

AUSTRALIAN PRODUCT INFORMATION – [CYKLOKAPRON® (TRANEXAMIC ACID)]

1. NAME OF THE MEDICINE

Tranexamic acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Cyklokapron tablet contains 500 mg of tranexamic acid.

Each 5 mL ampoule of Cyklokapron solution for injection contains 500 mg tranexamic acid.

Each 10 mL ampoule of Cyklokapron solution for injection contains 1000 mg tranexamic acid.

Each 20 mL vial of Cyklokapron solution for injection contains 2000 mg tranexamic acid.

Cyklokapron Solution for Injection is a clear and colourless solution contains 100 mg/mL tranexamic acid.

3. PHARMACEUTICAL FORM

Cyklokapron is available as film coated tablets and solution for injection.

Cyklokapron solution for injection is a sterile, clear, colourless solution. The pH is 6.5 to 8.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral Administration

Hereditary angioneurotic oedema.

Short term use in the treatment of hyphaema and in patients with established coagulopathies who are undergoing minor surgery.

Menorrhagia.

Intravenous Administration

Adults

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

Paediatrics

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

4.2 Dose and method of administration

Oral Administration

Traumatic Hyphaema

1.0 to 1.5 g every 8 hours for six to seven days.

Menorrhagia

Two tablets (1 g) four times a day, increasing to three tablets (1.5 g) four times a day if needed, for four days. Treatment should be initiated at the onset of visible bleeding, and continued for the first 4 days of the menstrual cycle. Patients should be assessed after three months of treatment.

No efficacy data are available from randomised, controlled clinical trials for treatment beyond three menstrual cycles.

Hereditary Angioneurotic Oedema

Patients who can sense the onset of attacks are best treated intermittently with 2 - 3 tablets, 2 - 3 times a day until symptoms subside. Others should be treated continuously with the same dose.

Prostatectomy

1 g orally six hours pre-operatively followed by 1 g orally 3 to 4 times a day until macroscopic haematuria is no longer present. Treatment beyond two weeks is not recommended.

Patients with Established Coagulopathies undergoing Minor Surgery

Conisation of the Cervix

1.0 to 1.5g (2 to 3 tablets) every 8 to 12 hours for 12 days post-operatively.

Dental operations/extraction

25 mg/kg is given orally two hours before operation. Factor VIII and Factor IX should be given as well as tranexamic acid. After the operation, 25 mg/kg of tranexamic acid is given 3 to 4 times a day for 6 to 8 days.

In Australia, there is no documented clinical evidence to support the use of Cyklokapron solution for injection for traumatic hyphaema, menorrhagia, hereditary angioneurotic oedema, prostatectomy, conisation of the cervix and dental operations or extractions. Cyklokapron tablets should be used in these clinical settings.

Dosage Adjustment in Renal Impairment for orally administered Cyklokapron

eGFR (mL/min/1.73m ²)	Dose	Dose frequency
60 - 89	15 mg/kg body weight	Twice daily
30 - 59	15 mg/kg body weight	Daily
<29	7.5 mg/kg body weight	Daily

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 15mg/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 (also see Section 5.1 Pharmacodynamic properties - Clinical trials).

Dosage Adjustment in the Elderly

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

Dosage Adjustment in Renal Impairment

Adult Cardiac Surgery

eGFR (mL/min/1.73m ²)	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/1.73m²)	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.

Use in Paediatric Population ≥ 2 years old

Paediatric Cardiac Surgery

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 (see Section 5.1 Pharmacodynamic properties - Clinical trials - Paediatrics Cardiac Surgery and Section 4.4 Special warnings and precautions for use - Paediatric use).

Dosage Adjustment in Paediatric Population ≥ 2 years with Renal Impairment

eGFR (mL/min/1.73m²)	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

Cyklokapron solution for injection is intended for intravenous administration (intravenous injection and infusion). 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.

Rapid intravenous injection may cause dizziness and/or hypotension (refer to Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects) - Post-marketing experience).

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 - 8°C for a maximum of 24 hours. Mixture not used within 24 hours of preparation, should be discarded.

4.3 Contraindications

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 excipients.

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 Dose and method of administration). 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.

Rapid intravenous injection of Cyklokapron solution for injection may cause dizziness and/or hypotension. 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 (refer to Section 4.2 Dose and method of administration and Section 4.8 Adverse effects (undesirable effects) - Post-marketing experience).

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 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 investigation is needed to assess the significance of this potential hazard. Safety data from pooling of published studies, indicated a statistically non-significant higher incidence in thromboembolic complications in the tranexamic acid group compared to non-active controls in adult patients undergoing total knee arthroplasty (risk difference = 0.023 [95% CI: -0.007 to 0.053]) and in adult patients undergoing total hip arthroplasty (risk difference = 0.012 [95% CI: -0.012, 0.036]).

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.

