminomethyl)cyclohexanecarboxylic acid)
Chemical Structure	$C_8H_{15}NO_2$ 
Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Tranexamic acid injection is a sterile solution of tranexamic acid in water for injection. It contains 100 mg of tranexamic acid per mL. The typical excipient is water for injection.[7] However, some formulations may also contain Hydrochloric acid and/or Sodium Hydroxide for pH adjustment.
Packaging and Presentation	The WHO EML recommends tranexamic acid injection 100 mg/mL in 10-mL ampoule.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of June 2022, there has been no tranexamic acid injection prequalified by the WHO PQP. It is recommended to check the updated information at the time of procurement, by going to https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

[7] Based on the formulation of an innovator product, Cyklokapron®.

SRA-approved products

Table T-1. Examples of SRA-Approved Tranexamic Acid Injection 100 mg/mL in 10-mL ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Tranexamic acid 100 mg/mL solution for injection	UK MHRA	Accord Healthcare Ltd, UK	PL 20075/0451	Type I glass 10-mL ampoule	2 years	This medicinal product does not require any special storage conditions.
Tranexamic Acid 100 mg/mL solution for injection/ infusion	UK MHRA	Ibigen S.r.l., Italy	PL 31745/0028	Type I glass 10-mL ampoule	3 years	Do not refrigerate or freeze.
Tranexamic Acid 100 mg/mL solution for injection	UK MHRA	Milpharm Ltd, UK	PL 16363/0476	Type I glass 10-mL ampoule	3 years	This medicinal product does not require any special storage conditions.
Tranexamic acid 100 mg/mL solution for injection/ infusion	UK MHRA	Stargen UK Ltd, UK	PL 21844/0031	Type I glass 10-mL ampoule	3 years	This medicinal product does not require any special storage conditions.
Cyklokapron® injection 100 mg/mL	US FDA	Pfizer, USA	NDA #019281	10-mL single-dose glass ampoule	Not specified	Store at 20°C to 25°C; excursions permitted to 15°C to 30°C [see USP Controlled Room Temperature].
Cyklokapron® tranexamic acid 1000 mg/10 mL solution for injection ampoule	TGA Australia	Pfizer Australia Pty Ltd, Australia	AUST R 166415	Type I glass 10-mL ampoule	3 years	Store below 25°C. Do not freeze. Protect from light.
				10-mL LDPE ampoule	2 years	
Tranexamic-AFT tranexamic acid 1000 mg/10 mL solution for injection ampoule	TGA Australia	AFT Pharmaceuticals Pty Ltd, Australia	AUST R 228945	Type I glass 10-mL ampoule	2 years	Store below 25°C. Do not freeze. Protect from light.
TRANEXAMIC ACID JUNO tranexamic acid 1000 mg/10 mL solution for injection ampoule	TGA Australia	Juno Pharmaceuticals Pty Ltd, Australia	AUST R 222348	Type I glass 10-mL ampoule	2 years	Store below 25°C. Do not freeze. Protect from light.

Note: Many of the Tranexamic acid injection 100 mg/mL that are approved by the US FDA (e.g. those supplied by Fresenius Kabi, Mylan, Exela Pharma, etc) are not included in the list above, as they are available in glass vials of 10 mL different from the presentations recommended by the WHO.

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may change over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA)
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross-check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/medicinal-products/union-register/member-states-registers-nationally-authorised-medicinal-products_en
- Swissmedic: https://www.swissmedicinfo.ch/ https://www.swissmedicinfo.ch/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other presentations of tranexamic acid injection on the market include:

- Tranexamic acid injection 100 mg/mL in 5-mL ampoule
- Tranexamic acid injection 100 mg/mL in 10-mL vial

They are used for the same indications, dosage, and administration. However, it is important to note that the WHO EML recommends tranexamic acid injection 100 mg/mL in 10-mL ampoule for convenient use in the treatment of PPH, which requires an administration of a fixed dose of 1 g in 10 mL intravenously (IV) at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes.[1]

When it is necessary to procure the vial presentation, it is important to ensure that glass vial meets compendial requirements such as USP<660> and USP<1660>, and rubber stopper meets compendial requirements such as USP<381> and USP<87>/<88> and its material composition is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines.

