

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CYKLOCLOT 100 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml ampoule contains 500 mg tranexamic acid.

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Short term use in the treatment of hyphaema and in patients with established coagulopathies who are undergoing minor surgery.
- Management of dental extraction in haemophiliacs.
- Hereditary angio-oedema

4.2 Posology and method of administration

Posology

CYKLOCLOT is given by slow intravenous infusion/injection. Administration by injection is usually changed to oral administration of tranexamic acid after a few days.

Traumatic hyphaema

1,0 to 1,5 g every 8 hours for six to seven days.

Patients with established coagulopathies undergoing minor surgery

Conization of the cervix: 1,0 to 1,5 g every 8 to 12 hours for 12 days post-operatively.

Dental operations/extractions

25 mg/kg two hours before the operation. Factor VIII and Factor IX should be given as well as tranexamic acid. After the operation, 25 mg/kg of tranexamic acid is given 3 to 4 times a day for 6 to 8 days.

Hereditary angio-oedema

Some patients are aware of the onset of illness; a suitable treatment for these patients is 1,0 -1,5 g two to three times daily for some days. Other patients are treated continually at this dosage.

Method of administration

CYKLOCLOT is administered intravenously by slow injection over a period of at least five minutes.

For incompatibilities, see section 6.2.

4.3 Contraindications

- Hypersensitivity to tranexamic acid or to any of the excipients (see section 6.1).
- Acute venous or arterial thrombosis (see section 4.4).
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding (see section 4.4).

- In case of massive upper urinary tract haemorrhage, to reduce the risk of ureteric obstruction.
- Patients with a pronounced thrombotic tendency or colour vision disorder.
- Thrombophlebitis, impaired liver function and subarachnoid bleeding.
- Severe renal impairment (risk of accumulation).
- History of convulsions.
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions).

4.4 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 intravenous (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 colour 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, colour vision, fundus, visual field etc.) are indicated. With pathological ophthalmic changes, particularly with diseases of the retina, the medical practitioner must decide after consulting a specialist on the necessity for the long-term use of tranexamic acid in each individual case.

Haematuria

In case of haematuria 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 is contraindicated (see section 4.3).

Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis (see section 4.5).

Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with tranexamic acid (see section 4.3). 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 haematological 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 haematological laboratory facilities and expertise are available.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed. Simultaneous treatment with anticoagulants must take place under the strict supervision of a medical practitioner experienced in this field. Medicines that act on haemostasis should be given with caution to patients treated with tranexamic acid. There is a risk of increased thrombus-formation potential, such as with oestrogens. Alternatively, the antifibrinolytic action of the medicine may be antagonised with thrombolytic medicines.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential /Contraception in males and females

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, CYKLOCLOT 100 mg/ml is not recommended during the first trimester of pregnancy.

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

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.

4.7 Effects on ability to drive and use machines

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

Since CYKLOCLOT may cause visual disturbances, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects

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

Tabulated summary of adverse reactions

Adverse reactions reported are presented in table below. Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

MedDRA System Organ Class	Frequency	Adverse reactions
Immune system disorders	Frequency unknown	Hypersensitivity reactions including anaphylaxis
Nervous system disorders	Frequency unknown	Convulsions particularly in case of misuse (see sections 4.3 and 4.4), dizziness
Eye disorders	Frequency unknown	Visual disturbances including impaired colour vision
Vascular disorders	Frequency unknown	Malaise with hypotension, with or without loss of consciousness (generally following

MedDRA System Organ Class	Frequency	Adverse reactions
		a too fast Intravenous injection, exceptionally after oral administration), arterial or venous thrombosis at any sites
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis allergic

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**”, found online under SAHPRA’s publications:

https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Signs and symptoms may include dizziness, headache, nausea, vomiting, diarrhoea, hypotension, and convulsions. It has been shown that convulsions tend to occur at higher frequency with increasing dose.

Management of overdose should be supportive. Maintain adequate diuresis (with fluids plus diuretics)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 8.1 Coagulants, haemostatics.

Pharmacotherapeutic group: Antihæmorrhagics. Antifibrinolytics. Aminoacids.

ATC code: B02AA02

Tranexamic acid exerts an anti-hæmorrhagic activity by inhibiting the fibrinolytic properties of plasmin. A complex involving tranexamic acid, plasminogen is constituted; the tranexamic acid being linked to plasminogen when transformed into plasmin.

The activity of the tranexamic acid-plasmin complex on the activity on fibrin is lower than the activity of free plasmin alone. *In vitro* studies showed that high tranexamic dosages decreased the activity of complement.

5.2 Pharmacokinetic properties

Absorption

Peak plasma concentrations of tranexamic acid are obtained rapidly after a short intravenous infusion after which plasma concentrations decline in a multi-exponential manner.

Distribution

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. The initial volume of distribution is about 9 to 12 litres. Tranexamic acid passes through the placenta. Following administration of an intravenous injection of 10 mg/kg to pregnant women, the concentration of tranexamic acid in serum ranged 10-53 microgram/mL while that in cord blood ranged 4-31 microgram/mL. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. Following administration of an intravenous injection of 10 mg/kg to patients undergoing knee surgery, concentrations in the joint fluids were similar to those seen in corresponding serum samples. The concentration of tranexamic acid in a number of other tissues is a fraction of that observed in the blood (breast milk, one hundredth; cerebrospinal fluid, one tenth; aqueous humor, one tenth). Tranexamic acid has been

detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.

Elimination

Tranexamic acid is excreted mainly in the urine as unchanged drug.

Urinary excretion via glomerular filtration is the main route of elimination. Renal clearance is equal to plasma clearance (110 to 116 mL/min). Excretion of tranexamic acid is about 90 % within the first 24 hours after intravenous administration of 10 mg/kg body weight. Elimination half-life of tranexamic acid is approximately 3 hours.

Other special populations

Plasma concentrations increase in patients with renal failure.

No specific pharmacokinetic study has been conducted in children.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Epileptogenic activity has been observed in animals with intrathecal use of tranexamic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

CYKLOCLOT may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions. Heparin may be added to CYKLOCLOT.

CYKLOCLOT should not be mixed with blood and infusion solutions containing penicillin.

6.3 Shelf life

2 years

Store at or below 30 °C.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

CYKLOCLOT is packed as 5 ml in USP type I clear glass ampoule.

Pack size: 1 ampoule in an outer carton.

6.6 Special precautions for disposal and other handling

CYKLOCLOT is for single use only. Any unused medicine or waste material should be disposed of in accordance with local requirements.

For intravenous infusion, CYKLOCLOT may be mixed with electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions. Heparin solutions may be added to CYKLOCLOT.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

106, 16th Road

Midrand

8 REGISTRATION NUMBER

540886

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 February 2023

10 DATE OF REVISION OF THE TEXT