There are no data on the use of tranexamic acid in women taking oral contraceptive agents.

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.

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 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 (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.

Convulsions have been reported in association with tranexamic acid treatment

Use in 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.

Use in 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 5.1 Pharmacodynamic properties - Clinical trials and Section 4.2 Dose and method of administration).

For both the adult and the paediatric patient, an eGFR ≥ 90 mL/min/1.73 m² 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.

Use in the elderly

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

Paediatric use

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 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 Dose and method of administration - Paediatric Cardiac Surgery and Section 4.4 Special warnings and precautions for use - Use in renal impairment).

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Clinically important interactions have not been observed with tranexamic acid tablets. There are no specific drug-drug interactions data for tranexamic acid. 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.

Cyklokapron solution for injection should not be mixed with blood for transfusion or infusion solutions containing penicillin.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Fertility was not affected in male or female rats at high oral doses (up to 850 - 880 mg/kg/day).

Use in pregnancy – Pregnancy Category B1

Drugs which have been taken by only a limited number of 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.

Previous studies in rats (at up to 1000 mg/kg/day PO) showed no effects of tranexamic acid on embryonic or neonatal development. In rabbits, increased foetal losses and lower litter weights were noted at 200 mg/kg IV and 400 mg/kg PO (but not at 100 mg/kg IV or 200 mg/kg PO). There was no effect on rat or rabbit young survival (including one IV teratology study in rabbits at 50 - 200 mg/kg).

The long-term clinical experience is limited to 21 pregnant women, treated for one to 18 weeks, in most cases to prevent further haemorrhage in connection with abruptio placentae. Whilst premature births were reported in infants who were born, all of these infants were born healthy. 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.

Use in lactation

Tranexamic acid is secreted in the mother's breast milk at a concentration of about a hundredth of the corresponding serum levels. While an antifibrinolytic effect in the infant is unlikely at therapeutic doses, caution should be exercised when tranexamic acid is administered to a nursing woman.

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 Adverse effects (undesirable effects)

Oral Administration

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 $<1\%$)

Immune System disorders: dermatitis allergic.

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 ($\geq 1\%$ 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.

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.

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.

Central Nervous System disorders

The most commonly reported CNS 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.

Table 1: Adverse events $\geq 1\%$ 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 patients¹ (N= 1055)
<i>Fatal</i> death	0.8%	6.8%	1.0%	2.2%	3.6%
<i>Cardiac disorders</i>					
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
<i>Central Nervous System disorders</i>					
stroke	0.2	1.5	0.2	1.8	3.1
<i>Renal disorders</i>					
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	-	-
<i>Respiratory, thoracic & mediastinal disorders</i>					
respiratory failure	-	-	-	-	9.5

Control group = Placebo or no antifibrinolytic treatment

¹782 of the 1055 patients are high risk cardiac surgery patients. Also refer to Table 2.

Table 2: Adverse events $\geq 1\%$ 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
Central Nervous System disorders			
stroke	2.5	2.8	3.1
Renal disorders			
renal dysfunction	12.0	12.8	9.2
renal failure	14.2	16.9	13.6
Respiratory, thoracic & mediastinal disorders			
respiratory failure	10.6	12.6	9.5
Vascular			
DVT or pulmonary embolism	1.0	0.9	0.8

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

¹779 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 ($\geq 1\%$ 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.

Cardiac disorders: cardiac ischaemia, ventricular arrhythmia, ventricular tachycardia.

Central Nervous System disorders: left hemiparesis, left-sided weakness, neurologic dysfunction, neurological complications.

Eye disorders: retinal artery embolus.

Gastrointestinal disorders: bowel infarction.

Immune System disorders: hypersensitivity including anaphylactic shock.

Respiratory, thoracic & mediastinal disorder: pulmonary complications, pulmonary oedema.

Vascular disorders: 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 ($\geq 10\%$) and commonly (≥ 1 to $<10\%$) reported adverse events. The frequency of vascular disorders, reported as DVT, are summarised in Table 3.

	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.

Gastrointestinal disorder: nausea.

Respiratory, thoracic & mediastinal disorder: dyspnoea, pulmonary embolism.

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

Rare side effects (≥ 0.01 to $< 0.1\%$)

Central Nervous System disorders: convulsion, dizziness.

Eye disorders: chromatopsia, visual impairment.

Vascular disorders: embolism, hypotension (after fast injection).

Rapid intravenous injection may cause dizziness and/or hypotension (refer to Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration). To avoid this response, 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

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

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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 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 1 mg/mL and 10 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 (α 2-PI & α 2-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.

