NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CYKLOKAPRON® 500 mg tablets.

CYKLOKAPRON® 100 mg/mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 500 mg tablet contains 500 mg tranexamic acid.

Each 5 mL ampoule contains 500 mg of tranexamic acid and 5 mL water for injections.

Each 10 mL ampoule contains 1000 mg tranexamic acid and 10 mL water for injections.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

CYKLOKAPRON 500 mg tablets are white, capsule shaped, film coated, engraved CY within arcs, dimensions 8.0 mm x 18.0 mm.

CYKLOKAPRON Solution for injection is a sterile, clear and colourless solution, containing 100 mg/mL tranexamic acid.

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:

- Prostatectomy and bladder surgery
- 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 (also see Section 4.4)).
- Gastrointestinal haemorrhage.

General fibrinolysis as in prostatic and pancreatic cancer; after thoracic and other major surgery:

- in obstetrical complications such as abruptio placentae and post-partum haemorrhage

- in leukaemia and liver diseases and in connection with thrombolytic therapy with streptokinase.

Hereditary angioneurotic oedema.

For the reduction of peri- and post-operative blood loss and the need for blood transfusion in adult patients undergoing cardiac surgery or total knee arthroplasty or total hip arthroplasty.

For the reduction of peri- and post-operative blood loss and the need for blood transfusion in paediatric patients undergoing cardiac surgery.

4.2 Dose and Method of Administration

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

Dose

Intravenous administration is necessary only if it is difficult to give adequate doses by mouth.

The recommended standard dose is 2-3 tablets of 0.5 g, or 5-10 mL by slow intravenous injection at a rate of 1 mL/minute, two to three times daily. For the indications listed below the following doses are recommended.

Prostatectomy

5-10 mL by slow intravenous injection every eight hours (the first injection being given during the operation) for the first three days after surgery; thereafter 1-1.5 g orally three to four times daily until macroscopic haematuria is no longer present.

Menorrhagia

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

Epistaxis

1.5 g orally three times daily for four to ten days. CYKLOKAPRON 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.

Haematuria

1-1.5 g orally 2-3 times daily until macroscopic haematuria is no longer present.

Conisation of the Cervix

1.5 g orally 3 times a day for 12 to 14 days post-operatively.

Dental Surgery in Patients with Coagulopathies

Immediately before surgery, 10 mg per kg body-weight should be given intravenously. After surgery, 25 mg per kg body-weight are given orally three to four times daily for six to eight days. It may be necessary to administer coagulation factor concentrate. This decision should be made after consulting a specialist on coagulation.

General Fibrinolysis

1.0 g (10 mL) by slow intravenous injection three to four times daily. With fibrinolysis in conjunction with diagnosed, increased intravascular coagulation, i.e., defibrillation syndrome, an anticoagulant such as heparin may be given with caution.

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.

Intravenous Administration

Adult Cardiac Surgery

After induction of anaesthesia and prior to skin incision, administer a pre-surgical loading dose of 15 mg/kg tranexamic acid, followed by infusion of 4.5 mg/kg/h for the duration of surgery. 0.6 mg/kg of this infusion dose may be added in the priming volume of the heart-lung machine.

Adult Total Knee Arthroplasty

Administration of 15 mg/kg tranexamic acid prior to release of the tourniquet followed by repeat bolus injection of 15 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.

Adult Total Hip Arthroplasty

Administration of 15 mg/kg tranexamic acid immediately prior to skin incision, followed by a repeat bolus of 15 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.

