1.3.1.1 CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

HEMOPRON® 500, solution for injection/infusion

HEMOPRON® 1 000, solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 10 mL ampoule contains 1 000 mg tranexamic acid (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 hyphaema and in patients with established coagulopathies who are undergoing minor surgery.
- 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.

Traumatic hyphaema:

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

Patients with established coagulopathies undergoing minor surgery:

Conisation of the cervix: 1,0 to 1,5 g every 8 to 12 hours postoperatively.

Dental operations/extractions in haemophiliacs:

Two hours before the operation, 25 mg/kg of HEMOPRON is given, as well as Factor VIII and Factor IX. After the operation, tranexamic acid at a dosage of 25 mg/kg is given 3 to 4 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.

Renal impairment

For patients with impaired renal function, HEMOPRON 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

Children

Data on efficacy and safety in children are limited.

Administration

HEMOPRON 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.

4.3 Contraindications

- Hypersensitivity to tranexamic acid, or to any of the excipients of HEMOPRON.
- In cases of massive upper urinary tract haemorrhage, HEMOPRON 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 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.

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.
- HEMOPRON must **not** be administered by the intramuscular route.
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions).

Convulsions

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

Visual disturbances

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

With continuous long-term use of HEMOPRON, 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 HEMOPRON 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 HEMOPRON, 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), HEMOPRON should not be administered (see section 4.3).

HEMOPRON 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 HEMOPRON (see section 4.3). If HEMOPRON 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 HEMOPRON until the cause of irregularity has been established.

Tranexamic acid should not be concomitantly administered with Factor IX Complex Concentrate or Anti-inhibitor Coagulant Concentrate, 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 HEMOPRON is frequently sufficient to control bleeding. Administration of HEMOPRON 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 HEMOPRON unless simultaneous treatment with anticoagulants can be given (see section 4.3).

Liver function

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

Renal impairment

For patients in renal failure, HEMOPRON 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

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

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 HEMOPRON 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 HEMOPRON has not been established in pregnancy.

Breastfeeding

Tranexamic acid passes into breast milk at a concentration of a 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

Side effects of HEMOPRON 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 reactions

System organ class	**Frequent**	**Less frequent**	**Frequency not known**
Immune system disorders			Hypersensitivity reactions including anaphylaxis
Nervous system disorders			Dizziness, convulsions particularly in case of misuse (see sections 4.3 and 4.4)
Eye disorders		Retinal/arterial occlusion	Visual disturbances including impaired colour vision (see section 4.4)
Vascular disorders		Thromboembolic events	Malaise with hypotension, with or without loss of consciousness (generally following a too fast

System organ class	Frequent	Less frequent	Frequency not known
			intravenous injection) Arterial or venous thrombosis at any sites
Gastrointestinal disorders	Diarrhoea Vomiting Nausea		
Skin and subcutaneous tissue disorders		Dermatitis allergic	
Musculoskeletal, connective tissue and bone disorders			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 providers are asked to report any suspected adverse reactions to SAHPRA on the SAHPRA website: "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:

Dizziness, headache, nausea and vomiting, diarrhoea. Faintness and hypotension may occur.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A, class 8.1: Coagulants, haemostatics

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.

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 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.

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.

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

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

6.3 Shelf life

30 months.

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. Do not freeze.

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.

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 HEMOPRON, see section 6.3.

6.5 Nature and contents of container

Type I 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, HEMOPRON 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).

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

7 HOLDER OF CERTIFICATES OF REGISTRATION

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8 REGISTRATION NUMBERS

HEMOPRON 500: 52/8.1/0808

HEMOPRON 1 000: 52/8.1/0809

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

13.07.2021

10 DATE OF REVISION OF THE TEXT

08.10.2021