SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Tranexamic Acid 500mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Tranexamic Acid 500 mg.
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets.
White capsule shaped, film coated tablets, marked with S132 on one side and a scoreline on the reverse.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Tranexamic acid is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin.

Indications
Short-term use for haemorrhage or risk of haemorrhage in increased fibrinolysis of fibrinogenolysis.

1. Local fibrinolysis as occurs in the following conditions:
   a) Prostatectomy
   b) Menorrhagia
   c) Epistaxis
   d) Conisation of the cervix
   e) Traumatic hyphaema

2. Management of dental extraction in haemophiliacs.
3. Hereditary angioneurotic oedema.

4.2 Posology and method of administration

Dosage and administration

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

1a  *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.

1b  *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.

1c  *Epistaxis:* Where recurrent bleeding is anticipated, oral therapy (2 tablets three times daily) should be administered for seven days.

1d  *Conisation of the cervix:* 3 tablets three times daily.

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

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

3.  *Hereditary angioneurotic oedema:* Some patients are aware of the onset of the 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 in section 4.1, the dosage is in the region of 20mg/kg/day. However, data on efficacy, posology and safety for these indications are limited.

*Elderly patients:* No reduction in dosage is necessary unless there is evidence of renal failure. (See guidelines below)

*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 micromole/l – dose Tranexmaic acid
4.3 Contraindications

- Hypersensitivity to tranexamic acid or any of the other ingredients listed in section 6.1.
- History of venous or arterial thrombosis (see section 4.4)
- Active thromboembolic disease
- Fibrinolytic conditions following consumption coagulopathy
- Severe renal impairment (risk of accumulation)
- History of convulsions

4.4 Special warnings and precautions for use

1. In case of haematuria of renal origin (especially in haemophilia), there is a risk of mechanical anuria due to formation of a ureteral clot.

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

3. In the long-term treatment of patients with hereditary angioneurotic oedema regular eye examination (e.g., visual acuity, slit lamp, intraocular pressure, visual fields) and liver function tests should be performed.

4. 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, an alternative treatment should be considered.

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

6. Patients who experience visual disturbance should be withdrawn from treatment.

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

8. The blood levels are increased in patients with renal insufficiency. Therefore a dose reduction is recommended (see section 4.2).
9. Before use of Tranexamic Acid, risk factors of thromboembolic disease should be investigated.

10. 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

Drugs that also have effects on haemostasis (e.g. etamsylate) should be given with caution to patients receiving tranexamic acid. In vitro, etamsylate produces a slight decrease in the activity of tranexamic acid, reducing the time of lysis. There is a theoretical risk of increased potential for thrombus formation e.g. with oestrogens. Tranexamic acid should therefore be administered with care to patients receiving oral contraceptives and other oestrogens. Tranexamic acid antagonises the action of thrombolytics.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Although there is no evidence from animal studies of a teratogenic effect, the usual caution with the use of drugs in pregnancy should be observed. Tranexamic acid crosses the placenta.

Lactation:
Tranexamic acid passes into breast milk to a concentration of approximately one hundredth of the concentration in the maternal blood. An antifibrinolytic effect in the infant is unlikely.

4.7 Effects on ability to drive and use machines

Since tranexamic acid may produce malaise, patients should be warned not to drive or operate machinery if affected.

4.8 Undesirable effects

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 <1/1000) and very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).

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<thead>
<tr>
<th>MeDRA System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare</td>
<td>-Allergic skin reactions</td>
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<tr>
<td></td>
<td>Not known</td>
<td>-Fixed drug eruption</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Very rare</td>
<td>-Digestive effects such a nausea vomiting and diarrhoea (disappear when dosage is reduced)</td>
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<tr>
<td>Nervous system disorders</td>
<td>Very rare</td>
<td>-Convulsions particularly in case of misuse (refer to sections 4.3)</td>
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<tr>
<td>Eye disorders</td>
<td>Rare</td>
<td>-Visual disturbances, including impaired colour vision, retinal/artery occlusion</td>
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| Vascular disorders       | Rare      | -Malaise with hypotension with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration)
|                          | Very rare | -Thromboembolic events
|                          |           | -Arterial or venous thrombosis at any sites |
| Immune system disorders  | Very rare | -Hypersensitivity reactions including anaphylaxis |

