PROPOSED ANNOTATED PROFESSIONAL INFORMATION:
DR. REDDY'S LABORATORIES (PTY) LTD.
MORWAK IV™ 500 (injection)
17.08.2021

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MORWAK IV™ 500, sterile solution for IV injection or infusion (ampoule)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL ampoule contains 500 mg tranexamic acid (100mg/mL)

3. PHARMACEUTICAL FORM

A clear, colourless solution in a 5 mL clear glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Tranexamic acid IV is administered by slow intravenous infusion or injection.

Traumatic hyphaema:

1,0 g to 1,5 g (two (2) to three (3) tablets) every eight (8) hours for six (6) to seven (7) days.

- **Patients with established coagulopathies undergoing minor surgery:**

Conisation of the cervix:

1,0 g to 1,5 g (two (2) to three (3) tablets) every eight (8) to twelve (12) hours for twelve (12) days post operatively.

- **Dental operations/extractions:**

Factor VIII and Factor IX should be administrated with MORWAK IV™ 500. MORWAK IV™ 500 25mg/kg is administered, three (3) to four (4) times a day for six (6) to eight (8) days.

- **Hereditary angioneurotic oedema:**

Patients aware of onset of illness are administered 1,0 g to 1,5 g, (two (2) to three (3) tablets) two (2) to three (3) times a day for some days. May be used prophylactically. Some patients may be treated continually at this dosage. Other patients receive continuous treatment at this dosage.

- **Menorrhagia:**

Tranexamic acid IV should only be initiated at the onset of heavy bleeding: at a dosage of 1,0 g to 1,5 g (two (2) to three (3) tablets) three (3) to four (4) times a day.

Special population

Elderly

No reduction in dosage is necessary unless there is any evidence of renal failure (see section 4.4).

Renal impairment

Dosages should be reduced in patients with renal impairment because of the risk of accumulation. The following dosages are recommended for patients with moderate to severe renal impairment. The dosage of tranexamic acid should be reduced according to the serum creatinine levels:

Serum creatinine measurement		**Dose IV**	**Administration**
Creatinine Cl	**mg/10 mL**		
Mild >50-80 mL/Min	1,35 to 2,82	10 mg/kg body weight	Twice daily
Moderate > 30-50mL/min	2,82 to 5,65	10 mg/kg body weight	Daily
Severe < 30mL/min	> 5,65	5 mg/kg body weight	Daily

Method of administration

Tranexamic acid is given as a slow intravenous injection/infusion, strictly limited to a maximum of one (1) mL per minute over a period of at least five (5) minutes.

Tranexamic acid may be mixed, with suitable precautions to prevent microbial contamination, with sterile solutions for infusion such as electrolyte, carbohydrate, Aminosol and dextran solutions. The solutions must be used immediately or on the day of preparation.

Heparin may be added to Tranexamic acid solution for injection.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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).
- Severe renal impairment (risk of accumulation).
- History of convulsions.
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions).

4.4 Special warnings and precautions for use

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 IV, 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 tranexamic acid, regular ophthalmologic examinations (eye examinations including visual acuity, colour vision, fundus, visual field inter alia.) are indicated. With pathological ophthalmic changes, particularly with diseases of the retina, the medical practitioner, after consulting a specialist, must decide on the necessity for the long-term use of tranexamic acid in each individual case.

Haematuria

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

Thromboembolic events

Risk factors of thromboembolic disease should be considered before administration of tranexamic acid IV. 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), tranexamic acid 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).

Tranexamic acid 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 tranexamic acid (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 1g tranexamic acid is frequently sufficient to control bleeding. Administration of tranexamic acid in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available.

Patients with subarachnoid bleeding or a history of subarachnoid bleeding should not use MORWAK IV™ 500.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

Medicines that act on haemostasis should be given with caution to patients on antifibrinolytic therapy such as MORWAK IV™ 500.

The concomitant use of MORWAK IV™ 500 with highly activated prothrombin products is not recommended.

The risk of thrombosis may be increased if MORWAK IV™ 500 is given with factor IX complex concentrates or factor VIII inhibitor bypassing fraction. These combinations are not recommended.