Special Populations

Renal Impairment

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

Serum creatinine (micromol/L)	**eGFR (mL/min/1.73m^2)**	**Dose IV**	**Dose Orally**	**Dose frequency**
120-249	60-89	10 mg/kg	15 mg/kg	twice daily
250-500	30- 59	10 mg/kg	15 mg/kg	daily
>500	< 29	5 mg/kg	7.5 mg/kg	daily

Adult Cardiac Surgery

eGFR (mL/min/1.73m^2)	**Dosage adjustment for CYKLOKAPRON solution for injection**		
	Loading	**Prime**	**Infusion**
60-89	15 mg/kg	0.6 mg/kg	3.75 mg/kg/h
30- 59	15 mg/kg	0.6 mg/kg	2.5 mg/kg/h
< 29	15 mg/kg	0.6 mg/kg	1.25 mg/kg/h

Adult Total Knee Arthroplasty

eGFR ($mL/min/1.73m^2$)	Dosage adjustment for CYKLOKAPRON solution for injection
60-89	Administration of 15 mg/kg tranexamic acid immediately prior to tourniquet release followed by a repeat bolus of 11.25 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.
30-59	Administration of 15 mg/kg tranexamic acid immediately prior to tourniquet release followed by a repeat bolus of 8.4 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.
<29	Administration of 15 mg/kg tranexamic acid immediately prior to tourniquet release followed by a repeat bolus of 6.3 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.

Adult Total Hip Arthroplasty

eGFR ($mL/min/1.73m^2$)	Dosage adjustment for CYKLOKAPRON solution for injection
60-89	Administration of 15 mg/kg tranexamic acid immediately prior to skin incision followed by a repeat bolus of 11.25 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.
30-59	Administration of 15 mg/kg tranexamic acid immediately prior to skin incision followed by a repeat bolus of 8.4 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.
< 29	Administration of 15 mg/kg tranexamic acid immediately prior to skin incision followed by a repeat bolus of 6.3 mg/kg at 8 hourly intervals after the initial dose. The last bolus dose is to be administered 16 hours after the initial dose.

Elderly

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

Paediatric Population

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

Paediatric Cardiac Surgery in Patients ≥ 2 Years Old

After induction of anaesthesia and prior to skin incision, administration of 10 mg/kg as an initial pre-surgical bolus dose followed by a repeat bolus dose of 10 mg/kg during surgery or as an infusion during surgery.

Tranexamic acid should only be used in the paediatric population ≥ 2 years old. Dose reduction is recommended for children ≥ 2 years old with mild to moderate renal impairment. It should not be used in children with severe renal impairment.

Paediatric population ≥ 2 years with renal impairment

eGFR (mL/min/1.73m^2)	**Dosage adjustment for CYKLOKAPRON solution for injection**
60-89	Administration of 10 mg/kg tranexamic acid after induction of anaesthesia and prior to skin incision followed by a bolus dose of 7.5 mg/kg at CPB bypass.
30-59	Administration of 10 mg/kg tranexamic acid after induction of anaesthesia and prior to skin incision followed by a bolus of 5.6 mg/kg at CPB bypass.
<29	Tranexamic acid should not be used in paediatrics with severe renal impairment.

Method of Administration

Rapid intravenous injection may cause dizziness and/or hypotension (refer to Sections 4.4, 4.8 and Post-marketing Report).

CYKLOKAPRON solution for injection is intended for slow intravenous injection and infusion (see Section 6.6). The recommended rate of administration is 50 mg/min. Undiluted CYKLOKAPRON solution for injection (100 mg/mL) may be administered at 0.5 mL/min by intravenous infusion or intravenous injection. Solutions diluted to 1% tranexamic acid (i.e., 1 g in 100 mL or 10 mg/mL), may be administered at 5 mL/min or solutions diluted to 2% tranexamic acid, may be administered at 2.5 mL/min by intravenous infusion.

For adult cardiac surgery, a loading dose is administered prior to surgery followed by a prolonged infusion during surgery. The recommended rate of prolonged infusion is 4.5 mg/kg patient body weight per hour. For a patient who weighs 100 kg, undiluted CYKLOKAPRON solution for injection (100 mg/mL) may be administered at 4.5 mL/hour. Solutions diluted to 1% tranexamic acid may be administered at 45 mL/hour and solutions diluted to 2% tranexamic acid may be administered at 22.5 mL/hour.

4.3 Contraindications

Intrathecal and epidural administration of tranexamic acid is contraindicated.

Patients with a history or risk of 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 (DVT), pulmonary embolism and cerebral thrombosis.

The preparation should not be given to patients with acquired disturbances of colour vision. If disturbances of colour vision arise during the course of treatment the administration of the preparation 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.