Thrombosis is a risk during treatment with inhibitors of fibrinolysis and there have been isolated case reports of cerebral thrombosis, arterial thrombosis, acute renal failure and coronary graft occlusion in patients receiving tranexamic acid. Controlled studies in various surgical areas – including coronary artery bypass grafting and total knee arthroplasty – have not found an increased risk of thrombosis compared with placebo. However, the incidence of cerebral ischaemia was higher in patients receiving tranexamic acid after subarachnoid haemorrhage than in placebo recipients. The absence of an increased risk of thrombosis in pregnant women with bleeding disorders in pregnancy is reassuring in this regard as this is a group with a greatly increased risk of thrombosis compared with the general population.

**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 via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

### 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 Pharmacodynamic properties
Pharmacotherapeutic group: Antifibrinolytics, B02A A02

Tranexamic acid is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin. The antifibrinolytic effect of tranexamic acid is produced by competitive inhibition of the activation of plasminogen to plasmin by blocking lysine binding sites on plasminogen molecules.

It is primarily the high affinity lysine binding site of plasminogen which is involved in its binding to fibrin. Saturation of this binding site with tranexamic acid displaces plasminogen from the fibrin surface. The antifibrinolytic effect of tranexamic acid is related mainly to the production of a reversible complex with a modified plasminogen and the associated conformation changes of this pro-enzyme.

Defective fibrin formation or excessive, rapid dissolution of fibrin results in excessive or recurrent bleeding. Tranexamic acid stabilises fibrin structures - thus preventing untimely dissolution of haemostatic fibrin. The antifibrinolytic activity of tranexamic acid is approximately 10 times that of e-aminocaproic acid. Anti-fibrinolytic treatment also increases collagen synthesis and tensile strength with granulation tissue, presumably by preserving the fibrin matrix.

5.2 Pharmacokinetic properties
Tranexamic acid is reasonably well absorbed by mouth with a bioavailability of 30-50%. Peak concentrations occur at around 3 hours. The absorption of the drug is not influenced by food.

Following intravenous administration of tranexamic acid at a dose of 10mg/kg body weight, plasma concentrations at 1, 3 and 5 hours respectively are 18, 10 and 5mg/l. The apparent elimination half life is about 2 hours(9).

At therapeutic concentrations, (5-10mg/l) tranexamic acid is very weakly protein bound, about 3% - explained by its binding to plasminogen which is saturated at very low concentrations. Its volume of distribution is about 1 l/kg.

Tranexamic acid is distributed into a number of tissues – including large intestine, kidneys and prostate. The drug also passes into seminal fluid, inhibiting its fibrinolytic activity but has no effect on sperm migration. Tranexamic acid also crosses the blood-aqueous barrier in the eye and the damaged blood-brain barrier and diffuses rapidly into joint fluid and synovial membranes.
Tranexamic acid crosses the placenta and its concentration in cord blood may reach that of the maternal blood. The concentration of tranexamic acid in breast milk of lactating women one hour after the last dose of a two day treatment was found to be about one hundredth of the peak serum concentration.

Approximately 90% of an (intravenous) dose of tranexamic acid is recovered in the urine by 24 hours post dose (30% at 1 hour; 45% at 3 hours). This suggests that very little metabolism of the drug occurs.

5.3 Preclinical safety data
Tranexamic acid crosses the placental barrier but does not have any teratogenic effect in the animal.

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose,
Pregelatinised starch,
Maize starch,
Colloidal silica,
Povidone,
Magnesium stearate,
Talc,
Croscarmellose sodium
Macrogol 400,
Hypermellose,
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store in the original container
6.5 **Nature and contents of container**
30, 40 or 60 tablets in clear PVC/PVDC (250 µm)/aluminium foil (20 µm) blisters in cardboard cartons.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Not applicable.

7 **MARKETING AUTHORISATION HOLDER**
Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
United Kingdom

Trading as
Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS
Or
Zentiva, One Onslow Street, Guildford, Surrey, GU1 4YS, UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 17780/0095

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/05/2009

10 **DATE OF REVISION OF THE TEXT**
18/07/2016