Clinical trials

The efficacy of tranexamic acid for use in adult cardiac surgery, total knee and hip arthroplasty as well as in paediatric cardiac surgery was established via meta-analysis of data from published, randomised, placebo or non-active controlled clinical trials. The outcome measures used in the meta-analyses for all surgical settings were reduction in mean post-operative blood loss (primary outcome) and reduction in the risk of transfusion of blood or blood products (secondary outcome), versus the control group. Estimates of the effect of the primary outcome are expressed as the mean difference in post-operative blood loss (mL) between treatment groups as well as savings in blood loss (%). Savings in blood loss is defined as % difference between the control group blood loss and the tranexamic acid group.

Meta-analyses to determine the efficacy of tranexamic acid were performed by grouping patients by total dose range as well as mean blood loss, versus the non-active control group. “Control” or “Control group” is defined as those patients who received a saline placebo or patients who received no antifibrinolytic treatment.

The studies were grouped into four dose categories based on the total dose administered, namely <20 mg/kg, 20 - 50 mg/kg, 51 - 100 mg/kg and >100 mg/kg. The blood loss groups in the meta-analyses were <300 mL, 300 - 600 mL, 601 - 900 mL and >900 mL. The mean blood loss versus control group was a surrogate measure of the underlying surgical risk. Heterogeneity by total dose was significant because of the varied doses and dosage regimens used in the pooled studies. Sub-grouping by blood loss categories reduced or minimised the heterogeneity caused by pooling of surgical procedures of substantially different complexity, as well as differences in post operative patient management.

Adult Cardiac Surgery

A total of 2112 adult cardiac patients were treated with tranexamic acid in 53 prospective, randomised, controlled (placebo or no-antifibrinolytic treatment) studies in the peer reviewed literature. Of these 53 studies, 37 were placebo controlled studies. In all of these 37 studies mean and standard deviation or confidence intervals were reported, which permitted pooling of results for meta-analysis. In these 37 studies, there were 1525 tranexamic acid treated patients and 1480 patients in the control group.

The mean age of patients in the studies varied between 44 and 75 years. In 33 studies that reported patient gender ratio, 69% were male and 31% were female. The most commonly used

medications by these patients were β -blockers or calcium channel blockers, aspirin and NSAIDs. Apart from aspirin, NSAIDs and anti-coagulants, the use of medications prior to surgery was poorly described in the studies.

The percentage breakdown of the various surgical procedures was 70% coronary artery bypass graft (CABG), 16% valve replacement, 5% CABG plus valve replacement and 9% made up of the following: repeat CABG, repeat valve replacement, atrio-septal repair or aortic dissection or aneurysm.

The cardiopulmonary bypass procedure was similar across studies with patients heparinised to activated coagulation time (ACT) >400 or 480 seconds during surgery and reversed with protamine after chest closure. CPB was mildly hypothermic (approximately 32°C) except for those studies designed to study normothermic perfusion effect on postoperative blood loss and platelet preservation. CPB times were usually reported in the studies and ranged from 1 - 2 hours.

There were 2 meta-analyses of the effect of tranexamic acid on post-operative blood loss for cardiac surgery (“Duplicates removed” and “Duplicates included”). The results for the tranexamic acid versus placebo-control comparisons presented below are the “Duplicates removed” meta-analysis. The results were similar for “Duplicates removed” and “Duplicates included” suggesting that no significant bias occurred, from repeat inclusions of the same control data, in the “Duplicates included” meta-analysis.

At doses of tranexamic acid that varied from 18 - 188 mg/kg total dose, post-operative blood loss was reduced by 240 mL [95% CI:188, 292, $p < 0.001$] compared to control. For the 20 - 50 mg/kg total dose group, the reduction in post-operative blood loss was 225 mL [95% CI: 177, 274, $p < 0.001$], compared to control. Similarity in effectiveness between a total dose ranging from 20 - 50 mg/kg and a total dose ranging between 18 - 188 mg/kg, resulted in the recommended total dose of 24 mg/kg for adult cardiac surgery (based on a 2 hour surgical procedure). This was also the most commonly used dose in published literature: <20 mg/kg (377 out of 1525 patients), 20 - 50 mg/kg (487/1525 patients), 51 - 100 mg/kg (269/1525 patients) and >100 mg/kg (392/1525 patients).

Categorised by blood loss, tranexamic acid (total dose 20 - 50 mg/kg), reduced post-operative blood loss in the 300 - 600 mL, 601 - 900 mL and >900 mL control blood loss categories by 134 mL, 256 mL and 370 mL vs the mean control group blood loss of 487 mL, 761 mL and 1060 mL, respectively. The mean savings in blood loss expressed as a percentage were 27.1% with the 300 - 600 mL category, 33.9% with the 600 - 900 mL category and 34.4% with the >900 mL category, respectively. Although the absolute difference in post-operative blood loss increased over the blood loss categories, similarity of the percentage reduction in the various categories above suggests that the same dose can be used in low as well as high risk surgical procedures.

