**PACKAGE INSERT**

## 1. PRODUCT NAME

Tafixyl 100 mg / ml Solution for Injection
Active Ingredient: Tranexamic acid

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 mg of tranexamic acid
One ampoule of 5 ml injection contains 500 mg of tranexamic acid
One ampoule of 10 ml injection contains 1000 mg of tranexamic acid

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection
Clear liquid free of particles in colourless glass ampoule
pH: 6.5 – 8

## 4. CLINICAL

### 4.1 Therapeutic indications

Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis.

Local fibrinolysis may occur in the following conditions: Menorrhagia, prostatectomy and bladder surgery, haematuria, gastrointestinal haemorrhage, epistaxis, ulcerative colitis, conisation of the cervix, and dental extraction in patients with coagulopathies.

General fibrinolysis may occur in the following conditions and situations: Prostatic and pancreatic cancer, after thoracic and other major surgery, in obstetrical complications such as ablatio placentae and postpartum haemorrhage, leukemia, liver diseases, in connection with thrombolytic therapy with streptokinase.

Hereditary angioneurotic oedema.

### 4.2 Posology and method of administration

*Tranexamic oral tablet is unavailable in this brand however, is available in other brands. Where correct dosing require the oral tablet, refer to the specific product information of these brands for their complete dosage and administration instructions.*

**TRANEXAMIC ACID MUST NOT BE USED FOR INTRATHECAL OR EPIDURAL ADMINISTRATION**

The recommended standard dose is 5 mL to 10 mL by slow intravenous injection at a rate of 1 mL/minute or 2 to 3 tablets of 0.5 g 2 to 3 times daily.

For the indications listed below, the following doses are recommended:

*General fibrinolysis*: 1.0 g (2 ampoules of 5 mL) by slow intravenous injection every 6 to 8 hours.

*Prostatectomy*: 0.5 g to 1.0 g (1 to 2 ampoules of 5 mL) by slow intravenous injection every 6 to 8 hours (the first injection being given during the operation) for the first 3 days after surgery, thereafter 1 g to 1.5 g orally (2 to 3 tablets) 2 to 3 times daily until macroscopic haematuria is no longer present.

*Haematuria*: 1 g to 1.5 g orally (2 to 3 tablets) 2 to 3 times daily until macroscopic haematuria is no longer present.

*Epistaxis*: 1.5 g orally (3 tablets) 3 times a day should be administered for 4 to 10 days. Tranexamic acid solution for injection may be applied topically to the nasal mucosa of patients suffering from epistaxis. This can be done by soaking a gauze strip in the solution, and then packing the nasal cavity.

*Menorrhagia*: 1 g to 1.5 g orally (2 to 3 tablets) 3 to 4 times daily for 3 to 4 days. Tranexamic acid therapy is initiated when bleeding has become profuse.

*Conisation of the cervix*: 1.5 g orally (3 tablets) 3 times a day for 12 to 14 days postoperatively.

*Dental extraction in patients with coagulopathies*: Immediately before surgery, Tranexamic acid 10 mg/kg body weight should be given intravenously. After surgery, 25 mg/kg body weight is given orally 3 to 4 times daily for 6 to 8 days. Coagulation factor concentrate might be necessary to administrate. This decision should be taken after consulting specialists on coagulation.

*Hereditary angioneurotic oedema*: 1 g to 1.5 g orally (2 to 3 tablets) 2 to 3 times daily as intermittent or continuous treatment, depending on whether the patient has prodromal symptoms or not.

For patients with moderate to severe impaired renal function, the following dosages are recommended:

| **Serum Creatinine (µmol / l)** | **Oral Dose** | **Intravenous Dose** |
|---|---|---|
| 120 - 249 | 15 mg/kg body weight twice daily | 10 mg/kg body weight twice daily |
| 250 - 500 | 15 mg/kg body weight daily | 10 mg/kg body weight daily |
| > 500 | 7.5 mg/kg body weight daily | 5 mg/kg body weight daily |

*Hepatic impairment*: No dosage adjustment is required in patients with hepatic impairment.

