SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CYKLOKAPRON® T 500, 500 mg film-coated tablets

CYKLOKAPRON® IV 500, 500 mg/5 mL injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg tranexamic acid.

Each 5 mL ampoule contains 500 mg tranexamic acid.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White, capsular, film-coated tablets, with arcs above and below the letters 'CY' engraved on one side and scored on the other.

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 g (2 ampoules of 5 mL) CYKLOKAPRON by slow intravenous injection (IV) or infusion (= 1 mL/minute) two to three times daily; or alternatively 1 – 2 (500 mg - 1 g) tablets two to three times daily.

Standard treatment of general fibrinolysis

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

Prostatectomy and bladder surgery

0,5 g (1 ampoule of 5 mL) to 1 g (2 ampoules of 5 mL) CYKLOKAPRON 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, thereafter 2 – 3 (1 g – 1,5 g) tablets 2 - 3 times daily.

Epistaxis

2 – 3 (1 g – 1,5 g) tablets every 8 - 12 hours for 10 days.

Conisation of the cervix

2 – 3 (1 g – 1,5 g) tablets every 8 - 12 hours, 12 days post-operatively.

Traumatic hyphaema

1,0 - 1,5 g (2 – 3) tablets every 8 hours for six to seven days.

Dental operations/extraction in haemophiliacs

25 mg/kg orally two hours before the operation. Factor VIII and Factor IX should be given as well as CYKLOKAPRON. After the operation, 25 mg/kg of CYKLOKAPRON 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 - 1,5 g (2 – 3) tablets two to three times daily for some days. Other patients are treated continually at this dosage.

Menorrhagia

2 – 3 tablets (1 g – 1,5 g) three to four times daily, given at the onset of heavy bleeding for the duration of the period.

Special populations

Renal impairment

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 (μmol/L)	**Oral dose**	**Intravenous dose**
120 - 250	15 mg/kg body weight twice daily	10 mg/kg body weight twice daily
250 - 500	15 mg/kg body weight daily	10 mg/kg body weight daily
> 500	7,5 mg/kg body weight daily	5 mg/kg body weight daily

Method of administration

CYKLOKAPRON is given orally or by slow intravenous infusion/injection. Administration by injection is usually changed to oral administration after a few days.

For the injection

CYKLOKAPRON solution for injection is administered intravenously by slow injection over a period of at least five minutes. For intravenous infusion, CYKLOKAPRON solution for injection may be mixed with electrolyte solutions, carbohydrate solutions, Aminosol and dextran solutions.

Heparin solutions may be added to CYKLOKAPRON solution for injection.

4.3 Contraindications

- Hypersensitivity to tranexamic acid or any of the excipients of CYKLOKAPRON (listed in section 6.1)
- In cases of massive upper urinary tract haemorrhage, CYKLOKAPRON should be avoided to reduce the risk of ureteric obstruction
- Patients with a pronounced thrombotic tendency or colour vision disorder should not be given CYKLOKAPRON
- Thrombophlebitis
- Impaired liver function
- Subarachnoid bleeding
- History of arterial or venous thromboembolism
- Active intravascular clotting
- Patients with hypercoagulopathies

4.4 Special warnings and precautions for use

Convulsions

Cases of convulsions have been reported in association with CYKLOKAPRON treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following IV injection of CYKLOKAPRON in high doses. With the use of the recommended lower doses of CYKLOKAPRON, the incidence of post-operative seizures was the same as that in untreated patients.

Patients with menorrhagia should not use CYKLOKAPRON until the cause of the menorrhagia has been established.

For patients in renal failure, CYKLOKAPRON should be given with caution because of the risk of accumulation.

Patients with a previous history of thromboembolic disease should not be given CYKLOKAPRON.

For patients who are to receive treatment with CYKLOKAPRON for longer than several days, an ophthalmological examination is advisable (including visual acuity, colour vision, eye-grounds, field of vision), before commencing treatment, and at regular intervals during treatment.

CYKLOKAPRON should be given with caution to patients on antifibrinolytic therapy.

Because of the absence of interaction studies, simultaneous treatment with anticoagulants must take place under the strict supervision of a medical practitioner experienced in this field.

4.5 Interaction with other medicines and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

The safety of CYKLOKAPRON has not been established in pregnancy and lactation.

Breastfeeding

CYKLOKAPRON passes into breast milk. Women using CYKLOKAPRON should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

CYKLOKAPRON may cause dizziness and may influence the ability to drive or use machines.

4.8 Undesirable effects

The frequency of side effects at a dose of 4 g /day.

Common (≥ 1/100 to < 1/10):

Gastrointestinal disorders: Nausea, vomiting, diarrhoea

Uncommon (≥ 1/1 000 to < 1/100):

Skin and subcutaneous tissue disorders: Allergic skin reactions

Rare (≥ 1/10 000 to < 1/1 000):

Cardiovascular disorders: Thromboembolic events

Eye disorders: Transient disturbance or impairment of colour vision

Patients who experience disturbances of colour vision should be withdrawn from treatment.

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 section 4.4)

Cases of giddiness have been reported. Rapid intravenous injection may cause dizziness and/or hypotension.

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 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 and convulsions. It has been shown that convulsions tend to occur at higher frequency with increasing dose.

Faintness and hypotension may occur.

Activated charcoal therapy and symptomatic treatment.

Maintain adequate diuresis with fluids.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 8.1 Coagulants, haemostatics

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

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 - 12 litres.

Tranexamic acid passes through the placenta. Following administration of an intravenous injection of 10 mg/kg to 12 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 17 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

It 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.

Paediatric population

No specific pharmacokinetic study has been conducted in children.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablets

Tablet core

Microcrystalline cellulose

Hydroxypropylcellulose

Talc

Magnesium stearate

Colloidal anhydrous silica

Povidone

Film-coat

Methacrylate polymers

Titanium dioxide

Talc

Magnesium stearate

Polyethylene glycol

Vanillin

Ampoules

Water for injections

6.2 Incompatibilities

CYKLOKAPRON solution for injection should not be mixed with blood and infusion solutions containing penicillin.

6.3 Shelf life

CYKLOKAPRON T 500: 36 months.

CYKLOKAPRON IV 500: 36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature of contents of container

CYKLOKAPRON T 500: Tablets in plastic containers of 24 and 100.

CYKLOKAPRON IV 500: Ampoules of 5 mL in packs of 5.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

CYKLOKAPRON T 500: H/8.1/807

CYKLOKAPRON IV 500: H/8.1/806

9. DATE OF FIRST AUTHORISATION

CYKLOKAPRON T 500: 06 June 1980

CYKLOKAPRON IV 500: 06 July 1980

10. DATE OF REVISION OF THE TEXT

09 January 2022

Manufacturer: Pfizer Manufacturing Belgium NV, Puurs, Belgium (IV)

Manufacturer: Pfizer Italia S.r.L., 63100 Ascoli, Italy (Tablets)

BOTSWANA: S2

CYKLOKAPRON T 500: Reg. No.: B9300420

CYKLOKAPRON IV 500: Reg. No.: B9300425

NAMIBIA: S2

CYKLOKAPRON T 500: Reg. No.: 90/8.1/001298

CYKLOKAPRON IV 500: Reg. No.: 90/8.1/001297

ZIMBABWE: PP

CYKLOKAPRON T 500: Reg. No.: 75/10.4/0575

CYKLOKAPRON IV 500: Reg. No.: 75/10.4/574