## 1. NAME OF THE MEDICINAL PRODUCT

**HEMSAMIC TABLETS**

## 2. Generic Name

**TRANEXAMIC ACID TABLETS BP 500 mg**

## 3. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet Contains:

Tranexamic Acid BP.....500 mg

Excipients .....QS

## 4. PHARMACEUTICAL FORM

Solid Oral Dosage Form. Film coated Tablets

### Clinical particulars

### 4.1 Therapeutic indications

Tranexamic Acid 500 mg Tablets are indicated for short term use for haemorrhage or risk of haemorrhage in those with increased fibrinolysis or fibrinogenolysis. Local fibrinolysis as occurs in the following conditions:

- Prostatectomy and bladder surgery
- Menorrhagia
- Epistaxis
- Conisation of the cervix
- Traumatic hyphaema
- Management of dental extraction in haemophiliacs.
- Hereditary angioneurotic oedema.

### 4.2 Posology and method of administration

**Condition for administration:** Oral.

Posology

**Adults**

**Local Fibrinolysis:** The recommended standard dose is 15-25mg/kg bodyweight (i.e. 2-3 tablets) two to three times daily. For the indications listed below the following doses may be used:

1 **a) Prostatectomy:** Prophylaxis and treatment of haemorrhage in high risk patients should commence pre- or post-operatively with tranexamic acid injection; thereafter 2 tablets three to four times daily until

macroscopic haematuria is no longer present.

1 **b) Menorrhagia:** Recommended dosage is 2 tablets 3 times daily as long as needed for up to 4 days. If very heavy menstrual bleeding, dosage may be increased. A total dose of 4g daily (8 tablets) should not be exceeded. Treatment with Tranexamic acid should not be initiated until menstrual bleeding has started.

1 **c) Epistaxis:** When repeated bleeding is anticipated oral therapy (2 tablets three times daily) should be administered for 7 days.

1 **d) Cervix Conisation:** 3 tablets three times daily.

1 **e) Traumatic Hyphaema:** 2-3 tablets 3 times daily. The dose is based on 25mg/kg three times a day.

2. **Haemophilia:** In the management of dental extractions 2-3 tablets every eight hours. The dose is based on 25mg/kg.

3. **Hereditary angioneurotic oedema:** Some patients are aware of the onset of illness; suitable treatment for these patients is intermittently 2-3 tablets two to three times daily for some days. Other patients are treated continuously at this dosage.

**Paediatric population:** In children, **for current approved indications as described above,** the dosage is in the region of 20 mg/kg/day. However, data on efficacy, posology and safety for these indications are limited.

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

**Renal insufficiency:** By extrapolation from clearance data relating to the intravenous dosage form, the following reduction in the oral dosage is recommended for patients with mild to moderate renal insufficiency:

| **Serum Creatinine (µmol/l)** | **Oral Dose** | **Dose Frequency** |
|---|---|---|
| 120-249 | 15 mg/kg body weight | twice daily |
| 250-500 | 15 mg/kg body weight | daily |

## 4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section
- Active thromboembolic disease.
- History of venous or arterial thrombosis.
- Fibrinolytic conditions following consumption coagulopathy.
- Severe renal impairment because of risk of accumulation.
- History of convulsions.

## 4.4 Special warnings and precautions for use

Caution is advised in treating those with massive haematuria from the upper urinary tract, especially in haemophiliacs, as there have been some cases of ureteric obstruction. Not to be used when disseminated intravascular coagulation is in progress. The blood levels are increased in patients with renal insufficiency. Therefore a dose reduction is recommended.

In those patients requiring long term administration of tranexamic acid, such as those with hereditary angioneurotic oedema, regular eye examinations (e.g. visual acuity, slit lamp, intraocular pressure, visual fields) and liver function tests should be performed.

Patients who experience visual disturbance should be withdrawn from treatment.

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

Patients with a previous thromboembolic event and a family history of thromboembolic disease (patients with thrombophilia) should use Tranexamic Acid Tablets only if there is a strong medical indication and under strict medical supervision.

The use of tranexamic acid in cases of increased fibrinolysis due to disseminated intravascular coagulation is not recommended.

Clinical experience with Tranexamic Acid Tablets in menorrhagic children under 15 years of age is not available.

The indications and method of administration indicated above should be followed strictly:

• In case of haematuria of renal origin, there is a risk of mechanical anuria due to formation of a ureteral clot.

• In renal insufficiency leading to a risk of accumulation, the dosage of tranexamic acid should be reduced according to the serum creatinine level.

