APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KLOTIGO 500 solution for injection/infusion

KLOTIGO 1 000 solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL ampoule contains tranexamic acid 500 mg (100 mg/mL solution for injection).

Each 10 mL ampoule contains tranexamic acid 1 000 mg (100 mg/mL solution for injection).

Sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection/ infusion.

A clear sterile solution, free from particles, with pH of 6,5 - 8,0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Short term use in the treatment of haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis. Local fibrinolysis occurs in the following conditions:
    - prostatectomy and bladder surgery

- epistaxis
- conisation of the cervix
- traumatic hyphaema.

- Management of dental extraction in haemophiliacs.
- Hereditary angioedema.
- Menorrhagia.

4.2 Posology and method of administration

Posology

Adults

Administration by injection is normally changed to oral administration of an oral dosage form of tranexamic acid after a few days.

Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis

Standard treatment of local fibrinolysis

0,5 g (1 ampoule of 5 mL) to 1 g (2 ampoules of 5 mL) KLOTIGO by slow intravenous injection (IV) or infusion (= 1 mL/minute) two to three times daily

Standard treatment of general fibrinolysis

1 g (2 ampoules of 5 mL) KLOTIGO by slow intravenous injection or infusion (= 1 mL/minute) every 6 to 8 hours, equivalent to 15 mg/kg body weight (BW).

Prostatectomy and bladder surgery

0,5 g (1 ampoule of 5 mL) to 1 g (2 ampoules of 5 mL) KLOTIGO by slow intravenous injection or infusion (1 mL/min), 2 - 3 times daily (the first injection being given during the operation)/ for the first three days after surgery.

Epistaxis

1,0 g to 1,5 g every 8 - 12 hours for 10 days.

Conisation of the cervix

1,0 g to 1,5 g every 8 to 12 hours for 12 days post-operatively.

Traumatic hyphaemia:

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

Dental operations/extractions in haemophiliacs:

Two hours before the operation, 25 mg/kg of KLOTIGO is given, as well as Factor VIII and Factor IX. After the operation, tranexamic acid at a dosage of 25 mg/kg is given three to four times a day for 6 to 8 days (normally as an oral dosage form).

Hereditary angioedema:

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.

Menorrhagia:

1,0 - 1,5 g three to four times daily (normally as an oral dosage form), given at the onset of heavy bleeding for the duration of the period.

Special populations

Renal impairment

For patients with impaired renal function, KLOTIGO should be given with caution (see section 4.4). Dosages should be reduced in patients with renal impairment.

For patients with moderate to severe impaired renal function, the following dosages are recommended:

Serum creatinine (micromole/L)	**Intravenous dose**
120 - 250	10 mg/kg body weight twice daily
250 - 500	10 mg/kg body weight daily
> 500	5 mg/kg body weight daily

Paediatric population

Data on efficacy and safety in children are limited.

Method of administration

KLOTIGO solution for injection is strictly limited to slow intravenous infusion (see section 6.6), or slow injection over a period of at least five minutes, i.e. 1 mL/minute (see sections 4.3 and 4.4).

For intravenous injection, use immediately after opening. Diluted infusion solutions are stable in the refrigerator at 2 - 8 °C for up to 24 hours (see section 6.3).

4.3 Contraindications

- Hypersensitivity to tranexamic acid or to any of the ingredients of KLOTIGO (see section 6.1)

In cases of massive upper urinary tract haemorrhage, KLOTIGO should be avoided to reduce the risk of ureteric obstruction.

- patients with pronounced thrombotic tendency or colour vision disorder (see section 4.4)
- thrombophlebitis, impaired liver function and subarachnoid bleeding
- fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding (see section 4.4)
- history of convulsions
- history of acute venous or arterial thrombosis (see section 4.4)
- severe renal impairment (risk of accumulation)
- active intravascular clotting
- intrathecal and intraventricular injection, intracerebral application (risk of cerebral

oedema and convulsions).

4.4 Special warnings and precautions for use

The indications for use and method of administration should be followed strictly:

- intravenous injections should be given very slowly (maximum 1 mL per minute)
- KLOTIGO must **not** be administered by the intramuscular route
- KLOTIGO must **not** be administered by intrathecal or intraventricular injection, or intracerebral application due to a risk of cerebral oedema and convulsions.

Convulsions

Convulsions have been reported in association with tranexamic acid, as in KLOTIGO, treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following intravenous (IV) injection of tranexamic acid, as in KLOTIGO, in high doses.

With the use of the recommended lower doses of KLOTIGO, the incidence of post-operative seizures was the same as that in untreated patients.

Visual disturbances

The patient should be monitored for visual disturbances, including visual impairment, blurred vision, impaired colour vision. If necessary, KLOTIGO should be discontinued.

With continuous long-term use of KLOTIGO, regular ophthalmologic examinations (eye examinations including visual acuity, colour vision, fundus, visual field etc.) are indicated (see section 4.3). With pathological ophthalmic changes, particularly with diseases of the retina, it

is recommended that the medical practitioner consult a

specialist on the necessity for long-term use of KLOTIGO in each individual case.