*Elderly*: No reduction in dosage is necessary unless there is evidence of renal failure.

## 4.3 Contraindications

Intrathecal and epidural administration of tranexamic acid is contraindicated.

Active thromboembolic disease, such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis.

Subarachnoid haemorrhage. The limited clinical experience shows that a reduced risk for re-bleeding is offset by an increase in the rate of cerebral ischaemia.

Hypersensitivity to tranexamic acid or any of the ingredients.

## 4.4 Special warnings and precautions for use

The indications and the above method of administration should be followed scrupulously:
- Intravenous injections should be given very slowly
- Tranexamic acid should not be administered intramuscularly.

Seizures

There have been reports of seizures in association with treatment with tranexamic acid. In the coronary artery bypass surgery, the majority of these cases were reported following the intravenous injection of tranexamic acid in high doses. With the use of lower doses recommended tranexamic acid, the incidence of post-operative seizures was the same as in untreated patients.

Visual disturbances

Attention should be paid to possible visual disorders including visual impairment, blurred vision, impaired colour vision and, if necessary, treatment should be discontinued. With continued long-term use of tranexamic acid solution for solution for injection, regular eye exams (eye checks including visual acuity, colour vision, fundus, visual field etc.) are indicated. With pathological ocular changes, particularly with retinal disease, the doctor should decide case by case basis after consulting an expert on the need to use solution for injection of tranexamic acid in the long term.

Haematuria

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

Thromboembolic events

Before use of tranexamic acid, risk factors of thromboembolic disease should be considered. In patients with a history of thromboembolic disease or in patients with increased incidence of thromboembolic events in the family (patients at high risk of thrombophilia), tranexamic acid injection should only be given if there is a strong

medical indication after consulting a doctor specializing in haemostaseology and under close medical supervision (see section 4.3 Contraindications).

Tranexamic acid should be administered with caution in patients on oral contraceptives given the increased risk of thrombosis (see section 4.5). If tranexamic acid has to be used in these patients, advise them to use an effective alternative (nonhormonal) contraceptive method.

Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should not, in most cases, be treated with tranexamic acid (see Section 4.3). If tranexamic acid is administered, it must be restricted to those in whom there is predominantly activation of the fibrinolytic system with severe acute haemorrhage. Characteristically, the blood 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; normal platelet count. The above premise assumes that the underlying disease state itself does not modify the various elements in this profile. In such cases a single acute dose of 1 g of tranexamic acid is often enough to control the bleeding. The administration of tranexamic acid in DIC should be considered when appropriate haematological laboratory facilities and expertise are available.

Others

Patients with irregular menstrual bleeding should not use tranexamic acid until the cause of the irregularity has been established. If menstrual bleeding is not adequately reduced by tranexamic acid, an alternative treatment should be considered.

The blood levels are increased in patients with renal insufficiency. Therefore a dose reduction is recommended (see section Dosage and method of administration).

Clinical experience with tranexamic acid in menorrhagic children under 15 years of age is not available.

Serious events including death were reported in patients erroneously treated with tranexamic acid via intrathecal or epidural injection.

**4.5 Drug interactions and other forms of interaction**

No interaction studies have been performed. Simultaneous treatment with anticoagulants should be done under strict supervision of a physician experienced in this area. Medications that act on haemostasis should be administered with caution to patients treated with tranexamic acid. There is a theoretical risk of increased potential to form a thrombus, such as oestrogen. Alternatively, the anti-fibrinolytic effect of the drug can be antagonized by thrombolytic drugs.

**4.6 Pregnancy and lactation**

Pregnancy

Available data from published studies, case series and case reports with tranexamic acid use in pregnant women in the second and third trimester and at the time of delivery have not clarified whether there is a drug-associated risk of miscarriage or adverse maternal or fetal outcomes. There are cases of fetal structural abnormalities that resulted in death of the newborn following administration of tranexamic acid to the mother during conception or the first trimester of pregnancy; however, due to other confounding factors the risk of major birth defects with use of tranexamic acid during pregnancy is not clear.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3 Preclinical safety data).

