PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TRANEXAMIC INJECTION PHARMA-Q solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRANEXAMIC INJECTION PHARMA-Q contains tranexamic acid 100 mg/ml

Each 10 ml ampoule or vial contain 1 000 mg tranexamic acid

Sugar free

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution practically free from particles filled in clear glass ampoules and vials.

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

TRANEXAMIC INJECTION PHARMA-Q is given by slow intravenous infusion/injection. Administration by injection is usually changed to oral tranexamic acid administration 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

TRANEXAMIC INJECTION PHARMA-Q is administered intravenously by slow injection over a period of at least five minutes. For intravenous infusion, TRANEXAMIC INJECTION PHARMA-Q may be mixed with electrolyte solutions, carbohydrate solutions, amino acid solutions, and dextran solutions. Heparin solutions may be added to TRANEXAMIC INJECTION PHARMA-Q solution for injection.

For incompatibilities, see section 6.2.

4.3 Contraindications

- Hypersensitivity to tranexamic acid or to any of the excipients of TRANEXAMIC INJECTION PHARMA-Q (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).
- Severe renal impairment (risk of accumulation).
- Impaired liver function and subarachnoid bleeding
- Patients with colour vision disturbances
- 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 should only be administered if there is a strong medical indication after consulting a medical practitioner experienced in haemostaseology and under strict medical supervision (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 theoretical 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 INJECTION PHARMA-Q 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 INJECTION PHARMA-Q 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 INJECTION PHARMA-Q may cause dizziness or 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 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://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdosage: Dizziness, headache, nausea and vomiting, diarrhoea. Faintness and hypotension may occur.

Treatment is symptomatic and supportive. Maintain adequate diuresis (with fluids plus diuretics).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 8.1 Coagulants, haemostatics.

Pharmacotherapeutic group: Antihaemorrhagics. Antifibrinolytics. Aminoacids.

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. [2, 3]

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

TRANEXAMIC INJECTION PHARMA-Q should not be mixed with blood and infusion solutions containing penicillin.

6.3 Shelf life

2 years

After first opening: the solution for injection is for single use only. Unused solution must be discarded.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze.

6.5 Nature and contents of container

10 ml in 10 ml clear glass ampoule with blue bands and white OPC mark packed in a PVC transparent rondo tray in a single carton.

10 ml in 10 ml flint USP Type-I glass vials with 20 mm rubber stoppers and 20 mm white aluminium flip-off seal and packed in a single carton.

6.6 Special precautions for disposal and other handling

TRANEXAMIC INJECTION PHARMA-Q is for single use only.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

50 Commando Road,

Industria West

Johannesburg

2093

8 REGISTRATION NUMBER

540223

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT