



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tranexamic acid

Proprietary Product Name: Cyklokapron

Sponsor: Pfizer Australia Pty Ltd

December 2010

TGA Health Safety
Regulation

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of indications/New dosage form
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	10 September 2010
<i>Active ingredient(s):</i>	Tranexamic acid
<i>Product Name(s):</i>	Cyklokapron
<i>Sponsor's Name and Address:</i>	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
<i>Dose form(s):</i>	Solution for Injection
<i>Strength(s):</i>	1000 mg /10 mL; 500 mg/5 mL
<i>Container(s):</i>	Glass Type I ampoules
<i>Pack size(s):</i>	500 mg/5 mL in packs of 5 and 10 ampoules 1000 mg/10 mL in packs of 1 and 10 ampoules
<i>Approved Therapeutic use:</i>	<u>Adults:</u> For the reduction of peri- and post-operative blood loss and the need for blood transfusions in patients undergoing cardiac surgery or total knee arthroplasty or total hip arthroplasty. <u>Paediatrics:</u> For the reduction of peri- and post-operative blood loss and the need for blood transfusions in patients undergoing cardiac surgery.
<i>Route(s) of administration:</i>	Intravenous (IV)
<i>Dosage:</i>	The IV dosage is dependent on patient age and the type of surgery (see Product Information, Attachment 1, for details).
<i>ARTG number(s)</i>	160658 and 166415

Product Background

Tranexamic acid is trans-4-aminomethylcyclohexane-carboxylic acid and is a competitive inhibitor of plasminogen activation and, at much higher concentrations, a non-competitive inhibitor of plasmin. This compound appears to interfere with the fibrinolytic process in the same way as aminocaproic acid. However, tranexamic acid is about 10 times more potent *in vitro* than aminocaproic acid.

Applications for marketing of this product were considered at three previous meetings of the Australian Drug Evaluation Committee (ADEC; now succeeded by the Advisory Committee for Prescription Medicines or ACPM) 42nd, 46th & 51st over the years 1971-1972. At that time the indications proposed were severe haemorrhaging associated with menorrhagia, prostatectomy or bladder surgery, post-partum haemorrhage and any other bleeding conditions where the primary cause was enhanced fibrinolysis. At the 90th meeting of the ADEC in March of 1980, an application for the 500 mg tablets with an indication restricted to hereditary angioneurotic oedema was recommended for approval. At the 130th meeting in August 1987 the ADEC had no objections to the extension of indications for tranexamic acid 500 mg tablets to include short-term use in the treatment of hyphaema and in patients with established coagulopathies who are undergoing minor surgery. Use for epistaxis or menorrhagia was not recommended for approval. At the same time an application to market an IV formulation for haemorrhage and risk of haemorrhage in increased fibrinolysis or

fibrinogenolysis was rejected on the grounds of inadequate data. The nonclinical data (specifically the pharmacokinetic (PK) data) were deficient. An increased incidence of gastrointestinal tract (GIT) adverse events (AEs), including diarrhoea, vomiting, salivation, as well as alkalosis, ocular and renal toxicity and intravascular clotting were highlighted by the nonclinical evaluator. In relation to the proposed indication of post-operative use in prostatectomy, there were insufficient data to allow a firm recommendation about how long after surgery the first dose should be administered as no clinical basis for slow IV infusion had been provided. A major unanswered question related to the effects of long-term use. At the 186th meeting of the ADEC in October 1996 the extension of indications for the tablet to include treatment of menorrhagia was recommended for approval.

The current submission from Pfizer to register Cyklokapron IV has been prompted by the continuing and increasing use of the drug under the Special Access Scheme (SAS) following worldwide marketing withdrawal of aprotinin (Trasylol) by Bayer in November 2007. Worldwide marketing withdrawal of Trasylol followed release of preliminary data from the BART (Blood Conservation Using Antifibrinolytics: A Randomised Trial in High-Risk Cardiac Surgery) clinical study which showed an increased risk of death in patients treated with aprotinin compared with tranexamic acid (TXA) or epsilon aminocaproic acid (EACA) for control of bleeding during high-risk cardiac surgery. The BART data were subsequently published [Fergusson 2008¹]. In discussions with the TGA in February and April of 2008, Pfizer received advice that the submission of a “hybrid” type of application would be considered. The “hybrid” application comprised data from the Cyklokapron IV application submitted to the TGA in 1987 and a ‘literature-based submission’ of relevant clinical and non-clinical published data.

Regulatory Status

Tranexamic acid 500 mg tablets are currently registered for the following indications in Australia:

- Hereditary angioneurotic oedema.

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

- Menorrhagia.

Tranexamic acid received first regulatory approval on 21 January 1966 in Austria.