Thirty five out of the 37 studies also reported the relative risk of transfusion vs control. The relative risk reduction due to tranexamic acid (20 - 50 mg/kg total dose) was 28% (RR = 0.72 [95% CI: 0.62, 0.83, $p < 0.001$]). The overall relative risk reduction of transfusion due to tranexamic acid (12 - 150 mg/kg total dose) was 29% (RR = 0.71 [95%CI: 0.63, 0.80, $p < 0.001$]).

The results of a meta-analysis that combined 22 studies and examined the risk of re-operation due to uncontrolled bleeding, indicated that at the highest blood loss category (>900 mL), there

was a risk reduction of 3.3% [95% CI: 0.5, 5.9] in favour of tranexamic acid patients, as compared with placebo. On average, tranexamic acid will abolish the need for re-operation for uncontrolled bleeding in 1 out of every 33 patients.

Adult Total Knee Arthroplasty

Sixteen prospective, randomised, placebo or non-active controlled studies were identified from peer review published literature. Of the 16 studies, 11 were pooled to determine the efficacy of tranexamic acid in reducing post-operative blood loss (primary outcome) and risk of transfusion (secondary outcome) in patients undergoing total knee arthroplasty. Only the “Duplicates included” meta-analysis was conducted as an estimate of the effect tranexamic acid on post-operative blood loss for total knee arthroplasty. The 11 studies included 365 tranexamic acid treated patients and 390 non-active control patients.

The mean age of patients in the studies varied between 65 and 77 years. The ratio of females to males was 65.9% vs 34.1%. Surgery was conducted using an inflated tourniquet and exsanguination of the operation site. Both cemented and non-cemented prostheses were used. Patients were instructed to stop taking aspirin from 1 - 14 days prior to surgery. All patients received low molecular weight heparin (LMWH) or aspirin post surgery for prophylaxis against thromboses. Three of the 16 studies reported that patients received physiotherapy from day 1 post surgery. Tranexamic acid was given prior to release of the tourniquet in all studies included in the meta-analysis.

Of the 365 tranexamic acid treated patients included in the meta-analysis, 34.5% of patients received a total dose of tranexamic acid <20 mg/kg, 43% received 20 - 50 mg/kg and 22.5% patients received doses >100 mg/kg. No patients received a total dose of tranexamic acid between 51 - 100 mg/kg. In the group where total tranexamic acid dose ranged from 14 - 150 mg/kg, the overall reduction in post-operative blood loss was 331 mL [95% CI: 246, 416, $p < 0.001$] compared to control. Similar results were obtained for the group in which 20 - 50 mg/kg total dose was administered 345 mL [95% CI: 179, 510, $p < 0.001$] and the group in which >100 mg/kg total dose was administered 359 mL [95% CI: 200, 518, $p < 0.001$], suggesting similar effectiveness for these two treatment groups.

Categorised by control blood loss, reductions in post-operative blood loss for tranexamic acid treated patients were 214 mL [95% CI: 155, 273, $p < 0.001$] in the 300 - 600 mL category and 557 mL [95% CI: 367, 748, $p < 0.001$] for the >900 mL category. The mean control group blood loss was 448 mL in the 300 - 600 mL category and 1329 mL in the >900 mL category, which equates to a blood saving of 47.5% and 41.9%, respectively. There were no data in the <300 mL or the 600 - 900 mL categories.

The meta-analysis to determine relative reduction in risk of transfusion comprised 15 pooled studies of 487 tranexamic acid treated patients and 514 control group patients. The results of this meta-analysis demonstrated that the overall relative risk of receiving a blood transfusion in patients given a total dose of tranexamic acid of 14 - 150 mg/kg, was significantly reduced by 64%, (RR = 0.36 [95% CI: 0.25-0.50]), as compared to control. The mean of this total dose range was 55 mg/kg (14 - 150 mg/kg) and is similar to the recommended total dose of 60 mg/kg.

The recommended total dose of 60 mg/kg comprises an initial bolus dose of 15 mg/kg prior to skin incision and repeat doses of 15 mg/kg at 8 hourly intervals. An intermittent dosing regimen is recommended so that the need for subsequent dosing is based on assessments of

ongoing blood loss. The majority of patients require anti-fibrinolytic cover maintained for the first 24 hours post-operatively. A fourth dose of 15 mg/kg may be administered if clinically significant blood loss is observed at 24 hours. The effectiveness of the recommended dose is expected to be comparable to that of the 20 - 50 mg/kg total dose and the >100 mg/kg total dose. Comparability of the recommended dose to the most commonly used dosage regimen in published studies, which consisted of 15 mg/kg boluses every 8 hours starting immediately or up to 30 minutes before the release of the tourniquet with fibrinolytic cover maintained for the first 24 hours post-operatively, suggests that the recommended dose is the most appropriate dose to provide peri-operative fibrinolytic cover when the main blood loss occurs.