Furthermore, tranexamic acid is also available in the tablet form of 500 mg, but it is indicated for hereditary angioneurotic oedema, short term use in the treatment of hyphemia and in patients with established coagulopathies who are undergoing minor surgery, and menorrhagia.

[1] World Health Organization. 2017. WHO recommendation on tranexamic acid for the treatment of postpartum hemorrhage. Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/259374/9789241550154-eng.pdf

STORAGE, STABILITY, AND DEGRADATION

Tranexamic acid injection is stable at room temperature and does not require cold chain storage. It is unlikely to undergo any significant degradation as a result of heat if it is properly manufactured, packaged, sterilized, and sealed.

Shelf life: 2–3 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C. Do not freeze.

Tranexamic acid injection is a very stable product. A study by de Guzman et al.[2] demonstrated that tranexamic acid remained functionally stable when stored for up to 12 weeks at temperatures ranging from –20°C to 50°C, as determined by the ability of tranexamic acid to completely inhibit streptokinase-induced fibrinolysis of the platelet-poor plasma. Furthermore, tranexamic acid remained chemically stable when stored for up to 12 weeks at temperatures from 4°C to 50°C and up to 4 weeks at –20°C as determined by high-performance liquid chromatography (HPLC). However, freezing should be avoided as cracks were observed in the ampoules within 1 week.

Furthermore, Loner et al.[3] reported that tranexamic acid remained stable under fluctuating extreme temperatures (seven days of freeze/thaw or heating cycles) and did not significantly degrade.

Tranexamic acid is not sensitive to light.[4,5,6]

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the US Pharmacopeia (USP) and British Pharmacopeia (BP), depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the two pharmacopeias are similar, except the assay, related substances, and/or bacterial endotoxin limits.

[2] de Guzman, R., Polykratis, IA., Sondeen, JL., Darlington, DN., Cap, AP., and Dubick, MA. 2013. "Stability of tranexamic acid after 12-week storage at temperatures from -20°c to 50°c." *Prehosp Emerg Care* 17(3): 394–400. doi: 10.3109/10903127.2013.792891.

[3] Loner, C., Estephan, M., Davis, H., Cushman, J., and Acquisto, N. 2019. "Effect of fluctuating extreme temperatures on tranexamic acid." *Prehospital and Disaster Medicine* 34(3): 340–342. doi:10.1017/S1049023X19004308.

[4] Medicines Evaluation Board. 2015. Public assessment report of Tranexaminezuur Sandoz 100 mg/ml, solution for injection (NL/H/3153/001/DC). Available at https://www.geneesmiddeleninformatiebank.nl/pars/h115236.pdf.

[5] Food and Drug Administration. 2009. Environmental assessment: Application number 22-430. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022430s000ea.pdf

[6] Huang, H., Liu, H., Zhou, H., Liang, Z., Song, D., Zhang, Y., Huang, W., Zhao, X., Wu, B., Ye, G., and Huang, Y. 2019. "Drug-release system of microchannel transport used in minimally invasive surgery for hemostasis." *Drug Des Devel Ther* 13: 881–896. doi: 10.2147/DDDT.S180842.

Table T-2. US Pharmacopeia Specifications for Tranexamic Acid Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Infrared spectroscopy (IR)	The IR spectra from the sample solution comply with that of the standard solution.	USP<197K>
b) HPLC	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay.	USP<621>
pH	6.5–8.0	USP<791>
Assay	90.0–110.0%	HPLC, USP<621>
Impurities	Any unspecified impurity: Not more than 0.1% Total impurities:* Not more than 0.5%	HPLC, USP<621>
Bacterial endotoxins	Not more than 0.5 USP endotoxin units/mg of tranexamic acid	USP<85>
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<1>
Particulate matter	Meet the requirements for small-volume injections	USP<788>

** Excluding process impurities monitored in the drug substance, e.g., Tranexamic acid related compound C ((RS)-4-(Aminomethyl)cyclohex-1-enecarboxylic acid hydrochloride); 4-(Aminomethyl)benzoic acid; cis-4-(Aminomethyl)cyclohexanecarboxylic acid; trans,trans-4,4'-[Iminobis(methylene)]dicyclohexanecarboxylic acid*