Tranexamic acid is approved in 47 countries and is currently marketed in 29 countries. The current regulatory status in Europe, USA, Canada and New Zealand of Cyklokapron is summarised below (Table 1). As one can observe there are a wide variety of approved indications, no two sets matching and no set matching the indications sought in Australia, except for the approved use in Germany in cardiopulmonary bypass surgery and in NZ after thoracic and other major surgery

There were no withdrawals for safety-related reasons for the period 01 August 2008 through 20 January 2010. There are no tranexamic acid (TXA) IV formulations registered in Australia. However, Cyklokapron IV is currently being supplied in Australia under the provisions of the SAS.

¹ Fergusson DA. *et al.*, 2008. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *New England Journal of Medicine* 358:2319-2331.

Table 1.

Country/Approval date	Approved indication
<u>Austria</u> 21/01/1966	Hemorrhages or hemorrhagic diathesis with increased fibrinolysis or fibrinogenolysis. Hereditary angioneurotic oedema (HANE).
<u>Belgium</u> 01/07/1970	Haemorrhagic syndromes caused by general or local fibrinolysis, such as Menorrhagias or metrorrhagias, haemorrhages in the ear, nose and throat areas (after tonsillectomies, dental extractions, etc.), as a consequence of thoracic, abdominal or gynaecological surgery or of obstetric origin (loosening of the placenta, post-partum haemorrhage), essential or traumatic haematurias, haematurias or haemorrhages resulting from prostatectomy or other operations on the urinary tract or haemorrhages from cirrhosis of the liver, neoplasias (of the prostate, etc.) and haemopathies (myeloid leukaemias). Antidote for fibrinolytic treatments (streptokinase, urokinase). Allergic dermatoses.
<u>United Kingdom</u> 07/08/1972 Re-registration: 01/11/2001	<u>Local fibrinolysis:</u> For short term use in prophylaxis and treatment in patients at high risk of peri- and post-operative haemorrhage following: prostatectomy, conisation of the cervix, surgical procedures and dental extractions in haemophiliacs, <u>General fibrinolysis:</u> haemorrhagic complications in association with thrombolytic therapy, haemorrhage associated with disseminated intravascular coagulation with predominant activation of the fibrinolytic system.
<u>Germany</u> ¹ 19/12/2005	Prevention and treatment of haemorrhages due to local or generalized hyperfibrinolysis that cannot be adequately treated with other therapeutic measures like, for example: -In conjunction with the administration of desopressin (DDAVP) when hemostaseologically indicated in von Willebrand's disease or haemophilia A -Hemorrhages during fibrinolytic therapy -Prostatic carcinoma with paraneoplastic hyperfibrinolysis and in promyelocytic leukemia Prevention and treatment of haemorrhages due to local or generalised hyperfibrinolysis with major operations, like, for example prevention of haemorrhages in cardiopulmonary bypass surgery. Use as an antidote for hemorrhages requiring treatment during fibrinolytic therapy.
<u>USA</u> ¹ 31/12/1986	Cyklokapron injection is indicated in patients with haemophilia for short-term use (two to eight days) to reduce or prevent haemorrhage and reduce the need for replacement therapy during and following tooth extraction.
<u>Canada</u> 15/02/1983	Hereditary angioneurotic oedema. Increased local fibrinolysis when the diagnosis is indicative of hyperfibrinolysis, as with conisation of the cervix, dental extraction in patients with coagulopathies (in conjunction with anti-haemophilic factor), epistaxis, hyphaema and menorrhagia (hypermenorrhea).
<u>New Zealand</u> 14/07/1983	1. 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, gastrointestinal haemorrhage. General fibrinolysis as in prostatic and pancreatic cancer; after thoracic and other major surgery; in obstetrical complications such as abruption placentae and post-partum haemorrhage; in leukaemia and liver diseases and in connection with thrombolytic therapy with streptokinase. 2. Hereditary angioneurotic oedema
<u>Sweden</u> 28/03/1969	Increased fibrinolysis or fibrinogenolysis with bleeding or risk of bleeding.

¹injection first approved in 1986.**Product Information**

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substance, tranexamic acid, is a synthetic lysine analogue. Details relating to tranexamic acid were evaluated previously, although Certificates of Suitability (CEP) has been provided replacing Drug Master Filings (DMF). “Cyklokapron” tablets refer to an European Directorate for Quality of Medicines and Healthcare (EDQM) Certificate of Suitability (*previously a DMF was referred to*). There is an additional (acceptable) test and limits for residual solvents.

Drug Product

Formulations and Manufacture

The drug product is tranexamic acid dissolved in Water for Injections. The sterile solution is filled into 5-mL or 10-mL ampoules and sealed. Sterility aspects have been accepted as satisfactory.

Specifications

The release tests and limits meet the British Pharmacopeia (BP) monograph for Tranexamic Acid Injection and the BP general requirements for ‘Parenteral Preparations’. Endotoxins and sterility have been evaluated and found acceptable by the TGA Office of Laboratories and Scientific Services (OLSS).

Stability

Data was provided to support a shelf life of 36 months when stored below 25°C, with the additional storage conditions, ‘Protect from light’ and ‘Do not freeze’. The impurity limits comply with International Conference on Harmonisation (ICH) guidance.

