1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

IMMATRA (injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each 5 ml ampoule contains 500 mg tranexamic acid. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

A clear colourless solution, free from visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Short term use in the treatment of hyphaema and in patients with established coagulopathies who are undergoing minor surgery.
2. Management of dental extraction in haemophiliacs.
3. Hereditary angioedema
4. Menorrhagia

4.2 Posology and method of administration

Posology

IMMATRA is given by slow intravenous infusion/injection. Administration by injection is usually changed to oral 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:

Factor VIII and Factor IX should be given as well as IMMATRA. After the operation, 25 mg/kg of IMMATRA 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:

IMMATRA solution for injection is administered intravenously by slow injection over a period of at least five minutes. For intravenous infusion, IMMATRA solution for injection may be mixed with electrolyte solutions, carbohydrate solutions, Aminosol and dextran solutions. Heparin solutions may be added to IMMATRA solution for injection. IMMATRA solution for injection should not be mixed with blood and infusion solutions containing penicillin.

Method of administration

The administration is strictly limited to slow intravenous injection.

4.3 Contraindications

Hypersensitivity to tranexamic acid or to any of the excipients of IMMATRA

In cases of massive upper urinary tract haemorrhage, antifibrinolytics should be avoided to reduce the risk of ureteric obstruction.

Patients with a pronounced thrombotic tendency or colour vision disorder should not be given IMMATRA.

Thrombophlebitis, impaired liver function and subarachnoid bleeding.

4.4 Special warnings and precautions for use

Intravenous injection or infusions should be given very slowly (maximum 1mL per minute)

Tranexamic acid should not be administered by 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.

Haematuria

In case of haematuria from the upper urinary tract, there is a risk for urethral obstruction.

The safety of IMMATRA has not been established in pregnancy.

IMMATRA passes into breast milk at a concentration of a hundredth of the corresponding serum levels. Caution should be exercised when IMMATRA is given to nursing women.

For patients in renal failure, IMMATRA 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 (μmol/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

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

For patients who are to receive continuous treatment with IMMATRA 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.

Medicines with actions on haemostasis should be given with caution to patients on antifibrinolytic therapy. The potential for thrombus formation may be increased by oestrogens as contained in oral contraceptives, for example, or the action of the antifibrinolytic antagonised by compounds such as the thrombolytics.

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. Medicinal products that act on haemostasis should be given with caution to patients treated with IMMATRA. 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

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

Pregnancy

There is insufficient clinical data on the use of IMMATRA in pregnant women.

As a result, although studies in animals do not indicate teratogenic effects, as precaution for use, IMMATRA is not recommended during pregnancy.

Breast-feeding

IMMATRA is excreted in human milk. Therefore, breast-feeding 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

Patients who experience disturbances in vision or dizziness should not drive or operate any machines.

4.8 Undesirable effects

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

Tabulated list 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. Frequency not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Immune system disorders	Frequency not known	Hypersensitivity reactions including anaphylaxis
Nervous system disorders	Frequency not known	Convulsions particularly in case of misuse (refer to sections 4.3 and 4.4)
Eye disorders	Frequency not known	Visual disturbances including impaired colour vision
Vascular disorders	Frequency not known	Malaise with hypotension with or without loss of consciousness (generally following a too fast intravenous injection, Arterial or venous embolism 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA 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

No case of overdose has been reported.

Signs and symptoms may include dizziness, headache, hypotension, and convulsions. It has been shown that convulsions tend to occur at higher frequency with increasing dose.

Management of overdose should be supportive and symptomatic

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, 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.

5.2 Pharmacokinetic properties

Peak plasma concentrations of IMMATRA are obtained rapidly after a short intravenous infusion after which plasma concentrations decline in a multi-exponential manner.

Distribution

The plasma protein binding of IMMATRA is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. IMMATRA does not bind to serum albumin. The initial volume of distribution is about 9 to 12 litres.

IMMATRA 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 µg/mL while that in cord blood ranged 4-31 µg/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.

Excretion

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.

Special populations

Plasma concentrations increase in patients with renal failure.

No specific dose effect or PK 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 and toxicity to reproduction.

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

IMMATRA solution for injection should not be added to blood for transfusion, or to injections containing penicillin.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

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

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.

Store in the original package

Keep out of reach of children.

6.5 Nature and contents of container

Clear colourless solution for Injection packed in 5 ml fiolax clear glass ampoule made of USP Type I glass having white OPC dot with green & yellow band.

The primary packs are then packed in carton along with leaflet. Pack size of 1, 5, 10, 20

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

The product is for single use only. Any unused medicinal product or waste material should be disposed

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (PTY) LTD

Unit 1, 96 Hartley Road

Durban, 4091

8 REGISTRATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT