New Zealand Data Sheet

1 TRANEXAMIC ACID TABLETS

TRANEXAMIC ACID TABLETS 500 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg tranexamic acid.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tranexamic Acid Tablets are white, film-coated, oblong tablets of 6 mm, marked on one side with 'TA500' with a break-line on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis. Local fibrinolysis may occur in the following conditions:

- menorrhagia
- epistaxis
- conisation of the cervix
- management of dental extraction in patients with coagulopathies
- ulcerative colitis
- haematuria (tranexamic acid therapy is not indicated in haematuria caused by diseases of the renal parenchyma – see also Section 4.4)
- gastrointestinal haemorrhage.

Hereditary angioneurotic oedema.

4.2 Dose and method of administration

Dose

Adults

The recommended standard dose is 2-3 tablets of 0.5 g, taken two to three times daily.

For the indications listed below the following doses are recommended.

Menorrhagia

1-1.5 g orally three to four times daily for 3-4 days. Tranexamic acid therapy is initiated when bleeding has become profuse.

Epistaxis

1.5 g orally three times daily for 4-10 days.

Haematuria

1-1.5 g orally two to three times daily until macroscopic haematuria is no longer present.

Conisation of the cervix

1.5 g orally three times a day for 12-14 days post-operatively.

Dental surgery in patients with coagulopathies (oral post-surgery administration only)

After surgery (when intravenous injection of tranexamic acid is administered immediately before surgery), 25 mg per kg body weight given orally three to four times daily for 6-8 days. It may be necessary to administer coagulation factor concentrate. This decision should be made after consulting a specialist on coagulation.

Hereditary angioneurotic oedema

1-1.5 g orally two to three times daily as intermittent or continuous treatment depending on whether the patient has prodromal symptoms or not.

Special Populations

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

Renal Impairment

Patients with impaired renal function may experience an increased elimination half-life for tranexamic acid. Dose reduction is recommended in adult patients with renal impairment.

Dose reduction is recommended in children ≥ 2 years old who are mildly or moderately renally impaired. Tranexamic acid is not recommended in children who are severely impaired.

For both the adult and the paediatric patient, an eGFR ≥ 90 mL/min/1.73 m^2 usually indicates kidney function within a 'normal range', but does not exclude patients with early kidney damage. If renal impairment is suspected, informed dose alterations decision may include other estimates of renal function including consultation with an experienced renal physician.

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

Serum creatinine (micromol/L)	eGFR (mL/min/1.73m^2)	Dose orally	Dose frequency
120-249	60-89	15 mg/kg	twice daily
250-500	30-59	15 mg/kg	daily
> 500	< 29	7.5 mg/kg	daily

Paediatric Population

In children, the dosage is in the region of 20 mg/kg/day, however data on efficacy, posology and safety for these indications are limited.

Method of Administration

Tranexamic Acid tablets are for oral administration only.

4.3 Contraindications

Patients with a history or risk of venous or arterial thrombosis should not be given tranexamic acid, unless at the same time it is possible to give treatment with anticoagulants.

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

Tranexamic acid should not be given to patients with acquired disturbances of colour vision. If disturbances of colour vision arise during the course of treatment the drug should be discontinued.

Patients with subarachnoid haemorrhage should not be given tranexamic acid as anecdotal experience indicates that cerebral oedema and cerebral infarction may be caused in such cases.

Fibrinolytic conditions following consumption coagulopathy.

Severe renal impairment (risk of accumulation).

History of convulsions.

Hypersensitivity to tranexamic acid or any of the ingredients listed in Section 6.1.

4.4 Special warnings and precautions for use

The dose of tranexamic acid should be reduced in patients with renal impairment because of the risk of accumulation (see Section 4.2). Isolated cases of obstruction of the urinary tract due to blood clots have been observed when tranexamic acid has been used to treat severe bleeding from the upper urinary tract.

Tranexamic acid therapy is not indicated in haematuria caused by diseases of the renal parenchyma. Intravascular precipitation of fibrin frequently occurs in these conditions and may aggravate the disease. In the case of haematuria of renal origin, there is a risk of mechanical anuria due to formation of a ureteral clot. In addition, in cases of massive renal haemorrhage of any cause, antifibrinolytic therapy carries the risk of clot retention in the renal pelvis.