Hypersensitivity to tranexamic acid or any of its ingredients.

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 addition, in cases of massive renal haemorrhage of any cause, antifibrinolytic therapy carries the risk of clot retention in the renal pelvis.

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 CYKLOKAPRON. 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.

Patients with a high risk for thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should use CYKLOKAPRON only if there is a strong medical indication and under strict medical supervision. The risk for thromboembolic events may be increased in patients using hormonal contraceptives. If CYKLOKAPRON has to be used in these patients, advise them to use an effective alternative (nonhormonal) contraceptive method.

CYKLOKAPRON 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 CYKLOKAPRON until the cause of the irregularity has been established. If menstrual bleeding is not adequately reduced by CYKLOKAPRON, an alternative treatment should be considered.

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

Rapid intravenous injection of CYKLOKAPRON solution for injection may cause dizziness and/or hypotension (see Sections 4.2 , 4.8 and Postmarketing experience**)**.

Convulsions have been reported in association with tranexamic acid treatment. Serious events including death were reported in patients erroneously treated with tranexamic acid via intrathecal or epidural injection (see Section 4.3).

Renal Impairment

Patients with impaired renal function may experience an increased elimination half life for the drug. The need for 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 (see Section 4.2).

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.

Paediatric Population

Clinical experience with CYKLOKAPRON 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 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 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.

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).

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

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.

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 disorders: Nausea, vomiting, diarrhoea.

Uncommon Side Effects (0.1 to < 1%)

Skin and subcutaneous disorders : Allergic skin reactions.

Intravenous Administration

The safety of tranexamic acid via intravenous administration was established by pooling published studies comprising a total of 5736 adult tranexamic acid patients undergoing cardiac surgery, total knee or hip arthroplasty. The adverse events are reported by system organ class with frequencies expressed as a percentage of patients treated. These should be interpreted within the surgical setting.

Adult cardiac surgery

Safety data were compiled by pooling 43 published studies comprising 2797 adult patients undergoing low risk cardiac surgery and 1055 adult patients undergoing high risk cardiac surgery. Low risk cardiac surgery is defined as CABG, valve replacement surgery or multiple procedures involving both CABG and valve replacement. High risk cardiac surgery includes repeat CABG, repeat valve replacement, atrio-septal repair or surgical repair of aortic dissection or aneurysm.

Patients receiving tranexamic acid patients were treated with total doses that varied from < 20 mg/kg to 100 mg/kg. Patient characteristics for the cardiac surgical demography were similar for the control group and the tranexamic acid treated group.

The frequency of adverse events by most relevant body system for all patients undergoing low and high risk cardiac surgery is provided in Table 1. The commonly reported (≥ 1% to < 10%) complications in association with tranexamic acid were renal; cardiac; respiratory, thoracic and mediastinal disorders. In low risk cardiac surgery, the adverse events were similar for the tranexamic acid treated patients and the control group. In high risk procedures, the risk of patients experiencing an adverse event was 3 fold greater in the tranexamic acid treated patients compared to the non-active control group.

The marked difference in adverse events in the high risk surgical group between the non-active control group and the tranexamic acid group was driven by the results of two published studies which contributed 782 of the 1055 patients. These patients, described as high risk surgical patients, had an average risk of mortality at least twice the norm for isolated primary CABG and a risk of repeat surgery exceeding 5%. More than 45% of these patients also presented with FC III angina and CHF. As safety data for the tranexamic acid treated high risk patient population were collected against active comparators, the incidences of adverse events in these patients should be interpreted compared to active comparators. Frequency of adverse events reported for this patient population and surgical setting in tranexamic acid treated patients versus active comparators are presented in Table 2.

Fatal events

Overall, there was a trend towards a lower risk of mortality in all cardiac surgery patients receiving tranexamic acid compared to the control group with the rates almost halved in high risk surgery patients.

Cardiac disorders

For patients undergoing low risk surgery, the incidence was higher in the tranexamic acid group compared to the control group. For patients undergoing high risk surgery, the incidence was higher. The most commonly reported adverse events were cardiogenic shock and myocardial infarction.