Haematuria

In case of haematuria from the upper urinary tract, there is a risk for urethral obstruction (see section 4.3).

Thromboembolic events

Before use of KLOTIGO, 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 an elevated risk of thrombophilia), KLOTIGO is contraindicated (see section 4.3).
KLOTIGO 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 not be treated with KLOTIGO (see section 4.3). If KLOTIGO is given it should be restricted to those in whom there is predominant activation of the fibrinolytic system with acute severe bleeding.
Patients with menorrhagia (irregular menstrual bleeding) should not use KLOTIGO until the cause of the irregularity has been established.
Tranexamic acid should not be administered concomitantly with Factor IX Complex Concentrates or Anti-inhibitor Coagulant Concentrates, as the risk of thrombosis may be

increased.

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 KLOTIGO is frequently sufficient to control bleeding. Administration of KLOTIGO in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available.

Patients with a previous history of thromboembolic disease should not be given KLOTIGO unless simultaneous treatment with anticoagulants can be given (see section 4.3).

Liver function

Liver function tests should be performed if KLOTIGO is used long-term (see section 4.3).

Renal impairment

For patients in renal failure, KLOTIGO should be given with caution because of the risk of accumulation. Dosage should be reduced in patients with renal impairment (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

No studies of interactions between KLOTIGO and other medicines have been conducted.

Medicines with actions on haemostasis should be given with caution to patients on KLOTIGO.

Simultaneous treatment with anticoagulants should take place under the strict supervision of a doctor with experience in this field.

There is a risk of increased thrombus-formation potential such as with oestrogens.

Alternatively, the antifibrinolytic action of KLOTIGO may be antagonised with thrombolytic medicines.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy

The safety of KLOTIGO has not been established in pregnancy.

Breastfeeding

Tranexamic acid passes into breast milk at a concentration of one hundredth of the corresponding serum levels. Therefore, breastfeeding is not recommended.

Fertility

There are no clinical data on the effects of tranexamic 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.

Side effects of KLOTIGO include visual disturbances and dizziness. Patients should be advised against driving and handling machinery if they develop these symptoms.

4.8 Undesirable effects

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Immune system disorders	Frequency unknown	Hypersensitivity reactions including anaphylaxis
Nervous system disorders	Frequency unknown	Dizziness (giddiness), convulsions, particularly in case of misuse (see sections 4.3 and 4.4)
Eye disorders	Less frequent	Visual disturbances including impaired colour vision (see section 4.4)
Cardiac disorders	Less frequent	Thromboembolic events
Vascular disorders	Less frequent	Malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection), arterial or venous thrombosis at any sites, thrombotic complications due to inappropriate use
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea

Skin and subcutaneous tissue disorders	Less frequent	Dermatitis allergic
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Musculoskeletal pain

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. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

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

Management of overdose:

Treatment would consist of enhancing diuresis (with fluids plus diuretics) activated charcoal therapy and symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics, Antifibrinolytics, Amino acids

ATC code: B02AA02

Pharmacological classification: A 8.1: Coagulants, haemostatics

Mechanism of action

Tranexamic acid exerts an inhibitory effect on the activation of plasminogen in the fibrinolytic system, i.e. on the conversion of plasminogen to plasmin.

Tranexamic acid is used in fibrinolytic bleeding conditions, which may occur in a number of different clinical conditions in which there is abnormal stimulation of the activation mechanism.

Tranexamic acid exerts an anti-haemorrhagic 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.

Tranexamic acid is absorbed and is excreted unchanged through the kidneys.

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 crosses the placenta and may reach one hundredth of the serum peak concentration in the milk of lactating women.

Tranexamic acid crosses the blood brain barrier.

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 in the urine mainly as the unchanged medicine.

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.

Pharmacokinetics in special patient groups

Plasma concentrations increase in patients with renal failure.

Paediatric population

No specific pharmacokinetic study has been conducted in children.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

After first opening: The solution for injection is for single use only. Unused solution for injection should be discarded.

Chemical and physical in-use stability of the infusion solutions have been demonstrated for 24 hours at 2 - 8 °C.

Mixtures not used within 24 hours of preparation, should be discarded. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Do not freeze.

6.4 Special precautions for storage

Store the ampoules at or below 25 °C. Keep ampoules in carton to protect from light.

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

6.5 Nature and contents of container

Type 1 transparent glass ampoules packed in a cardboard carton.

Each carton contains 5 x 5 mL or 5 x 10 mL ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intravenous infusion, KLOTIGO may be mixed with 0,9 % sodium chloride solution, 5 % glucose solution and Ringer's solution (compound sodium chloride).

The required volume may be added to the chosen infusion solution to achieve final concentrations of 1 gram or of 2 grams in 100 mL (1 % or 2 %).

The mixed solutions should be used immediately after preparation (see section 6.3).

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

Tel.: +27 21 707 7000

or 0860-PHARMA (742 762)

8. REGISTRATION NUMBER(S)

KLOTIGO 500: A52/8.1/0506

KLOTIGO 1 000: A52/8.1/0507

9. DATE OF FIRST AUTHORISATION

27 July 2021

10. DATE OF REVISION OF THE TEXT

29 January 2025