The estimated background risk for major birth defects and miscarriage for the indicated human population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

It is not known whether tranexamic acid use in pregnant women may cause a drug-associated risk of miscarriage or adverse maternal or fetal outcomes. For decisions regarding the use of tranexamic acid during pregnancy, the potential risk of tranexamic acid administration on the fetus should always be considered along with the mother's clinical need for tranexamic acid; an accurate risk-benefit evaluation should drive the treating physician's decision.

Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg/kg to pregnant women is about 30 mg/L, as high as in the maternal blood.

There were 13 clinical studies that described fetal and/or neonatal functional issues such as low Apgar score, neonatal sepsis, cephalohematoma and 9 clinical studies that discussed alterations to growth including low birth weight and preterm birth at 22-36 weeks of gestation in fetuses and infants exposed to tranexamic acid in utero.

Lactation

Published literature reports the presence of tranexamic acid in human milk. There are no data on the effects of tranexamic acid on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tranexamic acid and any potential adverse effects on the breastfed child from tranexamic acid or from the underlying maternal condition.

Fertility

There are no clinical data on the effects of tranexamic acid on fertility.

**4.7 Effects on ability to drive and use machines**

Tranexamic acid may cause dizziness and therefore may influence the ability to drive or use machines.

**4.8 Undesirable effects**

Adverse drug reactions reported in clinical trials, post-marketing experience are listed below according to organ class system.

**Tabulated list of adverse reactions**

Adverse reactions are presented in the table below. Adverse events are listed according to MedDRA primary system organ class. Within each organ class system, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies were defined as follows: very common (≥1 / 10); common (≥1 / 100 to <1/10); uncommon (≥1 / 1,000 to <1/100), not known (frequency cannot be estimated from the available data).

| **MedDRA system organ class** | **Frequency** | **Adverse events** |
|---|---|---|
| Skin and subcutaneous tissue disorders | Uncommon | - Allergic dermatitis |
| Gastrointestinal disorders | Frequent | - Diarrhea<br>- Vomiting<br>- Nausea<br>- Gastrointestinal disturbances occur in more than 30% of the patients at an oral administration of 6 g/day. The disturbances disappear when the dose is reduced. |
| Nervous system disorders | Unknown | - Seizures particularly in the event of misuse (see sections 4.3 and 4.4)<br>- Dizziness |
| Eye disorders | Unknown | - visual disturbances including impaired colour vision |
| Vascular disorders | Unknown | - Malaise with hypotension with or without loss of consciousness (usually after a given intravenous too fast, exceptionally after oral administration)<br>- Giddiness, nausea and hypotension occur when the intravenous injection is too fast<br>- Arterial or venous thrombosis at any site |
| Immune system disorders | Unknown | - Hypersensitivity reactions including anaphylaxis |

**Reporting of suspected adverse reactions**
The reporting of suspected adverse reactions after authorization of the product is important, since it allows continuous monitoring of the drug benefit-risk balance.

**4.9 Overdose**

Symptoms

Nausea, diarrhoea, dizziness, headache, and convulsions. Orthostatic symptoms and

hypotension may occur.
Risk of thrombosis in predisposed individuals.

Treatment of Overdosage

If justified, initiate vomiting, then gastric lavage, charcoal therapy and symptomatic treatment. Maintain adequate diuresis.

Toxicity

37 g of tranexamic acid caused mild intoxication in a 17-year-old after gastric lavage.

## 5. Pharmacological Properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 4.4.1 - Antihaemorrhagics, Antifibrinolytics, Amino acids
ATC code: B02AA02

Tranexamic acid is a competitive inhibitor of plasminogen activation, and at much higher concentrations, a noncompetitive inhibitor of plasmin, i.e., actions similar to aminocaproic acid. Tranexamic acid is about 10 times more potent in vitro than aminocaproic acid.

