SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Haemostop, 500 mg/5 mL, 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/infusion.

Clear, colourless solution with pH of 6,5- 8,0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Haemostop is indicated for the 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

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 in haemophiliacs:

25 mg/kg orally two hours before the operation. Factor VIII and Factor IX should be given as well as Haemostop. After the operation, 25 mg/kg of Haemostop is given 3 to 4 times a day for 6 to 8 days.

Hereditary angioedema:

Some patients are aware of the onset 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 - 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:

Dosages should be reduced in patients with renal impairment. For patients with moderate to severe impaired renal function, the following dosages are recommended (see section 4.4).

Serum creatinine		Dose IV	Administration
µmol/l	mg/10 ml		
120 to 249	1,35 to 2,82	10 mg/kg BW	Every 12 hours
250 to 500	2,82 to 5,65	10 mg/kg BW	Every 24 hours
> 500	> 5,65	5 mg/kg BW	Every 24 hours

Children:

Data on efficacy and safety in children are limited.

Method of administration

Haemostop is given by slow intravenous infusion/injection over a period of at least five minutes. Administration by injection is usually changed to oral administration after a few days. Haemostop is only available in an IV formulation. For oral administration refer to relevant prescriber's information for oral preparations.

4.3 Contraindications

- Hypersensitivity to tranexamic acid or to any of the excipients of Haemostop listed in section 6.1.
- In cases of massive upper urinary tract haemorrhage, antifibrinolytics should be avoided to reduce the risk of ureteric obstruction.
- 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).
- History of convulsions.
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions).
- Patients with colour vision disorder.
- Thrombophlebitis, impaired liver function, subarachnoid haemorrhage.

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 Haemostop treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following intravenous (IV.) injection of Haemostop in high doses. With the use of the recommended lower doses of Haemostop, 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 Haemostop, 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 Haemostop 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 Haemostop, 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), Haemostop 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).

Patients with a previous history of thromboembolic disease should not be given Haemostop unless simultaneous treatment with anticoagulants can be given.

Haemostop 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 Haemostop (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 Haemostop in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available.

Renal impairment

Dosages should be reduced in patients with renal impairment (see section 4.2).

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 Haemostop. 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, Haemostop is not recommended during pregnancy.

Breastfeeding

Haemostop is excreted in human milk. Therefore, breastfeeding is not recommended.

Fertility

There are no clinical data on the effects of Haemostop 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 Haemostop include visual disturbances and dizziness. If applicable, patients should be advised against driving and handling machinery.

4.8 Undesirable effects

The ADRs reported from clinical studies and post-marketing experience are listed below according to system organ class.

a) Summary of adverse reactions

Frequent side effects reported include diarrhoea, vomiting and nausea. Allergic dermatitis is reported less frequently. Other reported side effects are with unknown frequency and include hypersensitivity reactions including anaphylaxis, convulsions, visual disturbance including impaired colour vision, malaise with hypotension and arterial or venous thrombosis at any site.

b) *Tabulated summary of adverse reactions*

MedDRA System Organ Class	**Frequency**	**Adverse Reaction**
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)
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*	Allergic dermatitis

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 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

No case of overdose has been reported.

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 A8.1 Coagulants, haemostatics

Pharmacotherapeutic group: Antihaemorrhagics, Antifibrinolytics, Amino acids

ATC code: B02AA02

Mechanism of action

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.

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 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.

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

Water for Injection

6.2 Incompatibilities

Haemostop should not be mixed with blood for transfusion or with solutions containing penicillin.

6.3 Shelf life

2 years

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

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C.

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 and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Do not freeze.

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

6.5 Nature and contents of container

Haemostop is supplied in Type I clear glass 5 mL ampoules in an outer carton, each ampoule containing 500 mg tranexamic acid. The ampoules are packed in pocket ampoule in unit boxes, five ampoules per box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Haemostop 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 Haemostop.

Haemostop 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

Equity Pharmaceuticals (Pty) Ltd.

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Nellmapius Drive

Irene

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0157

8. REGISTRATION NUMBER

52/8.1/0073

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 22 June 2021

10. DATE OF REVISION OF THE TEXT