Nervous system disorders

The most commonly reported Central Nervous System disorder reported in published studies for all adult cardiac surgery patients is stroke. The incidence of stroke was higher in patients undergoing high risk than low risk cardiac surgery in both the tranexamic acid treated group and the control group. It is unknown whether this is due to an increased risk of cerebrovascular thromboembolic events.

Renal disorders

The majority of renal disorders reported in published studies for all cardiac surgery patients were renal dysfunction and renal failure. Renal disorders occurred more frequently in patients undergoing high risk surgery than low risk surgery. These were also reported more frequently in the tranexamic acid treatment groups than in the control groups. The reason for the increased incidence of renal disorders in the tranexamic acid treatment groups is unknown.

Table 1: Adverse events ≥ 1% in adult patients undergoing low and high risk cardiac surgery as reported in published studies

	Control		**Tranexamic acid**		
	Low risk surgery (N = 1040)	**High risk surgery (N = 207)**	**Low risk surgery (N = 2797)**	**High risk surgery (N = 273)**	**High risk surgery & high risk patients[1] (N = 1055)**
Fatal					
death	0.8%	6.8%	1.0%	2.2%	3.6%
Cardiac disorders					
arrhythmia	0.6	-	0.1	1.5	0.4
atrial fibrillation	2.2	2.4	0.8	0.7	0.6
cardiogenic shock	-	-	0.1	-	10.6
heart block	-	1.0	-	0.4	0.1
myocardial infarction	1.5	1.5	1.4	2.6	3.7
Nervous system disorders					
stroke	0.2	1.5	0.2	1.8	3.1
Respiratory, thoracic and mediastinal disorders					
respiratory failure	-	-	-	-	9.5
Renal and urinary disorders					
renal dysfunction/ impairment	0.3	0.5	0.1	-	9.2
renal failure	-	2.9	0.4	2.2	13.6
renal insufficiency	-	-	1.3	-	-

Control group = Placebo or no antifibrinolytic treatment.

[1]782 of the 1055 patients are high risk cardiac surgery patients. Also refer to Table 2.

Table 2: Adverse events ≥ 1% for adult high risk patients undergoing high risk cardiac surgery treated with tranexamic acid versus active comparator

	Aprotinin[1]* (N = 907)	**EACA[1]* (N = 780)**	**Tranexamic acid (N = 1055)[1]**
Fatal			
death	6.1%	4.0%	3.6%
Cardiac disorders			
cardiogenic shock	12.4	15.3	10.6
myocardial infarction	4.6	2.6	3.7

Nervous system disorders stroke	2.5	2.8	3.1
Vascular disorders DVT or pulmonary embolism	1.0	0.9	0.8
Respiratory, thoracic and mediastinal disorders respiratory failure	10.6	12.6	9.5
Renal and urinary disorders renal dysfunction renal failure	12.0 14.2	12.8 16.9	9.2 13.6

*****Aprotinin and EACA are not available in Australia; EACA = ε-aminocaproic acid.

[1]779 of 907 aprotinin, all 780 EACA and 782 of 1055 tranexamic acid patients are high risk cardiac surgery patients.

The incidences of DVT or pulmonary embolism for all three treatments were low (1.0 to 1.3%).

Overall, the commonly reported (≥ 1% to < 10%) adverse events in the high risk patients were similar or lower in the tranexamic acid patients compared with aprotinin and aminocaproic acid, except for central nervous system disorders reported as stroke.

Uncommon Adverse Events (≥ 0.01 to < 1%)

Reported incidences of adverse events in adult patients that are greater in tranexamic acid patients than the control group, are depicted below. Adverse events are listed by system organ class.

Immune system disorders
Hypersensitivity reaction, including anaphylactic shock.

Cardiac disorders
Cardiac ischaemia, ventricular arrhythmia, ventricular tachycardia.

Nervous system disorders
Left hemiparesis, left-sided weakness, neurologic dysfunction, neurological complications.

Eye disorders
Retinal artery embolus.

Respiratory, thoracic and mediastinal disorders
Pulmonary complications, pulmonary oedema.