Biopharmaceutics

No bioavailability data are required for the proposed products since bioavailability can be considered to be 100% for a product administered intravenously.

Quality Summary and Conclusions

Approval was recommended with respect to chemistry, quality control, sterility & endotoxin aspects. After its review at its 131st meeting, the Pharmaceutical subcommittee (PSC) of ACPM did not recommend any further review.

III. Nonclinical Findings

Introduction

No new nonclinical data have been submitted. Instead, the nonclinical part of this submission consisted of study reports previously submitted to the TGA (1984, 1987). At the request of the TGA (presubmission meeting 8 July 2008) the sponsor also conducted a literature search aimed at capturing any additional information made available since the previous application. The sponsor was asked to specifically address previous safety concerns of long-term use with the tranexamic acid injection: risk of haemorrhage, thrombosis, ophthalmic and renal toxicity and limited nonclinical data with the proposed IV formulation.

The sponsor considered that no new data relevant for the proposed indication and dosage form were identified in the literature search. However, a number of papers revealed in the

literature search appeared to have relevant pharmacological and toxicological information on tranexamic acid, but as these were only submitted in abstract format they could not be evaluated.

Although a new route of administration has been proposed, no new pharmacokinetic or local tolerance data have been submitted. A previous submission (in 1973) included some data on urinary excretion and serum levels after IV dosing in rabbits and the 1987 evaluation contained a one month IV study in dogs. The doses in the latter study were not considered high (20-500 mg/kg, as a divided dose) and plasma level analysis was limited (samples only taken immediately after morning dose). No data regarding trough levels or plasma kinetics following IV dosing were provided. In response to these concerns, the sponsor noted that the current application is for once only IV use in specified indications (and not for long-term use in general fibrinolysis) and claims support from clinical data obtained in the intervening 20 years since the previous nonclinical report.

Published references referred to in the nonclinical evaluation can be found in Appendix 1.

Pharmacology

The pharmacology and efficacy of tranexamic acid were reviewed in the previous nonclinical evaluation. The main action of tranexamic acid appears to be blockade of the lysine-binding sites of the plasminogen molecule, which are important for the binding of fibrin.

The effects of antifibrinolytics on bleeding time and blood loss in various haemorrhage models appears to be model-dependent and the success rate of tranexamic acid in these has varied from no effect (Ryan *et al.* 2006 and Drobin *et al.* 2005) to reduced bleeding time (Sperzel *et al.* 2007). This indicates that the effect of antifibrinolytics on the kinetics of the clotting process during haemorrhage is minimal, suggesting that these drugs may be more effective if administered *before* and during surgery, rather than when given solely during and *after* surgery.

Vascular permeability

The effect of inhibition of fibrinolysis in modulating microvascular pulmonary injury following emboli was investigated in dogs (Townsend *et al.*, 1990). Blood flow was reduced and lobar arterial pressure increased by emboli (with or without tranexamic acid) whereas inhibition of fibrinolysis (with tranexamic acid) nearly doubled the ratio of pre- to post-capillary resistance. While the capillary filtration coefficient did not alter significantly with emboli alone, the accompanying increases in pulmonary vascular resistance suggest that changes in microvascular permeability are associated with decreases in microvascular exchange, an effect exacerbated by inhibition of fibrinolysis with tranexamic acid. Although tranexamic acid did not clearly exacerbate emboli-induced injury, the changes in haemodynamic parameters may accelerate the rate of oedema formation.

There is conflicting evidence regarding the role of antifibrinolysis in the vascular permeability and oedema seen after pulmonary emboli but the mechanism may in part involve interference by tranexamic acid with neutrophil superoxide production. Tranexamic acid has been shown to reduce neutrophil superoxide generation, a measure of neutrophil activation (Lai and Malik, 1986).

Pharmacokinetics

No new data were submitted. The available information are summarised in Table 2 below (copied from the sponsor's Nonclinical Overview):

Table 2. Summary of pharmacokinetic parameters for tranexamic acid in various species.

Species	T _{1/2} (h)	V _d (L/kg)	Clearance (mL/k h)	GFR (mL/kg h)	% oral bioavailability
Rat (Sherman-Wykoff)	2	2	670	510	15
Rabbit (NZW white)	2.9	0.5	-	-	-
Dog	2	1	230	190	68
Man	2	0.2	96	107	53

GFR=glomerular filtration rate; t_{1/2}=half-life; V_d=volume of distribution.

The oral bioavailability of tranexamic acid was similar in dogs and humans but lower in rats. Tranexamic acid was eliminated by the kidney, with clearance rates similar to renal GFR in all species suggesting that there is no active secretion or re-uptake from the renal tubules. The volume of distribution was 5 to 10 times higher in rats and dogs compared to humans.

Human plasma exposure following IV dosing

No human IV pharmacokinetic data are available using the proposed dosage regimens for various surgeries suggested in the *Dosage and Administration* section of the PI.