Before use of tranexamic acid, risk factors of thromboembolic disease should be investigated. Although clinical evidence shows no significant increase in thrombosis, possible risk of thrombotic complications cannot be ruled out. Venous and arterial thrombosis or thromboembolism has been reported in patients treated with tranexamic acid. In addition, cases of central retinal artery and central retinal vein obstruction have been reported. A few patients have developed intracranial thrombosis with tranexamic acid but further observation is needed to assess the significance of this potential hazard.

There are no data on the use of tranexamic acid in women taking oral contraceptive agents. Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis.

Patients with a high risk for thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should use tranexamic acid only if there is a strong medical indication and under strict medical supervision.

Tranexamic acid should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

Blood in body cavities such as pleural space, joint spaces and urinary tract (e.g. renal pelvis, bladder) may develop 'indissoluble clots' in these cavities due to extravascular blood clots which may be resistant to physiological fibrinolysis.

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.

Patients with disseminated intravascular coagulation (DIC) who require treatment with tranexamic acid must be under the strict supervision of a physician experienced in treating this disorder.

Convulsions have been reported in association with tranexamic acid treatment.

Paediatric Population

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

Clinical experience in the paediatric population < 2 years old is limited and tranexamic acid should only be used if the benefit outweighs the risk. The benefit of an antifibrinolytic drug in neonates and infants aged < 2 year old is questionable, as bleeding under cardiopulmonary bypass (CPB) in this population is more related to the immaturity of the coagulation system than fibrinolysis. Published efficacy and safety data is inconclusive in neonates and infants aged < 2 years old. Due to the physiological characteristics of neonates and infants (immaturity of the blood-brain barrier and renal function), as well as the generalised inflammatory state related to CPB, there may be a potential risk of cerebral exposure to tranexamic acid evoking epileptic seizure (see also Section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Clinically important interactions have not been observed with tranexamic acid tablets. Because of the absence of interaction studies, simultaneous treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field.

4.6 Fertility, pregnancy and lactation

Pregnancy

Australian Pregnancy Categorisation: B1.

Drugs which have been taken by only a limited number or pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

The long-term clinical experience is limited to 21 pregnant women, treated for 1 to 18 weeks, in most cases to prevent further haemorrhage in connection with ablatio placentae. All women delivered alive and normal children except for prematurity. The short-term experience comprises 67 women with abruptio placentae treated with a single dose just before delivery by caesarean section. All deliveries went well and were not further complicated by haemorrhage.

There are no adequate and well-controlled studies in pregnant women. However, tranexamic acid is known to cross 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, tranexamic acid should be used during pregnancy only if clearly needed.

Breastfeeding

Tranexamic acid is secreted in the mother's milk at a concentration of about a hundredth of the corresponding serum levels but is not likely to influence the child at therapeutic doses.

Fertility

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

There are no clinical data in humans supporting the impact of tranexamic acid on fertility. Fertility was not affected in male or female rats up to the highest oral dose tested of approximately 900 mg/kg/day.

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

Gastrointestinal discomfort occurs in more than 30% of patients after oral administration of 6 g/day. The discomfort disappears when the dose is reduced.

Common side effects (1 to < 10%):
Gastrointestinal tract: Nausea, vomiting, diarrhoea.

Uncommon side effects (0.1 to < 1%):
Skin and subcutaneous tissue: Allergic skin reactions

Rare side effects (< 0.1%):
Thromboembolic events, impaired colour vision and other visual disturbances. Exceptional cases of giddiness have been reported.

Very rare adverse events have been reported, including:

- Cardiovascular disorders – malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration); arterial or venous thrombosis at any sites.
- Nervous system disorders – convulsions, particularly in case of misuse (see Section 4.3 and 4.4).
- General disorders – hypersensitivity reactions, including anaphylaxis.

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Overdose data are limited. There is one report of overdosage in which a seventeen-year-old ingested 37 g of tranexamic acid and after receiving treatment with gastric lavage, mild intoxication was reported.

Signs and Symptoms

Symptoms of overdose may include dizziness, headache, nausea, vomiting, diarrhoea, orthostatic symptoms hypotension and convulsions.

Treatment

There is no known antidote for tranexamic acid overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures should be instituted as required.

Activated charcoal may reduce absorption of tranexamic acid if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube once the airway is protected.