Gastrointestinal disorders
Bowel infarction.

Vascular disorder

DVT, pulmonary embolism.

Total Knee Arthroplasty and Total Hip Arthroplasty

Safety data in total knee arthroplasty comprises the pooling of 9 published studies involving 492 tranexamic acid treated patients and 406 non-active controls who underwent knee

arthroplasty. Pooling of 5 published studies, involving 261 tranexamic acid patients and 273 non-active controls provided safety data for adult patients who underwent hip arthroplasty.

The tranexamic acid treated patients who underwent knee arthroplasty received total doses that varied from <20 mg/kg to >100 mg/kg. Patients who underwent hip surgery were treated with total doses that varied from <20 mg/kg to 30 mg/kg. Patient characteristics for the non-active control group were the same as the tranexamic acid treated patients for both surgical settings.

In adult patients undergoing total knee and hip arthroplasty, vascular disorders were very commonly (≥ 10%) and commonly (≥ 1 to < 10%) reported adverse events. The frequency of vascular disorders, reported as DVT, are summarised in Table 3.

Table 3: Adverse events ≥ 1% in adult patients undergoing total hip and total knee arthroplasty

	Total Knee Arthroplasty		**Total Hip Arthroplasty**	
	Control (N = 406)	**Tranexamic acid (N= 492)**	**Control (N = 273)**	**Tranexamic acid (N= 261)**
Vascular disorders deep vein thrombosis (DVT)	6.2	11.8	1.5	2.7

Vascular disorders

Overall, there was a higher incidence of thromboembolic complications in the tranexamic acid group compared to controls in adult patients undergoing total knee arthroplasty and in adult patients undergoing total hip arthroplasty.

A non-statistically significant risk difference between tranexamic acid treated patients and non-active control patients undergoing total hip arthroplasty is 0.012 [95% CI: -0.012, 0.036], i.e., on average, a potential of 12 patients are at risk of thromboembolic complications attributable to tranexamic acid for every 1000 patients treated.

The risk difference between tranexamic acid treated patients and non-active control patients undergoing total knee arthroplasty is 0.056 [95% CI 0.019 to 0.093], i.e., on average, a potential of 6 patients are at risk of thromboembolic complications attributable to tranexamic acid for every 100 patients treated. About 50% of the incidences of DVT, in patients undergoing knee arthroplasty, were attributed to one study. In this study, positive venograms were reported in 46% of patients in both the tranexamic acid and control group. The high frequency of positive venograms is consistent with the results from published studies where a false-positive finding has been reported in 15% of patients. Discounting the result of this study, incidences of DVT for patients undergoing knee surgery were 5.7% (tranexamic acid group) and 3.4% (control group) or a non-statistically significant difference of 0.023 [95% CI -0.006 to 0.053], i.e., on average, a potential of 23 patients are at risk of thromboembolic complications attributable to tranexamic acid for every 1000 patients treated.

Various published literature that reported that a 2-5% incidence of DVT can normally be expected in orthopaedic surgery, also suggested the effect of tranexamic acid is more pronounced in the surgical wound than in the periphery.

Uncommon Adverse Events (≥ 0.01 to < 1%)

Reported incidences of adverse events in adult patients that are greater in tranexamic acid patients than the control group, are depicted below. The adverse events are listed by system organ class.

Cardiac disorders

Cardiac problems, chest pain, myocardial infarction.

Respiratory, thoracic and mediastinal disorders

Dyspnoea, pulmonary embolism.

Gastrointestinal disorders

Nausea.

Paediatric Cardiac Surgery

No specific safety reports were made from the published studies. Three published studies reported that there were no drug related complications. However, safety data from adult studies should be considered as guidance for the possible types of adverse events which may occur in the paediatric cardiac surgical setting.

Post-marketing Experience

The following adverse events have been reported in association with tranexamic acid therapy.

Nervous system disorders

Seizure (convulsion), dizziness.

Eye disorders

Chromatopsia, visual impairment.

Vascular disorders

Embolism, hypotension (after fast injection).