Single bolus IV infusions of 10 mg/kg tranexamic acid in man yielded a plasma level of 37.4 mg/L (Fiechtner *et al.*, 2001). Assuming linear kinetics this would yield a plasma tranexamic acid concentration of approximately 56 mg/L following a single IV bolus of 15 mg/kg.

A single IV infusion of about 15 mg/kg gave plasma levels of 85 mg/L after 0.17 h and 20 mg/L after 2 h. Both of these values have been used to estimate animal: human safety margins in this report.

Toxicology

Previous nonclinical evaluation of tranexamic acid by the TGA yielded recommendations for short term oral use only, due to concerns about ocular and renal toxicity, intravascular clotting and the limited nonclinical pharmacokinetic data for the IV route.

In contrast to earlier applications, the current application is for once only IV use in specified indications and not for long term, general fibrinolysis use. Therefore, the previous nonclinical data needs to be re-assessed with these changes in mind.

Previous nonclinical IV studies of acute toxicity (IV studies in mice, rat, rabbit and dog giving LD₅₀ values of 0.9-1.5 g/kg) and repeat-dose toxicity (13 days in rabbits; 4-14 days in cats; ≤ 1 week to 1 month in dogs; 1-2 weeks in monkeys) have revealed ocular and thromboembolic toxicity. In humans, fatalities (incidence of 0.8%) following tranexamic acid treatment were mostly associated with major surgery (a risk factor in itself) and thrombosis in a major organ (cardiac, cerebral, pulmonary or GI).

Ocular toxicity

Previous evaluations of tranexamic acid have noted ocular toxicity, mainly in the dog, but some lesions were also observed in a 12-month rat study (focal retinal atrophy) and in cynomolgus monkeys given repeated infusions of 200 mg/kg tranexamic acid over 1-2 weeks (minimal peripheral retinal atrophy).

Repeat dose oral studies in dogs have suggested that irreversible ocular toxicity arises from chronic antifibrinolysis, with a poor correlation to the plasma levels of tranexamic acid (TGA Nonclinical Evaluation, 1987). The reversible reflectivity changes (greyish and/or pale areas in the tapetal fundus and sometimes changed tapetal reflectivity) observed at 800-1200 mg/kg/day tranexamic acid after 3 to 5 weeks were associated with plasma levels of 150-200 mg/L, approximately 2-4-fold that anticipated in the clinic following IV administration at 15 mg/kg. There was some uncertainty as to the lowest dose which resulted in anterior retinal atrophy and temporary retinal lesions in dogs and the differences in plasma levels between the high dose (HD) and low dose (LD) animals was small. A previously evaluated 22-month (carcinogenicity) study in rats) suggested an ocular no adverse effect level (NOAEL) of 400 mg/kg/day following 12 months of tranexamic acid, which is about 4 times the total daily human dose of 50 mg/kg/day on a mg/m² basis.

With respect to the intended clinical route, retinal damage has been seen in dogs and cats given daily IV nearly lethal doses (2 g/kg/day and 250-500 mg/kg/day, respectively) for 7 days (including proliferation of the pigment epithelium and degenerative changes in the outer layers of the canine retina). Plasma kinetics were not available for cats and monkeys but the mg/kg doses were much larger than those proposed for humans (33-133x).

The dog appears to be the most sensitive species for demonstrating the ocular toxicity of tranexamic acid and the apparent margin of safety with respect to plasma levels in dogs after repeated oral dosing compared to humans given a 15 mg/kg single IV dose appears to be small (2-4-fold). However, it is the local concentration of tranexamic acid at the retina that is most relevant for this toxicity rather than the bulk plasma concentration. In this respect it is notable that the volume of distribution of tranexamic acid is 5 times higher in dog than man, which would likely expose the dog retina to higher local concentrations than in humans.

Furthermore, tranexamic acid has been instilled topically to treat traumatic hyphema in clinical trials in adults and children and direct ocular application to rabbits at one drop of 100 mg/mL solution once every 8 hours for three days yielded no adverse ocular effects, despite achieving local aqueous humour levels of 15 mg/L (Damji *et al.*, 1988).

Clinically, three reports (0.4%) of visual disturbance or eye pain have been reported in patients receiving tranexamic acid IV and the Product Information notes impaired colour vision and other visual disturbances as well as cases of giddiness/dizziness.

Overall, ocular toxicity concerns are greatly reduced by the fact that drug will only be given once (compared to weekly or monthly in dogs) and is not intended for use in general fibrinolysis.

Renal toxicity

Concern for renal toxicity was raised in previously evaluated 18 month and 22 month old rat carcinogenicity studies. During the second 9 months of the first study, mortality of treated males (but not females) was significantly increased and death was associated with renal pelvic concrement, increased serum creatinine levels and increased kidney weights. The kidney lesions were frequently associated with pyelonephritis. These lesions were of particular concern as they occurred at relatively low plasma exposures, that is, similar or lower than those expected in humans. Furthermore, renal toxicity has also been associated with the serine protease antifibrinolytic agent, aprotinin.