In addition to this, monitor vital signs to detect a possible hypotensive episode. Monitor fluid and electrolyte status in patients with severe vomiting or diarrhoea and administer IV fluids and replace electrolytes as necessary. Monitor urine output and maintain adequate diuresis. Monitor for clinical evidence of thromboembolic complications (e.g. chest pain, shortness of breath, flank pain, extremity pain). Because there is a risk of thrombosis in predisposed individuals; anticoagulant therapy should be considered in these patients.

In symptomatic patients, support respiratory and cardiac function. Monitor blood count, renal function, pulse oximetry and/or blood gases and obtain a chest X-ray. Obtain an ECG and institute continuous cardiac monitoring.

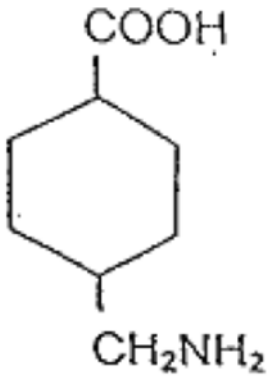
For advice on the management of an overdose please contact the National Poisons Centre on 0800 POISON (telephone 0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifibrinolytics – Amino acids,
ATC code: B02AA02

Chemical structure



Chemical name: trans-4-aminomethylcyclohexane-carboxylic acid.

Molecular formula: $C_8H_{15}NO_2$

Molecular weight: 157.2

Mechanism of action

Tranexamic acid is a competitive inhibitor of plasminogen activation and at much higher concentrations a non-competitive inhibitor of plasmin, thus implying that tranexamic acid interferes with the fibrinolytic process in the same way as aminocaproic acid. Tranexamic acid is about 10 times more potent *in vitro* than aminocaproic acid.

Tranexamic acid binds considerably more strongly than aminocaproic acid to both the strong and weak 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 in normal subjects. On the other hand, tranexamic acid in concentrations of 10 mg/mL and 1 mg/mL blood prolongs the thrombin time.

Clinical pharmacodynamics data that examined the *in vivo* effect of tranexamic acid on prothrombotic and fibrinolytic factors showed similar changes in anti-thrombin (ATIII and TAT) and anti-plasmin (α2-PI & α2-PIP) complexes in both the tranexamic acid treated patients and placebo in cardiac surgery. One study involving total knee arthroplasty, PF1&2 coagulation factor levels increased to a similar extent in both the tranexamic acid and the patients receiving placebo.

D-Dimer levels were significantly lower during and up to 24 hours after surgery in tranexamic acid treated patients compared with placebo. Fibrin Split Products (FSP) increased significantly in patients who received placebo. These results suggest that tranexamic acid inhibits fibrinolysis compared with non-active controls in cardiac surgery. In one study involving knee arthroplasty, there was no evidence of inhibition in fibrinolysis of peripheral blood in tranexamic acid treated or placebo patients. However, there was evidence of inhibition of fibrinolysis in wound blood in the tranexamic acid treated patients compared to placebo.

5.2 Pharmacokinetic properties

Absorption

Absorption from the gastrointestinal tract is only about 50% at reasonably low oral doses. However, a parallel intake of food has no effect on the gastrointestinal absorption of the drug following a dose of 2 g or on the maximum plasma concentration.

Distribution

Tranexamic acid does not bind to serum albumin. The plasma protein binding is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen.

Three hours after a single oral dose of 25 mg/kg, the peak serum level was 15.4 g/L and the aqueous humour level was 1.6 g/L. The plasma peak level after 1 g orally is 8 mg/L and after 2 g, 15 mg/L, both obtained three hours after dosing.

When administered 36 to 48 hours before surgery in 4 doses of 10 to 20 mg/kg, an antifibrinolytically active concentration (10 g/mL) of tranexamic acid remains in different tissues for about 17 hours and in the serum for up to seven or eight hours.

Tranexamic acid passes through to the placenta. The concentration in cord blood after an intravenous injection of 10 mg/kg to women could be fairly high, about 30 µg/mL of foetal serum.

The concentration in breast milk is about one hundredth of the serum peak concentration obtained.

Tranexamic acid passes to semen and inhibits its fibrinolytic activity but does not influence the sperm migration.

Tranexamic acid crosses the blood-brain barrier.