Table T-3. British Pharmacopeia Specifications for Tranexamic Acid Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification (IR)	The IR spectra from the sample solution comply with that of the standard solution.	Appendix II A
pH	6.5–8.0	Appendix V L
Assay	95.0–105.0%	HPLC, Appendix III D
Related substances**	Impurity A: Not more than 1% Impurity B: Not more 0.5% Impurity C: Not more than 0.1% Impurity D: Not more than 0.1% Any other impurity: Not more than 0.1% Total impurities: Not more than 2.0%	HPLC, Appendix III D
Bacterial endotoxins	Less than 35 IU/mL	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A

** *Impurity A = (1r,4r,1'r,4'r)-4,4'-[azanediylbis(methylene)]di(cyclohexane-1-carboxylic acid)*
Impurity B = (1s,4s)-4-(aminomethyl)cyclohexane-1-carboxylic acid
Impurity C = (4RS)-4-(aminomethyl)cyclohex-1-ene-1-carboxylic acid
Impurity D = 4-(aminomethyl)benzoic acid

TRANEXAMIC ACID ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

- Treatment of PPH
- Treatment of adult patients with trauma and significant risk of ongoing hemorrhage

Posology, method, and duration of administration

Treatment of PPH

Use tranexamic acid injection within 3 hours and as early as possible after onset of PPH. Do not initiate tranexamic acid more than 3 hours after birth, unless being used for bleeding that restarts within 24 hours of completing the first dose.

Tranexamic acid should be administered at a fixed dose of 1 g in 10 mL (100 mg/mL) IV at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose.

Tranexamic acid should be administered slowly as an IV injection over 10 minutes, since bolus injection carries a potential risk of transient lowering of blood pressure.

Treatment of adult patients with trauma and significant risk of ongoing hemorrhage

Standard treatment of local fibrinolysis: 0.5 g (5 mL) to 1 g (10 mL) tranexamic acid by slow intravenous injection or infusion (= 1 mL/minute) two to three times daily.

Standard treatment of general fibrinolysis: 1 g (10 mL) tranexamic acid by slow intravenous injection or infusion (= 1 mL/minute) every 6 to 8 hours, equivalent to 15 mg/kg body weight (BW).

Renal impairment: In renal insufficiency leading to a risk of accumulation, the use of tranexamic acid is contraindicated in patients with severe renal impairment (see also "Contraindications" section below). For patients with mild to moderate renal impairment, the dosage of tranexamic acid should be reduced according to the serum creatinine level:

Table T-4. Tranexamic Acid Dosage for Patients with Mild to Moderate Renal Impairment

SERUM CREATININE (MICROMOL/L)	MG/10 ML	DOSE IV	ADMINISTRATION
120 to 249	1.35 to 2.82	10 mg/kg BW	Every 12 hours
250 to 500	2.82 to 5.65	10 mg/kg BW	Every 24 hours
> 500	> 5.65	5 mg/kg BW	Every 24 hours

Hepatic impairment: No dose adjustment is required in patients with hepatic impairment.

Health care professionals should administer tranexamic acid injection by the intravenous route only. There have been reports of tranexamic acid being mistaken for obstetric spinal anesthesia used for caesarean deliveries resulting in inadvertent intrathecal administration, which may cause serious undesirable adverse effects. Therefore, careful handling of tranexamic acid injection is necessary to prevent medication errors.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the product
- Acute venous or arterial thrombosis (see "Special warnings and precautions for use" section below)
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding (see "Special warnings and precautions for use" section below)
- Severe renal impairment (risk of accumulation)
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)

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 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 color 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, color 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.

Hematuria

In case of hematuria 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 hemostaseology and under strict medical supervision (see "Contraindications" section above).

Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis (see "Interaction with other medicinal products and other forms of interaction" section below).

Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with tranexamic acid (see "Contraindications" section above). 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 hematological 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 hematological laboratory facilities and expertise are available.

Interaction with other medicinal products and other forms of interaction

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 hemostasis should be given with caution to patients treated with tranexamic acid. There is a theoretical risk of increased thrombus-formation potential, such as with estrogens. Alternatively, the antifibrinolytic action of the drug may be antagonized with thrombolytic drugs.

Fertility, pregnancy and lactation

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 studies in animals do not indicate teratogenic effects, as precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy.