Adult Total Hip Arthroplasty

Eleven prospective, randomised, blinded, placebo or non-active controlled studies were pooled into a meta-analysis to determine the efficacy of tranexamic acid in reducing post-operative blood loss (primary outcome) and risk of transfusion (secondary outcome) in patients undergoing total hip arthroplasty. No “Duplicates” were included in the meta-analysis of pooled studies in total hip arthroplasty.

Of the 11 studies, 10 included patients undergoing total hip arthroplasty for the treatment of osteoarthritis or osteonecrosis and 1 was for patients who had hip arthroplasty to repair hip fracture. The 11 studies included 262 tranexamic acid treated patients. Of these patients, 203 (72.0%), received total doses of tranexamic acid in the range 10 - 15 mg/kg and the remainder received 20 - 30 mg/kg. There were 274 non-active control patients. There were no studies in the meta-analysis that used tranexamic acid at the recommended total dose of 60 mg/kg.

The mean age of the patients in the studies varied from 44 - 73 years. A similar number of males (48.7%) and females (51.3%) were included in the studies. Seven studies reported that patients were requested to stop taking NSAIDs from 1 - 7 days prior to surgery. These 7 studies also reported that patients received LMWH as prophylaxis against thrombosis. Three studies expressly stated no LMWH regimen was used and in one study no information was provided.

Overall, tranexamic acid (10 - 30 mg/kg total dose), reduced post-operative blood loss by 159 mL [95% CI: 101-216 mL, (p <0.001)] versus control. Post-operative blood loss was reduced by 144 mL [95% CI: 80, 208, p <0.001] for the 10 - 19 mg/kg total dose range and 239 mL [95% CI: 60, 417, p = 0.009] for the 20 - 30 mg/kg total dose range. Blood loss reduction was not clinically significant (1 unit of blood) for those patients who received a total dose <20 mg/kg, or in those that received a single dose of 10 mg/kg without repeat doses or infusion. These doses were considered inadequate to ensure maintenance of plasma levels at or above the IC₅₀ for antifibrinolysis. There was a trend to improved reduction in blood loss with total doses >20 mg/kg and for doses given over an extended period. Clinically significant blood loss reduction was only observed when a total dose of 30 mg/kg was administered.

Reductions in post-operative blood loss, by control blood loss categories, were 119 mL [95% CI: 63, 174, p <0.001] for the 300 - 600 mL category, 269 mL [95% CI: 128, 410, p <0.001] for 600 - 900 mL category, and 292 mL [95% CI: 155, 429, p <0.001] for >900 mL category for patients who were given tranexamic acid. The mean control group blood loss values for the same blood loss categories were 425 mL, 789 mL and 974 mL, respectively. The savings in blood loss due to tranexamic acid were 28.0%; 34.1% and 30.0%, respectively. These results suggested that tranexamic acid is likely to be more effective in patients at risk of higher volume blood loss (>600 mL) than patients at risk of lower volume blood loss.

Results of the meta-analysis from 10 studies that were pooled, reported that tranexamic acid (10 - 30 mg/kg total dose) reduced the risk of allogenic blood transfusion by 40% (RR: 0.60 [0.44, 0.82], $p = 0.001$), compared to control. The 10 - 19 mg/kg and the 20 - 30 mg/kg tranexamic acid dose groups reduced the risk of blood transfusion by 41% [95% CI: 7, 63, $p = 0.02$] and 42% [95% CI: 10, 63, $p = 0.02$], respectively, compared to control.

There are limited well-designed dose selection studies in hip arthroplasty. Six studies included in the meta-analysis did not use sufficiently high doses to adequately control blood loss. Published pharmacokinetic studies in hip arthroplasty show that a total dose of 20 mg/kg of tranexamic acid, given as an initial dose of 10 mg/kg which was repeated 3 hours later, was too low to maintain plasma levels 10 $\mu\text{g/mL}$ over 8 hours. *In vitro* studies showed a dosing regimen comprising 10 mg/kg as an initial dose followed by an infusion of 1 mg/kg tranexamic acid, should maintain plasma levels at or above the IC_{50} for antifibrinolysis (see Section 5.2 Pharmacokinetic properties). Meta-analysis of published studies suggests that the recommended dosing regimen in knee surgery is effective in reducing blood loss and the need for blood transfusion. As the haemostatic responses of hip and knee surgery are very similar, the same dosage regimen is expected to be effective for hip surgery.

Paediatric Cardiac Surgery

Six prospective, randomised, placebo or non-active controlled studies in paediatric cardiac surgery were identified in peer reviewed literature. The 6 studies included 247 patients treated with tranexamic acid, of whom 130/247 received total doses of 20 - 50 mg/kg. Three studies, representing 165/247 (66.8%) of patients treated with tranexamic acid, reported sufficient information for inclusion in the meta-analysis. There were 76 non-active control patients, included in the meta-analysis.

