SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRANEXAMIC ACID 100 mg/mL PHARMC Solution for injection

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.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Short-term use for 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

Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis

Standard treatment of local fibrinolysis

0,5 g (1 ampoule of 5 mL) to 1,0 g (2 ampoules of 5 mL) TRANEXAMIC ACID 100 mg/mL PHARMC by slow intravenous injection (IV) or infusion (= 1 mL/minute) two to three times daily.

Standard treatment of general fibrinolysis

1,0 g (2 ampoules of 5 mL) TRANEXAMIC ACID 100 mg/mL PHARMC 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 1,0 g (2 ampoules of 5 mL) TRANEXAMIC ACID 100 100 mg/mL PHARMC 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 (1 ampoule of 5 mL) to 1,5 g (1½ ampoules of 5 mL) every 8 – 12 hours for 10 days.

Conisation of the cervix

1,0 (1 ampoule of 5 mL) to 1,5 g (1½ ampoules of 5 mL) every 8 to 12 hours for 12 days post-operatively.

Traumatic hyphaema

1,0 g (1 ampoule of 5 mL) to 1,5 g (1½ ampoules of 5 mL) every 8 hours for 6 to 7 days.

Dental operations/extractions in haemophiliacs

25 mg/kg before the operation, together with Factor VIII and Factor IX. After the operation, 25 mg/kg is given 3 to 4 times a day for 6 to 8 days.

Hereditary angioedema

Some patients are aware of the onset of illness; a suitable treatment for these patients is 1,0 g (1 ampoule of 5 mL) to 1,5 g (1½ ampoules of 5 mL) two to three times daily for some days. Other patients are treated continually at this dosage.

Menorrhagia

1,0 g (1 ampoule of 5 mL) to 1,5 g (1½ ampoules of 5 mL) three to four times daily, given at the onset of heavy bleeding for the duration of the period.

Special populations

In renal insufficiency leading to a risk of accumulation, the use of tranexamic acid is contraindicated in patients with severe renal impairment (see section 4.3). For patients with mild to moderate renal impairment, the dosage of tranexamic acid should be reduced according to the serum creatinine level:

Serum creatinine (micromol/L)	Intravenous dose	Administration
120 – 250	10 mg/kg body weight	Every 12 hours
250 – 500	10 mg/kg body weight	Every 24 hours
> 500	5 mg/kg body weight	Every 24 hours

Paediatric population

Data on efficacy and safety in children are limited.

Method of administration

The administration is strictly limited to slow intravenous injection or infusion (see section 6.6) of 100 mg/ml over a period of at least five minutes.

Administration by injection is usually changed to oral administration after a few days.

4.3 Contraindications

- Hypersensitivity to tranexamic acid or to any of the excipients (see section 6.1).
- In cases of massive upper urinary tract haemorrhage, TRANEXAMIC ACID 100 mg/mL PHARMC should be avoided to reduce the risk of ureteric obstruction.
- Patients with a pronounced thrombotic tendency or colour vision disorder (see section 4.4).
- Thrombophlebitis.
- Impaired liver function.
- Subarachnoid bleeding.
- 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).
- 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.
- TRANEXAMIC ACID 100 mg/mL PHARMC must not be administered by intrathecal or intraventricular injection, or intracerebral application due to a risk of cerebral oedema and convulsions.

Convulsions

Cases of convulsions have been reported in association with tranexamic acid as in TRANEXAMIC ACID 100 mg/mL PHARMC treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following intravenous (I.V.) 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 as in TRANEXAMIC ACID 100 mg/mL PHARMC, 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 100 mg/mL PHARMC, 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 100 mg/mL PHARMC is contraindicated (see section 4.3).

TRANEXAMIC ACID 100 mg/mL PHARMC should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis (see section 4.5).

TRANEXAMIC ACID 100 mg/mL PHARMC should not be administered concomitantly with Factor IX Complex Concentrates or Anti-inhibitor Coagulant Concentrates, as the risk of thrombosis may be increased.

Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with TRANEXAMIC ACID 100 mg/mL PHARMC (see section 4.3). If TRANEXAMIC ACID 100 mg/mL PHARMC 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 100 mg/mL PHARMC is frequently sufficient to control bleeding. Administration of TRANEXAMIC ACID 100 mg/mL PHARMC in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available.

Menorrhagia

Patients with menorrhagia should not use TRANEXAMIC ACID 100 mg/mL PHARMC until the cause of the menorrhagia has been established.

4.5 Interactions 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, TRANEXAMIC ACID 100 mg/mL PHARMC is not recommended during the first trimester of pregnancy.

Limited clinical data on the use of tranexamic acid as in TRANEXAMIC ACID 100 mg/mL PHARMC in different clinical haemorrhagic settings during the second and third trimesters did not identify deleterious effect for the foetus.

Breastfeeding

Tranexamic acid as in TRANEXAMIC ACID 100 mg/mL PHARMC 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 TRANEXAMIC ACID 100 mg/mL PHARMC may cause dizziness and 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 MedDRA system organ class.

Tabulated summary of adverse reactions

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
Cardiovascular disorders	Less frequent	Thromboembolic events
Eye disorders	Less frequent	Visual disturbances including impaired colour vision
Vascular disorders	Frequency unknown	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	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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

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

Category and class: A 8.1 Coagulants, haemostatics.

Pharmacotherapeutic group: Antihaemorrhagics, Antifibrinolytics. Amino acids.

ATC code: B02AA02

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.

Paediatric population

In children over one year old

Literature review identified study results with tranexamic acid suggest reduced blood loss and reduced blood product requirements in paediatric cardiac surgery under cardiopulmonary

bypass (CPB) where there is a high risk of haemorrhage, especially in cyanotic patients or patients undergoing repeat surgery. The most adapted dosing schedule appeared to be:

- first bolus of 10 mg/kg after induction of anaesthesia and prior to skin incision,
- continuous infusion of 10 mg/kg/h or injection into the CPB pump prime at a dose adapted on the CPB procedure, either according to a patient weight with a dose of 10 mg/kg dose, either according to CPB pump prime volume, last injection of 10 mg/kg at the end of CPB.

While studied in very few patients, the limited data suggest that continuous infusion is preferable, since it would maintain therapeutic plasma concentration throughout surgery.
No specific dose-effect study or PK study has been conducted in children.

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

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

TRANEXAMIC ACID 100 mg/mL PHARMC 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 TRANEXAMIC ACID 100 mg/mL PHARMC.

TRANEXAMIC ACID 100 mg/mL PHARMC should not be mixed with blood and infusion solutions containing penicillin.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

TRANEXAMIC ACID 100 mg/mL PHARMC is packed as 5 ml in USP type I clear glass ampoule. Pack size: 1 or 5 ampoule(s) in an outer carton.

6.6 Special precautions for disposal and other handling

TRANEXAMIC ACID 100 mg/mL PHARMC is for single use only.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Reconstitution method

For intravenous infusion, TRANEXAMIC ACID 100 mg/mL PHARMC solution for injection may be mixed with electrolyte solutions, carbohydrate solutions, aminosol and dextran solutions. Heparin solutions may be added to TRANEXAMIC ACID 100 mg/mL PHARMC solution for injection. TRANEXAMIC ACID 100 mg/mL PHARMC solution for injection should not be mixed with blood and infusion solutions containing penicillin.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharmacorp (Pty) Ltd

29 Victoria Link

Route 21 Corporate Park

Irene, 0178, RSA

8. REGISTRATION NUMBER: 48/8.1/1085

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION: 04 May 2021

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