However, tranexamic acid is cleared significantly faster from the kidney (at rate close to GFR) with a 4 h urinary recovery rate of 90% compared to only 25-40% recovery after 48 h with aprotinin.

Given that only a single animal species has demonstrated renal toxicity and this has been after 9 months of daily dosing, the risk for renal toxicity in a clinical setting of once only dosing would appear to be minimal. The frequency of clinical renal adverse events has mainly been reported in high risk surgical patients (22.75% compared to 0.29% in placebo and 1.79% in low risk patients).

Thrombosis

The ADEC previously expressed some concern with respect to intravascular clotting, but this point was not raised in the 1973 or 1979 nonclinical evaluations. In the 1987 nonclinical evaluation, the main toxic changes observed in canine IV compared to oral studies were associated with thrombosis (possibly due to the higher, albeit transient, plasma concentrations compared to oral dosing); one dog died from thrombus (in meningeal artery of the cerebrum) in the 1-year chronic study and dogs given 20-500 mg/kg/day tranexamic acid IV for one month showed (apart from emesis and salivation) increased lysis time and thromboembolism in peripheral arteries (1/4 HD and 1/4 MD dog) and thrombophlebitides in the subserosa of the urinary bladder (1/4 HD dog).

A greater thrombus weight also was noted in rats pre-treated with tranexamic acid compared to aprotinin (Sperzel *et al.* 2007). Pharmacology studies have shown that chronic antifibrinolysis results in the persistence of thrombi, consistent with the IV study in dogs, but that thrombi may resolve when plasma levels of tranexamic acid fall below a 'critical level' (Moser *et al.* 1991). In humans, antifibrinolytic cover is only proposed to be maintained during surgery (short-term) and given the elimination $t_{1/2}$ of tranexamic acid of ca 2 h, plasma levels will decrease from the estimated peak levels of ca 56-85 mg/L to 16 mg/L (the proposed surgery 'maintenance' level) in *ca.* 4 h.

Postmarketing adverse event reports in humans note thromboembolic events as a relatively rare side effect (0.01-0.1%; proposed Product Information). The PI also notes in the "Precautions" section that "possible risk of thromboembolic complications cannot be ruled out".

Convulsions

The use of tranexamic acid has been contraindicated as an adjunct in the treatment of central nervous system (CNS) haemorrhage after cortical application was observed to cause epileptic seizures in cats (Furtmüller *et al.*, 2001). In addition, the main symptom after high single IV doses was convulsions in mice, rats and dogs, but the convulsive dose was not given (lethal dose 50% (LD₅₀) values of 0.9-1.5 g/kg across the three species). Somewhat lower doses administered to cats (125-500 mg/kg IV for 4-14 days) and rabbits (60-180 mg/kg IV for 13 days) did not cause mortalities (clinical signs were not discussed in reports) whereas a higher IV dose (2 g/kg/day) given to monkeys caused one unexpected and unexplained death. Clinical signs reported from the monkey study included emesis, salivation and tremors, indicative of general CNS toxicity. More recently, it has been shown that tranexamic acid exhibits hyperexcitability and convulsive properties in rats (1-5 mg/mL tranexamic acid applied directly onto the lumbar spinal cord), probably involving the GABA receptor (Furtmüller *et al.* 2002). Therefore, tranexamic acid administrations in, or near the CNS, should probably be avoided in any species (Schlag *et al.*, 2000)².

The concentration of tranexamic acid in human cerebrospinal fluid (CSF) is estimated to be 10% of that in plasma (Åstedt, 1987³ and PI). At the proposed clinical IV regimen this would result in *ca.* 6-9 mg/L tranexamic acid in the CSF. No convulsions were observed in dogs receiving tranexamic acid IV at up to 500 mg/kg/day for one month. Plasma levels of 550-660 mg/L were measured at this NOEL for convulsions, corresponding to 55-66 mg/L in the CSF if 10% equilibration is assumed (about a 6 to 11-fold safety margin).

Overall, while a predictive convulsive maximum plasma concentration (C_{max}) is lacking in animal studies, convulsions only appeared in animals at very high IV doses and there is some evidence in dogs that a moderate safety margin exists, at least for once only treatment. It is recommended that the clinical data be carefully examined for any adverse CNS findings indicative of tranexamic-induced hyperexcitability.

Clinical signs: vomiting, salivation and diarrhoea

Clinical symptoms of vomiting, salivation and diarrhoea were observed after IV and oral administration in animals. From the data, it is difficult to evaluate the frequency and severity of these symptoms, but they would probably be more severe following IV dosing, because of the higher plasma levels reached. Of relevance was that the emesis occurred during the infusion and there were signs of alkalosis, which were not seen after oral administration (1987 Nonclinical Evaluation). Nausea, vomiting and diarrhoea occur in humans given tranexamic acid and there is a possibility of increased severity of these symptoms following IV administration.