Tranexamic acid concentration in cerebrospinal fluid is about one tenth that of plasma.

The drug passes into the aqueous humour, the concentration being about one tenth of the plasma concentration.

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

Biotransformation

Only a small fraction of the drug is metabolised. The total amount of metabolites excreted in urine during 72 hours is less than 5%. 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.

Elimination

After an intravenous dose of 1 g, the plasma concentration time curve shows a triexponential decay with a half-life of about 2 hours for the terminal elimination phase. The initial volume of distribution is about 9 to 12 litres.

Urinary excretion is the main route of elimination via glomerular filtration. Overall renal clearance is equal to overall plasma clearance (110 to 116 mL/min) and more than 95% of the dose is excreted in urine as the unchanged drug. Excretion of tranexamic acid by glomerular filtration is about 90% at 24 hours after intravenous administration of 10 mg/kg bodyweight. After oral administration of 10 to 15 mg/kg body weight the urinary excretion at 24 hours is 39% and at 48 hours is 41% of the ingested dose or 78% of the absorbed material.

Renal impairment

Tranexamic acid is eliminated unchanged in urine. Patients with impaired renal function may experience an increased elimination half-life for the drug and may require dose reduction (see Section 4.2).

Hepatic Impairment

Pharmacokinetic data from patients with pre-existing hepatic impairment, who were treated with tranexamic acid, are not available. As tranexamic acid is excreted unchanged, dose adjustment due to hepatic impairment is not required.

5.3 Preclinical safety data

Focal areas of retinal degeneration have developed in cats, dogs and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. The incidence of such lesions has varied from 25% to 100% of animals treated and was dose related. At lower doses some lesions have appeared to be reversible.

Limited data in cats and rabbits showed retinal changes in some animals with doses as low as 126 mg/kg/day (only about 3 times the recommended human dose) administered for several days to two weeks.

No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials. However, visual abnormalities, often poorly characterised, represent the most frequently reported postmarketing adverse event in Sweden. For patients who are to be treated continually for longer than several days, an ophthalmological examination, including visual acuity, colour vision, eye-ground and visual fields, is advised before commencing and at regular intervals during the course of treatment. Tranexamic acid should be discontinued if changes in examination results are found.

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.

In published, pre-clinical animal studies, epileptic activities were induced by topical application of tranexamic acid to the cortex of anesthetised cats. Similarly, intravenous infusion of high doses (500-600 mg/kg) of tranexamic acid induced seizure-like activity in conscious cats. Severe hind limb spasms developed into generalized convulsions in a rat model following application of tranexamic acid to the lumbar spinal cord. Tranexamic acid within a fibrin sealant similarly induced limb spasms and convulsions in this rat model. Fibrin sealant containing tranexamic acid evoked generalised seizures in rats following application to the cerebral cortex of anesthetised rats. CNS hyperexcitability may be the result of antagonism of γ -aminobutyric $acid_A$ receptors by tranexamic acid.

Genotoxicity

Tranexamic acid was not mutagenic in *B. subtilis* and had no chromosomal effects in Chinese hamster cells. The incidence of chromosomal breakage was increased at 3 g/kg in rat bone marrow. No lethal mutagenicity was detected in a dominant lethal test at 100 mg/kg and 3 g/kg. The weight of evidence in a limited range of mutagenicity tests suggests that tranexamic acid is not mutagenic.

Carcinogenicity

A dietary carcinogenicity study in Shermann-Wyckoff rats showed an increase in the incidence of biliary hyperplasia, cholangioma and adenocarcinoma of the liver at high doses. However, these findings have not been reproduced in a number of other lifetime studies in either SD or CDF1 mice. A possible treatment-related increase in the incidence of leukaemia was noted in mice receiving dietary tranexamic acid at doses equivalent to up to 5 g/kg/day for 20 months.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone
Croscarmellose sodium
Colloidal anhydrous silica
Purified talc
Magnesium stearate
Titanium dioxide
Macrogol 8000
Vanillin
Amino methacrylate copolymer

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Blister packs of 60 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Boucher & Muir (NZ) Limited t/a Mercury Pharma (NZ)
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 3 February 2011

10 DATE OF REVISION OF TEXT

20 May 2019

Summary table of changes:

Section changed	Summary of new information
3.0	Tablet description updated