- serum creatinine between120 and 250 µmol/l,: TXA iv 10 mg/kg twice daily.

- serum creatinine between 250 and 500 µmol/l: TXA iv 10 mg/kg once daily (every 24 hours).

- serum creatinine > 500 µmol/l, TXA iv 10 mg/kg every other day (every 48 hours).

• Before use of TXA, risk factors of thromboembolic disease should be investigated.

• Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis

## 4.5 Interaction with other medicinal products and other forms of interaction

Some products that may interact with this drug include: "blood thinners" (anticoagulants such as warfarin, heparin), drugs that prevent bleeding (including factor IX complex, anti-inhibitor coagulant concentrates), estrogens, hormonal birth control (such as pills, patch, ring), tibolone, tretinoin.

Check all prescription and nonprescription medicine labels carefully since many medications contain pain relievers/fever reducers (NSAIDs such as aspirin, ibuprofen, naproxen) that may increase risk of bleeding.

Low-dose aspirin should be continued if prescribed for specific medical reasons such as heart attack or stroke prevention (usually 81-162 milligrams a day).

## 4.6 Pregnancy and Lactation

### Pregnancy

### Pregnancy (Category B)

Reproduction studies performed in mice, rats, and rabbits have not revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid.

There are no adequate and well-controlled studies in pregnant women. However, tranexamic acid is known to pass the placenta and appears in cord blood at concentrations approximately equal to maternal concentration. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Nursing Mothers

Tranexamic acid is present in the mother's milk at a concentration of about a hundredth of the corresponding serum levels. Caution should be exercised when Tranexamic Acid Injection is administered to a nursing woman.

## 4.7 Effects on ability to drive and use machines

Tranexamic acid has no or negligible influence on the ability to drive and use machines

## 4.8 Undesirable effects

### Side effects:

Side effects are uncommon and include gastrointestinal effects, dizziness, fatigue, headache, and hypersensitivity reactions. This medication needs to be used cautiously in people with kidney disease and who are at a high risk for blood clots. Tranexamic acid is safe to use in pregnant women. However, caution should be used in lactating women.

**Adverse Reactions:**

Adverse events are listed below by system organ class and frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Immune system disorders

*Very rare:* Hypersensitivity reactions including anaphylaxis

Nervous System Disorders

*Very rare:* Convulsions, particularly in case of misuse

Eye disorders

*Rare:* Colour vision disturbances, retinal vein/artery occlusion

Vascular disorders

*Rare:* Thromboembolic events

*Very rare:* Arterial or venous thrombosis at any sites. Malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration).

Gastro-intestinal disorders

*Very rare:* Digestive effects such as nausea, vomiting and diarrhoea, may occur but disappear when the dosage is reduced.

Skin and subcutaneous tissue disorders

*Rare:* Allergic skin reactions

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### 4.9 Overdose

No cases of overdosage have been reported. Symptoms may be nausea, vomiting, orthostatic symptoms and/or hypotension. Initiate vomiting, then stomach lavage, and charcoal therapy. Maintain a high fluid intake to promote renal excretion. There is a risk of thrombosis in predisposed individuals. Anticoagulant treatment should be considered.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamics properties

**Pharmacotherapeutic group**:

Tranexamic acid is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin. 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 per mL does not aggregate platelets in vitro. In patients with hereditary angioedema, inhibition of the formation and activity of plasmin by tranexamic acid may prevent attacks of angioedema by decreasing plasmin-induced activation of the first complement protein (C1).

Tranexamic acid competitively inhibits activation of plasminogen (via binding to the kringle domain), thereby reducing conversion of plasminogen to plasmin (fibrinolysin), an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. Tranexamic acid also directly inhibits plasmin activity, but higher doses are required than are needed to reduce plasmin formation.

## 5.2 Pharmacokinetic properties

**Absorption**

Peak plasma Tranexamic acid concentration is obtained immediately after intravenous administration (500mg). Then concentration decreases until the 6th hour. Elimination half-life is about 3 hours.

Absorption from the human gastrointestinal tract is not complete (40%).

Tranexamic acid binds considerably more strongly than EACA to both the strong and weak sites in the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds. The pharmacological significance of the binding to these different sites has not yet been evaluated. Tranexamic acid does not bind to serum albumin. The plasma protein binding seems to be fully accounted for by its binding to plasminogen and appears to be negligible at therapeutic plasma levels of 5-10 mg/L.

Possible routes of biotransformation are acetylation or deamination followed by oxidation or reduction. After oral administration approximately 50% of the parent compound, 2% of the deaminated dicarboxylic acid, and 0.5% of the acetylated product are excreted.