Antifibrinolytic medicines such as MORWAK IV™ 500 and thrombolytic medicines have antagonistic effects and concomitant use may reduce the efficacy of both.

The potential for thrombus formation may be increased if MORWAK IV™ 500 is given with oestrogen.

MORWAK IV™ 500 therapy combined with chlorpromazine in subarachnoid haemorrhage is not recommended.

4.6 Fertility, pregnancy and lactation

Women with childbearing potential

Women with childbearing potential must use effective contraception during treatment with MORWAK IV™.

Pregnancy

Safety of MORWAK IV™ has not been established in pregnancy, there is no or limited amount of data from the use of tranexamic acid in pregnant women. Although studies in animals do not indicate teratogenic effects, as a precaution for use, tranexamic acid IV is not recommended during the first trimester of pregnancy.

Limited clinical data on the use of tranexamic acid in different clinical haemorrhagic settings during the second and third trimesters did not identify deleterious effects on the foetus.

Lactation

MORWAK IV™ is excreted in human breast milk. Caution must be exercised in recommending MORWAK IV™ in lactating women and the expected benefit must justify the potential risks to the infant.

Fertility

There is no clinical data on the effects of tranexamic acid 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.

The rapid administration of MORWIK IV™ may lead to dizziness or syncope or in patients with history of convulsions. Caution should be exercised in these patients and a general warning issued to patient's post-administration of tranexamic acid IV.

4.8 Undesirable effects

Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency.

Immune system

Frequency unknown: Hypersensitivity reactions including anaphylaxis.

Nervous system disorders

Frequency unknown: Convulsions particularly in the case of inappropriate administration (see sections 4.3 and 4.4).

Eye disorders

Frequency unknown: Visual disturbances including transient impaired colour vision.

Vascular disorders

Frequency unknown: Malaise with hypotension, with or without loss of consciousness (generally following a rapid intravenous injection, exceptionally after oral administration), arterial or venous thrombosis at any sites. Cases of dizziness have been reported.

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. 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

Signs and symptoms may include dizziness, headache, nausea and vomiting, diarrhoea and convulsions. Faintness and hypotension may occur.

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

Management of overdose should be supportive and symptomatic.

Maintain a high fluid intake and diuresis to promote renal excretion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 8.1 Coagulants, haemostatics

Tranexamic acid is an inhibitor of fibrinolysis as it is a lysine analogue that competes for lysine binding sites on both plasminogen and plasmin. In the fibrinolysis process, plasminogen is converted to plasmin by plasminogen activators; plasmin breaks down the fibrin matrix of blood clots. Tranexamic acid can therefore reverse haemorrhage in conditions associated with excessive fibrinolysis.

5.2 Pharmacokinetic properties

Absorption

Peak plasma concentrations are reached rapidly after slow intravenous administration; concentrations then decline in a multi-exponential manner.

Distribution

The plasma protein binding of tranexamic acid is about 3 % at therapeutic plasma levels. This 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 to 53 microgram/mL while that in cord blood ranged 4 to 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

Tranexamic acid is excreted unchanged mainly in the urine. Elimination via glomerular filtration is the main route of elimination.

Renal clearance is equal to plasma clearance (110 to 116 mL/min). Excretion is about 90 % within the first 24 hours after intravenous administration of 10 mg/kg body weight. The elimination half-life is approximately 3 hours.

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

Sterile water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Unopened powder vial:

2 years

After first opening:

The solution for injection/infusion is for single use only.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C, however, from a microbiological point of view, the product should be used immediately. If not used immediately, and any unused solution must be discarded.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light. Do not freeze.

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

For storage conditions after first opening of the medicinal product, (see section 6.3).

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

MORWAK IV™ 500 is packed in a 5 mL, Type-I clear, colourless, glass ampoule with a one-point-cut, blue dot just above the neck of the ampoule. The ampoules are securely packed in printed cardboard cartons (5 x 5 mL ampoules per carton).

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBER

48/8.1/1017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 August 2021