Renal and urinary disorders

Renal cortical necrosis (e.g., after severe blood loss, such as after post-partum haemorrhage).

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://pophealth.my.site.com/carmreportnz/s/

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 risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Tranexamic acid is a competitive inhibitor of plasminogen activation and at much higher concentrations a noncompetitive 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 µg/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

Adults

Tranexamic acid is eliminated unchanged in urine. Patients with impaired renal function may experience an increased elimination half life for the drug. Immediately after a dose of tranexamic acid was given, plasma levels of tranexamic acid were similar in all cardiac surgery patients. This reflects distribution into body fluid. A linear increase in plasma levels was observed with decreasing renal function (increasing serum creatinine levels) at 24 hours, confirming the need for dose reduction in renally impaired patients (see Section 4.2).

There were no pharmacokinetic studies addressing dose adjustment in the presence of renal failure in patients undergoing orthopaedic surgery. However, the results of pharmacokinetic studies in adult patients undergoing cardiac surgery are also relevant to adult orthopaedic surgical patients (see Sections 4.2 and 4.4).

Paediatrics

There were no specific pharmacokinetic studies in the paediatric population. Clinical experience in paediatric patients < 2 years old is limited and tranexamic acid should only be used if the benefit outweighs the risk. Tranexamic acid should only be used in children aged ≥ 2 years old. In children ≥ 2 years old who are mildly or moderately renally impaired, dose reduction is recommended. Tranexamic acid is not recommended in children with severe renal impairment (see Sections 4.2 and 4.4).

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 anesthetized 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 generalized seizures in rats following application to the cerebral cortex of anesthetized 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.

Reproductive and Developmental Toxicity

There is no clinical data in humans supporting the impact of tranexamic acid on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablets

Colloidal silicon dioxide

Hyprolose

Macrogol 8000

Magnesium stearate

Methacrylic acid copolymer

Microcrystalline cellulose

Povidone

Purified talc

Titanium dioxide

Vanillin.

Solution for Injection

Water for injection.

6.2 Incompatibilities

CYKLOKAPRON solution for injection should **NOT** be mixed with blood for transfusion or infusion solutions containing penicillin.

6.3 Shelf Life

Tablets and Solution for Injection: 36 months.

6.4 Special Precautions for Storage

Tablets: Store below 30°C

Solution for injection: Store below 25°C. Do not freeze. Protect from light. This product does not contain antimicrobial agents. It is for single use in one patient only. Any unused product should be discarded.

6.5 Nature and Contents of Container

CYKLOKAPRON 500 mg tablets are supplied as bottles of 100 tablets.

CYKLOKAPRON 500 mg/5 mL solution for injection is supplied as packs of 10 x 5 mL ampoules.

CYKLOKAPRON 1000 mg/10 mL solution for injection is supplied as packs of 1 x 10 mL ampoule and 10 x 10 mL ampoules.

6.6 Special Precautions for Disposal and Other Handling

CYKLOKAPRON solution for injection can be mixed with the following solutions:

- 0.9% NaCl solution
- 5% glucose solution
- Dextran 40
- Dextran 70
- Ringer's solution (Compound Sodium Chloride).

The required volume of CYKLOKAPRON solution for injection may be added to the chosen infusion solution to achieve final concentrations of 1 or 2 g in 100 mL (10 or 20 mg/mL, 1% or 2%).

The mixture should be used immediately after preparation. If storage is necessary, the mixture should be stored at 2 – 8ºC for a maximum of 24 hours. Mixture not used within 24 hours of preparation, should be discarded.

7. MEDICINE SCHEDULE

S4, Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand.
Toll Free Number: 0800 736 363.
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

14 July 1988.

10. DATE OF REVISION OF THE TEXT

19 March 2026.

Section changed	Summary of new information
All	CYKLOKAPRON – for consistency throughout the document.
4.3, 4.5, 4.7, 4.8, 4.9, 6	Minor editorial changes, alignment with the MedDRA SOC (section 4.8), or alignment with the DS template.
4.8	Addition of 'Seizure' and 'Renal cortical necrosis'
8	Addition of the sponsor's website address.