The mean age of the patients in the studies varied from 1 day to 15 years old. The average weight of the study populations varied from 3 to 60 kg. The sex of the patients were reported in 2 studies, and of these patients, 74.2% (121/163) were male.

All surgery was conducted using CPB. Those studies that described the CPB procedure used heparinisation during surgery, reversed with protamine upon chest closure. Two studies reported using transfusion protocols, 2 reported not using protocols and 2 did not comment.

Meta-analyses to determine the efficacy were performed and were grouped by age, total dose and dosage regimen. The effect of tranexamic acid on post-operative blood loss for cardiac surgery included 2 meta-analyses (“Duplicates removed” and “Duplicates included”). The results for the tranexamic acid versus placebo-control comparisons presented below are the “Duplicates removed” meta-analysis.

Distribution of patients by age group was 2.9% for <2 years old, 56.6% for 2 - 4 years old and 40.5% for >4 years old. When grouped by total dose of tranexamic acid, 17% received <20 mg/kg, 80% received 20 - 50 mg/kg and 3% received >100 mg/kg. The most common dosage regimen was a single pre-surgical dose (50%), the next most common regimen comprised a pre-surgical dose and a post surgery dose (32%) and the least common regimen comprised a pre-surgical dose and a maintenance dose (18%).

Post-operative blood loss (40 - 220 mg/kg total dose) was reduced by 9.0 mL/kg [95% CI: 4.0, 14.0, $p < 0.001$]. When given a total dose 20 - 50 mg/kg, the mean control group blood loss was 36.8 mL, representing a blood saving of 31% for tranexamic acid treated patients.

By age group, the reductions in post-operative blood loss due to tranexamic acid were 14.1 mL/kg [95% CI: 12.6, 40.8] in the <2 years old; 10.7 mL/kg [95% CI: 4.3, 17.0] in the 2 - 4 years old and 10.8 mL/kg [95% CI: 1.0, 20.6] in the >4 years old, compared to control. The mean control group blood loss values were 37.9 mL/kg, 39.2 mL/kg and 31.6 mL/kg in the <2 years old, 2 - 4 years old and >4 years old group categories, respectively. This represents a blood saving of 28.2%, 27.5% and 44.6% with $p = 0.3$, $p = 0.001$ and $p = 0.03$, respectively.

Only one of the three studies reported sufficient data for analysis of the reduction in risk of blood transfusion. From this study, the combined tranexamic acid treatment (18 - 50 mg/kg total dose) reduced packed red blood cell (RBC) use in 24 hours by 5.0 mL/kg [95% CI: 2.2, 7.9] compared to placebo. The results of one study that was not included in the meta-analysis showed a reduction in post-operative blood loss of 29% in children weighing <15 kg but packed RBC requirements were greater in tranexamic acid treated patients than placebo (refer to Table 4). There was no meta-analysis examining the relative risk of blood transfusion in tranexamic acid and control patients.

As the validity of the meta-analysis is questionable because of the small patient numbers, the results should be interpreted cautiously. The results of the relevant clinical studies may be more informative when examined individually and have been summarised in the table below.

Study	N	Age	Load (mg/kg)	Infusion (mg/kg/h)	Prime (mg/kg)	Difference (mL/kg)	Saving	P-value	TFN
^Chauhan 2004	60	2m-15 yr	50	-	-	-5	14%	NS	NS
			10	1 mg/kg/h, iv	-	-8	22%	<0.05	SS
			10	2 x 10 mg/kg, bol	-	-16	44%	<0.05	SS
			20	20 mg/kg, bol	-	-14	39%	<0.05	SS
^Zonis 1996	82	1d-14 yr	50	-	-	-6	22%	NS	n/a
Reid 1997	41	6m-12 yr	100	10 mg/kg/h, iv	10	-8	29%	0.03	SS
~ Shore-Lesserson 2002	unknown	unknown	20	2 mg/kg/hr, iv	200 mg	-8	29%	0.046	SS*

N: total no. of patients (i.e. TXA plus control); d: day(s); m: month(s); yr: year(s); Difference: TXA post-operative blood loss minus control blood loss post-operative blood loss; Saving: % saving in post-operative blood loss due to TXA; TFN: transfusion requirements of red blood cells and/or products; SS: transfusion requirement was statistically significantly greater with placebo than TXA, SS*: transfusion requirement was statistically significantly greater with TXA than placebo; iv: intravenous; bol: bolus; ^: study included in meta-analysis; ~: study not included in meta-analysis.