Limited nonclinical data on the proposed IV formulation

The formulations used in the various published studies have not been described. Tranexamic acid is soluble in water (*ca.* 170 mg/mL) and the available commercial products are simple aqueous solutions. The sponsor argues that it is improbable that these studies used a more complex formulation and considers that the available data are relevant to the proposed marketing formulation and therefore support this application. This argument is acceptable.

² Schlag *et al.* 2000. Convulsive seizures following subdural application of fibrin sealant containing tranexamic acid in a rat model. *Neurosurgery* 47:1463-1467. Convulsions occurred within 0.5 h of treatment and at concentrations as low as 1 mg/mL.

³ Åstedt B. 1987, Clinical Pharmacology of Tranexamic Acid. *Scandinavian Journal of Gastroenterology*, 22: 22-25.

The duration of studies with the injection formulation ranged from one month (dog), to two weeks (in cats and monkeys at ≤ 500 mg/kg and 2 g/kg/day, respectively) and are considered sufficient for a once only indication in humans.

Carcinogenicity/Genotoxicity

No new studies were submitted.

Current data suggest that tranexamic acid is not mutagenic. Several carcinogenicity studies have been conducted with variable results⁴. A possible treatment-related increase in the incidence of leukemia was noted in male mice receiving dietary tranexamic acid at doses equivalent to up to 5g/kg/day for 20 months (n=12/57 compared to 5/59 controls). An additional study in two strains of newborn mice given a single subcutaneous (SC) injection of 0.01 mg/g tranexamic acid also showed an increase in leukemia compared to controls (38% compared to 33%, not statistically significant- strain not described; and 46% compared to 32%, respectively, $p < 0.05$, in female AKR⁵ mice). The nonclinical evaluator concluded that in view of the species specificity of this tumour it was not possible to extrapolate it to humans. However, the major concern was that a single low dose of tranexamic acid to neonatal animals may have been sufficient to increase the incidence of spontaneously occurring disease.

Chronic studies in Sherman-Wyckoff rats have shown an increased incidence of liver neoplasms (hepatocellular adenoma, cholangioma and adenocarcinoma) and biliary hyperplasia. The clinical relevance of such findings is low given that these findings could not be replicated in standard strains of rats and mice usually used in lifetime carcinogenicity studies.

Reproductive toxicity

No new studies were submitted. This is considered acceptable for a drug with a proposed once only use.

Previous studies in rats given 1 g/kg/day or 1.2% tranexamic acid in the diet showed no effects on parental fertility or embryonic or neonatal development. In contrast, increased foetal losses and lower litter weights were noted in rabbits at 200 but not 100 mg/kg/day. There was no effect on rat pup survival. Reproductive effects are not considered to be of concern with a once only indication for tranexamic acid.

Paediatric indication

The sponsor seeks to register tranexamic acid for the use in children >2 years old during cardiac surgery - "administration of 10 mg/kg before surgery followed by a repeat dose of 10 mg/kg during surgery or as an infusion during surgery".

No specific nonclinical data in juvenile animals have been submitted to support administration of tranexamic acid to children and therefore the appropriateness of use in this patient population will rely on the available clinical data. Some of the clinical data include ten spontaneous adverse reaction reports after tranexamic acid use in children under 12 years of age which were considered mild (vomiting and extravasation). No thrombotic complications, renal findings or cerebrovascular events were reported in four placebo controlled studies in 173 children (from three months to 14 years old undergoing cardiac

⁴ Slight increases in pancreatic exocrine adenomas and thyroid adenomas in SD rats were noted but not considered to be of human concern.

⁵ AKR mice have a high incidence of spontaneous leukemia.

surgery). Tranexamic acid has been used in children (25 mg/kg/day) to treat hyphema and was found to significantly reduce the incidence of secondary haemorrhage⁶.

Local tolerance

Whilst no specific local tolerance issues (for example, injection site reactions) have been noted in nonclinical IV studies, the data are limited. Therefore, the potential for local tolerance issues with tranexamic acid via the IV route should be explored in the available clinical data.

Nonclinical Summary and Conclusions

- A previous application for the IV formulation was rejected by the TGA in 1987 due to nonclinical concerns over ocular and renal toxicity, intravascular clotting and the generally limited information on the IV route and formulation. Cyklokapron IV has been available in Australia under the SAS.
- No new nonclinical data were submitted. An updated Nonclinical Overview and a literature search of published papers on tranexamic acid since 1987 were provided by the sponsor.
- Previous concerns for tranexamic acid toxicity following long-term use were largely mitigated by the once only nature of the indication proposed in the current application. Nevertheless, the pharmacological properties of this drug carry the possibility of thromboembolic complications at therapeutic IV doses and convulsions at supra-therapeutic IV doses (circa 6 to 11-fold safety margin to the NOEL in dogs).
- Approval of the paediatric indication (that is, the use during cardiac surgery in children >2 years old) will have to rely on clinical data as no nonclinical data in juvenile animals have been submitted.
- There are no nonclinical objections to the registration of an IV formulation of tranexamic acid for the once only, surgical indications in adults. Longer term use of tranexamic acid in conditions of general fibrinolysis may carry risks of ocular and/or renal toxicity and is therefore not recommended.
- Given the pharmacological properties of tranexamic acid, even once only use via the IV route carries the risk of possible thromboembolic complications at therapeutic doses and possible CNS hyperexcitability or convulsions at supra-therapeutic IV doses (6-fold safety margin to the NOEL in dogs). Therefore, careful clinical monitoring of such adverse events is warranted.
- The clinical data should be assessed for local tolerance issues (for example, injection/infusion site reactions) as the nonclinical local tolerance data for the IV route were limited.