**Distribution**

Tranexamic acid administered parenterally is distributed in a two-compartment model. Tranexamic acid is delivered in the cell compartment and the cerebrospinal fluid with delay. The distribution volume is about 33% of the body mass.

Tranexamic acid crosses the placenta, and may reach one hundredth of the serum peak concentration in the milk of lactating women. Tranexamic acid crosses the blood brain barrier.

**Elimination**

Tranexamic acid is eliminated by glomerular filtration, excretion being about 30% at one hour, 55% at three hours and 90% at 24 hours after intravenous administration of 10 mg per kg body weight. After oral administration of 10-15 mg per kg body weight, excretion was 1% at one hour, 7% at three hours and 39% at 24 hours.

Intravenous administration of 10 mg per kg body weight gave plasma concentrations of 18.3 µg, 9.6 µg and 5 µg per mL one, three and five hours after the injection.

When administered 36-48 hours before surgery in four doses of 10-20 mg per kg body weight, an antifibrinolytically active concentration (10 µg/mL) of tranexamic acid remained up to 17 hours in the tissues investigated, and up to 7-8 hours in the serum (Andersson et al, 1968).

Tranexamic acid crosses the placenta. After an intravenous injection of 10 mg per kg the concentration can

rise to about 30 µg per mL of fetal serum. Tranexamic acid also passes over into the breast milk during lactation in concentrations 1/100 of the corresponding serum levels.

After both oral and intravenous administration tranexamic acid passes into the semen and inhibits its fibrinolytic activity, but without affecting the motility of the spermatozoa (Liedholm, 1973). The ability of tranexamic acid to cross the blood-brain barrier has been demonstrated when administered to patients with ruptured intracranial aneurysms.

Tranexamic acid diffuses rapidly to the joint fluid and to the synovial membrane. In the joint fluid the same concentration was obtained as in the serum. The biological half-life in the joint fluid was about 3 hours.

Three hours after a single oral dose of 25 mg per kg body weight, the peak serum level was 15.4 mg per L and the aqueous humour level was 1.6 mg per L.

## 5.3 Preclinical safety data

### Carcinogenesis, Mutagenesis, Impairment of Fertility

An increased incidence of leukemia in male mice receiving tranexamic acid in food at a concentration of 4.8% (equivalent to doses as high as 5 g/kg/day) may have been related to treatment. Female mice were not included in this experiment.

Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long-term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic / neoplastic changes in the liver. No mutagenic activity has been demonstrated in several *in vitro* and *in vivo* test systems.

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

| **S. No.** | EXCIPIENTS | **Specification** | **Quantity per tablet** | **Active or Inactive** |
|---|---|---|---|---|
| 1. | **Ingredients** | | | |

| | | | | |
|---|---|---|---|---|
| 2. | Starch (Maize) | BP | 70.000 mg | Inactive |
| 3. | Carmellose Calcium | BP | 50.000 mg | Inactive |
| 4. | Microcrystalline cellulose | BP | 60.000 mg | Inactive |
| 5. | Copovidone (K-30) | BP | 15.000 mg | Inactive |
| 6. | Purified Talc | BP | 6.000 mg | Inactive |
| 7. | Magnesium Stearate | BP | 10.000 mg | Inactive |
| 8. | Polacrilin Potassium | USP | 7.000 mg | Inactive |
| 9. | Croscarmellose Sodium | BP | 10.000 mg | Inactive |
| 10. | Colloidal Anhydrous Silica | BP | 2.000 mg | Inactive |
| 11. | Uniqcoat FC White | IH | 10.000 mg | Inactive |
| 12. | Isopropyl Alcohol | BP | 120.00 mg | Inactive |
| 13. | Dichloromethane | BP | 80.00 mg | Inactive |

**Incompatibilities**

Not applicable.

**6.2**

**Incompatibilities**

Not applicable.

**6.3 Shelf life**

36 months from the date of manufacturing.

**6.4**

**Special precautions for storage.**

Store in a cool & dry place below 30°C. Protect from Light.

Keep all medicines out of the reach of children.

**6.5 Nature and contents of container**

3 x 10 Alu Alu Strip are packed in a printed carton along with 1 package insert.

**6.6 Special precautions for disposal and other handling**

Any unused portion should be discarded as per local regulations

**7 APPLICANT**

**SYNERMED NIG LTD**

**NO 3 ABIKE JOKOGBOLA STREET, SOLEBO ESTATE, AGA , IKORODU**

**LAGOS**

**8 MANUFACTURER**

ZEST PHARMA

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