Limited clinical data on the use of tranexamic acid in different clinical hemorrhagic settings during the second and third trimesters did not identify deleterious effect for the fetus.

Tranexamic acid should be used throughout pregnancy only if the expected benefit justifies the potential risk.

Breastfeeding

Tranexamic acid is excreted in human milk. Therefore, breastfeeding is not recommended.

Fertility

There are no clinical data on the effects of tranexamic acid on fertility.

Effects on ability to drive and use machines

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

Undesirable effects

The ADRs reported from clinical studies and post-marketing experience are listed below according to system organ class.

Table T-5. Tabulated List of Adverse Reactions from Tranexamic Acid

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 particularly in case of misuse (see "Contraindications" and "Special warnings and precautions for use" sections above)
Eye disorders			Visual disturbances including impaired color 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	Diarrhea Vomiting Nausea		
Skin and subcutaneous tissue disorders		Dermatitis allergic	

Overdose

No case of overdose has been reported.

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.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of tranexamic acid injection products. When assessing the complete quality/chemical, manufacturing and control (CMC) documentation, assessors should consider the following particular information on tranexamic acid injection.

API

As of June 2022, no tranexamic acid API is prequalified by the WHO PQP.
There are five manufacturers of tranexamic acid API that have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Table T-6. Manufacturers of Tranexamic Acid API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Tranexamic acid (monograph number 875)	Shilpa Medicate Ltd. Raichur, India	R0-CEP 2018-048-Rev 00	8/8/2019	Chemistry
Tranexamic acid (monograph number 875)	Kyowa Pharma Chemical Co., Ltd. Takaoka, Japan	R1-CEP 2012-271-Rev 01	4/30/2020	Chemistry
Tranexamic acid (monograph number 875)	Asahi Kasei Finechem Co., Ltd. Osaka, Japan	R1-CEP 2008-186-Rev 01	5/5/2020	Chemistry
Tranexamic acid (monograph number 875)	Hunan Dongting Pharmaceutical Co., Ltd. Changde, China	R1-CEP 2006-142-Rev 02	8/27/2020	Chemistry
Tranexamic acid (monograph number 875)	Ami Lifesciences Private Ltd. Karakhadi, India	R0-CEP 2019-250-Rev 02	4/4/2022	Chemistry

Other manufacturers of tranexamic API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[1]

The specifications of tranexamic API should be in line with a pharmacopeial monograph (Ph.Eur./BP or USP), with additional tests/limits for residual solvents and bacterial endotoxins. If intended for use

[1] WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 46th report. Technical Report Series No. 970. Geneva: WHO.

in the aseptic manufacture of tranexamic acid injection without a further appropriate sterilization procedure, it must comply with the test for sterility.

Tranexamic acid is hygroscopic. It should be kept in tight containers, and store at a temperature not exceeding 30°C or if sterile, in a sterile, airtight, tamper-evident container.

Excipients

The typical excipient of tranexamic acid injection is water for injection.[2] However, some formulations may also contain Hydrochloric acid and/or Sodium Hydroxide for pH adjustment.

There are no special concerns on the excipients. No excipient with the risk of transmitting TSE/BSE is used.

Manufacturing process

Tranexamic acid injection is a straightforward product to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.
The manufacturing process of tranexamic acid injection is a standard process, which is conducted under appropriate aseptic conditions, including the steps of preparation of the solution (with pH adjustment if necessary), filtration and filling and sealing of the ampoules. Finally, steam sterilization by autoclaving of the filled ampoules is performed. The headspace of the ampoules should be replaced with nitrogen during the filling process to prevent oxidation of the API. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

For the sterilization process using an autoclave, details such as F0 range, temperature range and peak dwell time for the FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule should be used.

Suitability of container should be demonstrated, including the following properties:

[2] Based on the formulation of an innovator product, Cyklokapron®.

Safety

- The material must meet compendial requirements such as USP<660> and USP<1660>. Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
  - One-time test reported as part of product development
  - Routine leak testing performed as part of the product manufacture

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 1003, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Cyklokapron® (tranexamic acid 100 mg/mL injection, Pharmacia and UpJohn Co/Pfizer). The composition of the proposed product should be the same as the comparator product.