Zonis *et al.*, The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. *Journal of Thoracic and Cardiovascular Surgery*, 1996, 111(5): 982-987

Shore-Lesserson *et al.*, Tranexamic Acid Reduces Postoperative Bleeding but Not Transfusions in Pediatric Cardiac Surgical Patients. *Anesthesiology Abstracts of Scientific Papers Annual Meeting*, 2002, no. 2002, p. Abstract No. A-135

Chauhan *et al.*, Dose comparison of tranexamic acid in pediatric cardiac surgery. *Asian Cardiovascular & Thoracic Annals*, Jun 2004, 12(2):121-4

Only one study included in the meta-analysis examined the effect of different doses of tranexamic acid on postoperative blood loss and blood product requirements. In this study, 150 children were assigned, 30 per group, to the following 5 groups: Group A: the control group (who did not receive any tranexamic acid); Group B: who received 50 mg/kg of tranexamic acid at induction of anaesthesia; Group C: 10 mg/kg at induction followed by an

infusion of 1 mg/kg/h; Group D: 10 mg/kg at induction, 10 mg/kg at bypass and 10 mg/kg after protamine; Group E: 20 mg/kg at induction and after protamine.

Among the 4 groups given tranexamic acid, Group D (triple dose) had the best results (a reduction in post-operative blood loss of 16 mL/kg and % blood savings of 44%). This was followed by Group E (double dose) and Group B (single bolus dose) showed the worst results (a reduction in post-operative blood loss of 5 mL/kg and a % blood savings of 14%), i.e., the most effective regimen was the one comprising 10 mg/kg at induction, 10 mg/kg at bypass and 10 mg/kg after protamine (refer to results in Table 4).

The recommended dose, a total dose of 20 mg/kg, given as a pre-surgical bolus dose of 10 mg/kg and a repeat bolus dose of 10 mg/kg after CPB, is similar to that used in adult cardiac surgery. This is within the most commonly used dose range of 20 - 50 mg/kg. The dosage regimen is also consistent with data in adult cardiac surgery, which indicated that the best results were achieved by a dosage regimen comprising a pre-surgical dose followed by a repeat dose so that plasma levels in the antifibrinolytic range are maintained during surgery (see Section 4.4 Special warnings and precautions for use - Paediatric use and Section 4.2 Dose and method of administration - Paediatrics Cardiac Surgery)

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.

Metabolism

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.

Excretion

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.

Adult Cardiac Surgery

There were no studies conducted in the patients with cardiac impairment. Published pharmacokinetic studies were conducted in healthy volunteers.

Published studies that examined tranexamic acid kinetics in patients undergoing cardiopulmonary bypass (CPB) surgery suggest that a “two compartment model” to predict plasma levels, adjusted for weight (mg/kg) dose, was a reasonable predictor of actual levels in patients.

In vitro studies showed that a dosing regimen of 10 mg/kg as an initial dose followed by an infusion of 1 mg/kg tranexamic acid resulted in adequate plasma concentration to prevent fibrinolysis. Tissue plasminogen activator activity is reduced by 80% at a tranexamic acid concentration of 10 µg/mL, and plasmin induced platelet activation is inhibited at a tranexamic acid concentration of 16 µg/mL (half maximal inhibitory concentration, IC₅₀).

Whilst the *in vivo* concentration needed to inhibit fibrinolysis is unknown, published studies consider it likely to be <52 µg/mL. From published studies, the relationship is linear between total dose (assuming a 4 hours surgical procedure) and tranexamic acid steady state plasma concentration (C_{ss}). Based on linear pharmacokinetics, the estimated C_{ss} is approximately 42.5 µg/mL for the recommended dose in adult cardiac surgery, i.e., a total dose of 33 mg/kg for 4 hours of surgical time.

A common feature in published pharmacokinetic studies was a pre-surgical loading dose, administered after induction of anaesthesia but before skin incision, followed by a maintenance infusion for the duration of surgery, with or without an additional dose added to the CPB prime.

Studies that examined the need for extended infusion of tranexamic acid beyond chest closure concluded that tranexamic acid administered after chest closure is not effective in reducing blood loss.

The effect of renal impairment on tranexamic acid plasma concentration was investigated in 28 patients with chronic renal disease. Plasma levels 24 hours post dose showed a linear increase with decreasing renal function (increasing serum creatinine levels). In healthy volunteers, following administration of a single intravenous dose of 10 mg/kg, plasma concentrations after 1, 3 and 5 hours were 18.3, 9.6 and 5 mg/L, respectively. In renally impaired patients, after administration of the same dose, the serum concentrations after 5 hours were 13.1 mg/L (serum creatinine 120 to 249 µmol/L), 18.0 mg/L (serum creatinine 250 to 500 µmol/L), and 20.7 mg/L (serum creatinine >500 µmol/L), i.e., the highest concentrations occurred in the group with the highest creatinine values. These results suggest that dose adjustment is necessary in renally impaired patients.

