PROPOSED PROFESSIONAL INFORMATION FOR FIBTIN INJECTION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FIBTIN INJECTION 500 mg/5 mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL ampoule contains 500 mg tranexamic acid.

Sugar free.

For the 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 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

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 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 FIBTIN INJECTION. After the operation, 25 mg/kg of FIBTIN INJECTION 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 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, given at the onset of heavy bleeding for the duration of the period.

Renal insufficiency:

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

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 (micromol/L)	Oral dose
120 – 250	15 mg/kg body weight twice daily
250 – 500	15 mg/kg body weight daily

> 500	7,5 mg/kg body weight daily

Children

Data on efficacy and safety in children are limited.

Method of administration

Tranexamic acid is given by slow intravenous injection.

Administration by injection is usually changed to oral administration after a few days. FIBTIN INJECTION is administered intravenously by slow injection over a period of at least five minutes.

Heparin solutions may be added to FIBTIN INJECTION. FIBTIN INJECTION should not be mixed with blood and infusion solutions containing penicillin (see section 6.6).

4.3 Contraindications

- Hypersensitivity to tranexamic acid or to any of the excipients listed in section 6.1.
- In cases of massive upper urinary tract haemmorhage, FIBTIN INJECTION 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.
- 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.

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).
- FIBTIN INJECTION should not be administered by the intramuscular route.
- FIBTIN INJECTION 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 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, blurred vision, 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 physician 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 FIBTIN INJECTION, 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), FIBTIN INJECTION should only be administered if there is a strong medical indication after consulting a medical practictioner experienced in haemostaseology and under strict medical supervision (see section 4.3).

FIBTIN INJECTION should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis (see section 4.5).

Tranexamic acid should not be administered concomitantly with Factor IX Complex Concentrates or Anti-inhibitor Coagulant Concentrates, as the risk of thrombosis may be increased.

Patients with menorrhagia (irregular menstrual bleeding) should not use FIBTIN INJECTION until the cause of the irregularity has been established.

Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with FIBTIN INJECTION (see section 4.3). If FIBTIN INJECTION 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 FIBTIN INJECTION 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 FIBTIN INJECTION. There is a theoretical risk of increased thrombus-formation potential, such as with oestrogens. Alternatively, the antifibrinolytic action of FIBTIN INJECTION may be antagonised with thrombolytic medicines.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy

The safety of FIBTIN INJECTION has not been established in pregnancy.

FIBTIN INJECTION crosses the placenta, therefore the usual caution with use of medicines in pregnancy should be observed.

Lactation

FIBTIN INJECTION passes into breastmilk to a concentration of approximately one hundredth of the concentration in the maternal blood. Caution should be exercised when FIBTIN INJECTION is given to nursing women.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

FIBTIN INJECTION can cause side effects, such as dizziness and vision problems, and can affect the ability to drive a vehicle and use machines. Caution is advised when driving a vehicle or operating machinery until the effects of FIBTIN INJECTION are known.

4.8 Undesirable effects

Immune system disorders

Frequency unknown: hypersensitivity reactions including anaphylaxes

Nervous system disorders

Frequency unknown: dizziness, convulsions particularly in case of misuse (see sections 4.3 and 4.4)

Eye disorders

Frequency unknown: colour vision disturbances, retinal/artery occlusion

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

Gastro-intestinal disorders

Frequent: nausea, vomiting, diarrhoea (digestive effects may disappear when the dosage is reduced)

Skin and subcutaneous tissue disorders

Less frequent: allergic dermatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of FIBTIN INJECTION is important. It allows continued monitoring of the benefit/risk balance of FIBTIN INJECTION. Health care providers are asked to report any suspected adverse reactions 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

Symptoms of overdose may be 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 symptomatic and 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.

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.

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 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.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

Before opening: 3 years.

Store at or below 25 °C.

After first opening:

FIBTIN 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, FIBTIN INJECTION 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

Do not freeze.

Protect from light.

Keep the ampoules in the outer carton until required for use.

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

6.5 Nature and contents of container

5 x 5 ml Type I clear glass ampoules packed into a PVC trays and enclosed in an outer carton.

10 x 5 ml Type I clear glass ampoules packed into two PVC trays and enclosed in an outer carton.

Not all packs or pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

FIBTIN INJECTION may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions. Heparin solutions may be added to FIBTIN INJECTION. FIBTIN INJECTION should not be mixed with blood and infusion solutions containing penicillin.
FIBTIN INJECTION 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

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

48/8.1/0251

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTORISATION

28 April 2021

10. DATE OF REVISION OF THE TEXT

28 April 2021

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