IV. Clinical Findings

Introduction

The clinical aspects of the application consisted of a literature based submission aimed at supporting the registration of Cyklokapron IV (TXA) for use in cardiac surgery in adults and children and orthopaedic surgery in adults (total knee arthroplasty and total hip arthroplasty). The sponsor undertook and provided separate meta-analyses of published studies supporting the use of TXA for each of the proposed indications. The meta-analyses undertaken and

⁶ Deans R, Noel LP, Clarke WN. (1992). Oral administration of tranexamic acid in the management of traumatic hyphema in children. *Can J Ophthalmol.* ;27(4):181-3.

provided by the sponsor are considered to be the pivotal efficacy data. The pivotal safety data are derived from the studies included in the meta-analyses supplemented by additional published studies providing relevant safety data. The sponsor has pooled the safety data from the relevant published studies for each indication. In addition to the initial data, the sponsor also provided extra analyses and comments on these data in response to a request from the clinical evaluator. The sponsor has also identified and provided published studies containing pharmacodynamic and/or pharmacokinetic data considered to be directly relevant to the submission.

The submitted clinical data included the clinical (and nonclinical) search strategies used to identify relevant studies from the published literature. The clinical search strategy was primarily aimed at identifying randomized trials which compared TXA with placebo or no anti-fibrinolytic control and/or active anti-fibrinolytic control. In addition, the clinical search strategy aimed to identify relevant reviews and meta-analyses focussing on the use of TXA for the proposed indications. The sponsor provided comprehensive lists of all selected and rejected studies with reasons for rejection. These lists have been examined and are considered to be appropriate. Clinical summaries of the data supporting each of the indications, synopses and tabular listings of each of the submitted published studies, the clinical expert overview and relevant appendices to this overview, and two *Cochrane Reviews* [Henry 2008; Tzortzopoulou 2008] were included. The meta-analyses in the *Henry 2008 Cochrane Review* are relevant to the proposed indications as they related to anti-fibrinolytic use to minimise peri-operative and post-operative blood loss and to reduce the need for blood transfusion in cardiac and orthopaedic surgery in adults. The meta-analyses in the *Tzortzopoulou 2008 Cochrane Review* are not directly relevant to the proposed indications as they relate to anti-fibrinolytic use to reduce blood loss in scoliosis surgery in children and adolescents, an indication for which the sponsor was not seeking approval and will not be discussed further. The clinical part of the current Australian submission consisted of the reports of the meta-analyses undertaken by the sponsor supporting the use of TXA in cardiac and orthopaedic surgery, pooled safety data from published studies, post-marketing safety data and copies of 126 published studies. The submitted published studies included 72 adult cardiac surgery studies (5736 TXA treated patients), 25 adult orthopaedic studies (777 TXA treated patients) involving knee (495 TXA treated patients) or hip surgery (282 TXA treated patients) and 6 paediatric cardiac surgery studies. In addition, the submission included 17 published studies including clinical pharmacology studies.

Each of the meta-analyses undertaken and provided by the sponsor has been considered and evaluated, as has all the pooled safety data submitted by the sponsor. In addition, all relevant data from the published studies included in the meta-analyses and the published studies contributing to the pooled safety analyses have been reviewed and evaluated, as have the post-marketing safety data. Furthermore, all published studies identified by the sponsor as containing relevant clinical pharmacodynamic and/or pharmacokinetic have been reviewed and evaluated. In addition, all responses provided by the sponsor have been considered and information from these responses included in the clinical evaluation report where considered relevant.