Adult Hip Surgery

In one published study that reported details of tranexamic acid kinetics in patients undergoing hip surgery, a total dose of 20 mg/kg of tranexamic acid was given via an initial dose of 10 mg/kg followed by a repeat dose of 10 mg/kg 3 hours later. The median age of the 10 patients with normal renal function was 77 years [range: 51 - 80]. Tranexamic acid concentration from blood collected before administration of the first dose and then at 3, 4, 5, 10 hours and 16 - 24 hours after the first dose showed that a plasma concentration >10 µg/mL was not maintained over 8 hours in all 10 treated patients.

There were no pharmacokinetic data on the recommended dose of 60 mg/kg in orthopaedic surgery given as an initial 15 mg/kg bolus repeated at 8 hourly intervals to a maximum time of 24 hours after surgery.

Special Populations

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 Dose and method of administration).

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 Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration).

Children and Adolescents

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 Section 5.1 Pharmacodynamic properties - Clinical trials, Section 4.4 Special warnings and precautions for use, and Section 4.2 Dose and method of administration).

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

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 Sherman-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

Each Cyklokapron tablet contains the following inactive ingredients: microcrystalline cellulose, purified talc, magnesium stearate, colloidal anhydrous silica, povidone, hypolose, titanium dioxide, macrogol 8000, vanillin and the proprietary ingredient, Eudragit E100(ID Number 1753)

Each 5 mL ampoule of Cyklokapron solution for injection contains 5 mL Water for Injections as the inactive ingredient.

Each 10 mL ampoule of Cyklokapron solution for injection contains 10 mL Water for Injections as the inactive ingredient.

Each 20 mL vial of Cyklokapron solution for injection contains 20 mL Water for Injections as the inactive ingredient.

6.2 Incompatibilities

Cyklokapron solution for injection should not be mixed with blood for transfusion or infusion solutions containing penicillin.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Tablets: Store below 30°C (bottles); Store below 25°C (blisters).

Solution for Injection 500 mg/5 mL ampoules and 1000 mg/10 mL ampoules: Store below 25°C. Do not freeze. This product does not contain antimicrobial agents. It is for single use in one patient only. Any unused product should be discarded.

Solution for Injection 500 mg/5 mL ampoules and 1000 mg/10 mL LDPE ampoules: Store below 25°C. This product does not contain antimicrobial agents. It is for single use in one patient only. Any unused product should be discarded.

Solution for Injection 2000 mg/20 mL vial: Store below 30°C. 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 Tablets are available in a HDPE bottle of 20 and 100 tablets. They are also available as PVC/PVDC/Al blister packs of 36 tablets, 96 tablets and 108 tablets.

Cyklokapron Solution for Injection containing 500 mg tranexamic acid and 5 mL Water for Injections is supplied as packs of 5 x 5 mL and 10 x 5 mL glass ampoules.

Cyklokapron Solution for Injection, containing 500 mg tranexamic acid and 5 mL Water for Injections, is also supplied as packs of 10 x 5 mL LDPE ampoules

Cyklokapron Solution for Injection containing 1000 mg tranexamic acid and 10 mL Water for Injections is supplied as packs of 1 x 10 mL and 10 x 10 mL glass ampoules.

Cyklokapron Solution for Injection, containing 1000 mg tranexamic acid and 10 mL Water for Injections, is also supplied as packs of 10 x 10 mL LDPE ampoules.

Cyklokapron Solution for Injection containing 2000 mg tranexamic acid and 20 mL Water for Injections is supplied as a pack of 5 x 20 mL “Theatre Pack” glass vial with a siliconised, halobutyl rubber stopper. Each vial is individually packaged inside a sealed polyester peel pouch.

*Not all pack sizes and presentations are distributed in Australia

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

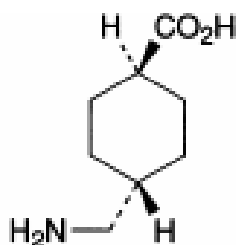
6.7 Physicochemical properties

Tranexamic acid is a white crystalline powder that is odourless or almost odourless. It is freely soluble in water and in glacial acetic acid, practically insoluble in methanol, ethanol, acetone, diethyl ether and benzene.

The pKa: 4.3 and 10.6.

Chemical structure

The chemical structure of tranexamic acid is:



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

The molecular formula of tranexamic acid is C₈H₁₅NO₂ and its molecular weight is 157.2.

CAS number

1197-18-8.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Blister pack of 36 tablets - Pharmacist Only Medicine (S3).

All other packs and presentations - Prescription Only Medicine (S4).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Cyklokapron 500 mg tablets (bottle): 05 Sept 1991.

Cyklokapron 500 mg tablets (blister) : 05 August 1999

Cyklokapron 500 mg/5ml and 1000mg/10ml Solution for injection: 16 September 2010

Cyklokapron 2000 mg/20ml Solution for injection: 15 April 2014

10. DATE OF REVISION

07 April 2020

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
All	Reformatted in line with the new TGA PI form
3; 4; & 6	Minor Editorial updates
8	Sponsor details updated
9	Section updated to align with ARTG information