Tranexamic acid binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds. Tranexamic acid in a concentration of 1 mg/mL does not aggregate platelets in vitro.

Tranexamic acid in concentrations up to 10 mg/mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. However, tranexamic acid in concentrations as low as 1 mg/mL can prolong the thrombin time.

### 5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations are obtained quickly after a short intravenous infusion after which decrease plasma concentrations of multiexponential manner.

Distribution

The plasma protein binding of tranexamic acid is from about 3% to therapeutic plasma levels, and appears to be completely explained by its binding to plasminogen. Tranexamic acid is not bound to serum albumin. The initial volume of distribution is about 9 to 12 litres.

Tranexamic acid crosses the placenta. After administration of an intravenous injection

of 10 mg / kg to 12 pregnant women, the concentration of tranexamic acid in serum ranged from 10-53 ug / mL while the umbilical cord blood ranged between 4-31 ug / ml. Tranexamic acid diffuses rapidly into the joint fluid and synovium. After administration of an intravenous injection of 10 mg / kg to 17 patients undergoing knee surgery, concentrations in joint fluids were similar to those observed in the corresponding serum samples. The concentration of tranexamic acid in a number of other tissues is observed in a fraction of blood (milk, one hundredth, cerebrospinal fluid, one-tenth, aqueous, one-tenth). Tranexamic acid was detected in semen which inhibits the fibrinolytic activity but does not influence the migration of sperm. An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to 7 or 8 hours.

Elimination

It is mainly excreted in the urine unchanged. Urinary excretion via glomerular filtration is the major route of elimination. The renal clearance is equal to the clearance (110-116 ml / min). The excretion of tranexamic acid is about 90% in the first 24 hours after intravenous administration of 10 mg / kg body weight. The elimination half-life of tranexamic acid is about 3 hours.

Special populations

Plasma concentrations increase in patients with renal failure.

**5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity.

Animal Toxicology and/or Pharmacology

Nonclinical studies have shown a retinal toxicity associated with tranexamic acid. Toxicity is characterised by retinal atrophy commencing with changes to the retinal pigmented epithelium and progressing to retinal detachment in cats. The toxicity appears to be dose related, and changes are partially reversible at lower doses. Effects (some fully reversible) are seen in cats at clinically relevant doses, effects in dogs are only observed at multiples of the clinical dose. Studies suggest that the underlying mechanism may be related to a transient retinal ischaemia at higher dose exposures, linked to the known sympathomimetic effect of high plasma levels of tranexamic acid. The clinical relevance of these findings is unknown.

The epileptogenic activity was observed in animals with intrathecal use of tranexamic acid.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium hydroxide
Hydrochloric acid

Nitrogen
Injecting Water

**6.2 Incompatibilities**

Tafixyl solution for injection can be mixed with 0.9% sodium chloride solution, 5% glucose solution, Ringer's solution (compound sodium chloride). The mixture should be used immediately after preparation. If storage is necessary, the mixture should be stored at 2°C – 8°C for a maximum of 24 hours. Mixture not used within 24 hours of preparation, should be discarded.

Tranexamic acid injection may be mixed with heparin.

Tranexamic acid injection should NOT be added to blood for transfusion or to injections containing penicillin.

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

Keep the ampoules for injection in the original package

**6.5 Nature and contents of container and special equipment for use, administration or implantation**

Type I transparent glass ampoule for injection
One ampoule of 5 ml injection contains 500 mg of tranexamic acid.
One ampoule of 10 ml injection contains 1000 mg of tranexamic acid.

5 ampoules/pack

**6.6 Special precautions for disposal**

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

**7. MARKETING AUTHORIZATION HOLDER**

Novem Healthcare Pte Ltd
23 New Industrial Road #03-08
Solstice Business Center
Singapore 536209

**8. DATE OF REVISION OF TEXT**

Jun 2022