Meta-Analyses

The submission included two meta-analyses (with subgroup meta-analyses) supporting the application to register TXA for use in adult cardiac surgery. The primary efficacy endpoint was post-operative blood loss and this was supported by a meta-analysis of 37 studies. The secondary efficacy endpoint was blood transfusion requirements and this was supported by a meta-analysis of 35 studies. The submission included two meta-analyses (with subgroup

meta-analyses) supporting the application to register TXA for the use in total knee arthroplasty. The primary efficacy endpoint was post-operative blood loss and this was supported by a meta-analysis of 16 studies. The secondary efficacy endpoint was blood transfusion requirements and this was supported by a meta-analysis of 15 studies. The submission included two meta-analyses (with subgroup meta-analyses) supporting the application to register TXA for use in total hip arthroplasty. The primary efficacy endpoint was post-operative blood loss and this was supported by a meta-analysis of 11 studies. The secondary efficacy endpoint was blood transfusion requirements and this was supported by a meta-analysis of 10 studies. The submission included two meta-analyses (with subgroup meta-analyses) supporting the application to register TXA for use in paediatric cardiac surgery. The primary efficacy endpoint was post-operative blood loss and this was supported by a meta-analysis of three studies. The secondary efficacy endpoint was blood transfusion requirements and this was supported by a purported meta-analysis pooling the results from one study. The sponsor rated the quality of all studies included in the meta-analyses grading them from 0 (highest) to 5 (lowest). The criteria used by the sponsor to grade the studies are provided in Table 3.

Table 3: Grading assigned by the sponsor to submitted studies.

Study Grade	Definition
0	Level I: large, randomized, placebo-controlled, double-blind.
1	Level Ia: randomized, placebo-controlled, double-blind.
2	Level Ib: randomized, controlled, blinded. Not stated whether control was placebo or no treatment.
3	Level II: randomized, partial blinding, active comparator.
4	Level I or II: but conference abstract.
5	Level I or II: but ethics oversight not specifically stated.

The meta-analyses included all studies in the Cochrane Reviews of *Henry 2008* supplemented with additional studies identified by the sponsor. It is considered that the sponsor has satisfactorily identified all appropriate published studies and included all relevant studies in the meta-analyses and the submission.

The sponsor used the same methodology in all the meta-analyses for all indications. The primary efficacy outcome in all meta-analyses was post-operative blood loss. In order to be included studies had to report post-operative blood loss as mean \pm standard deviation (SD) or mean with 95% confidence interval (CI). Studies reporting post-operative blood loss as median with interquartile (IQ) range or total range were not included. Intra-operative blood loss was not a primary outcome measure because there were insufficient data for meaningful analysis. The sponsor justified the exclusion of intra-operative blood loss as an outcome measure as "reasonable because [it] is predominantly a function of surgical technique, not disturbed haemostasis". This comment was considered by the clinical evaluator to be an over simplification as disturbed haemostasis could be expected to be a feature of prolonged surgical procedures, particularly cardiac surgery involving cardiopulmonary bypass (CPB). Nevertheless, post-operative blood loss is considered to be an acceptable primary outcome measure to assess the pharmacological effects of TXA. The secondary efficacy outcome was the reduction in the need for allogeneic blood transfusion (whole blood and/or packed red

blood cells) assessed by the number of patients requiring transfusion. The need for allogeneic blood transfusion was chosen as a secondary efficacy outcome rather than a primary efficacy outcome as blood transfusion protocols were considered likely to vary among the studies due to different clinical practices in different surgical centres.

The sponsor chose the mean difference in post-operative blood loss (mL) between treatment groups as the estimate of effect for the primary efficacy outcome. The effect size was reported as mean difference with 95% CI. The sponsor decided not to follow the usual procedure of standardizing the variances in effect between treatment groups within each study. The variances of the control groups tended to be larger than the treated groups suggesting that the assumption of equal variance between treatment groups was not justified. The relative risk with 95% CI of the number of patients needing blood transfusion in the treatment groups was chosen by the sponsor as the estimate of effect for the secondary efficacy outcome. The sponsor selected a random-effects model for comparing both the differences in post-operative blood loss and the relative risk of blood transfusion. This model was adopted as it was considered to be the most conservative as it gave the widest range of confidence intervals for the effects. The model assumes that effects between studies differ significantly rather than being fixed. The random-effects model takes into account the variation in effect among studies as well as the sampling variation within each study.

The meta-analyses included statistical estimates of the heterogeneity among the studies. These estimates included the I^2 statistic which describes the percentage of total variation across the studies due to heterogeneity rather than chance. The I^2 statistic falls between 0 and 100% with values 25%, 50% and 75% being "tentatively" categorized as low, moderate and high, respectively [Higgins 2003]. The I^2 statistic has been used in the clinical evaluation report as the primary estimate of heterogeneity because of the ease of its interpretation. Heterogeneity was assessed among all studies grouped together and among studies subgrouped on the basis of TXA dose or categorized on the basis of control group blood loss. Where substantial heterogeneity was identified in subgroups the sponsor explored this by repeating the analysis with selected studies omitted in order to assess their contribution to the heterogeneity. The sponsor undertook exploratory analysis of the effect that excluding these studies had on the treatment estimate of post-operative blood loss. The sponsor did not undertake a formal analysis of publication bias and/or missing studies. However, the sponsor's comprehensive search strategy makes it likely that no important studies have been overlooked. Overall, it is considered that the methodology adopted by the sponsor for the meta-analyses was satisfactory.

Published references referred to in the clinical evaluation can be found in Appendix 1.

Pharmacokinetics

Cardiac Surgery Overview

The submission included a series of studies aimed at establishing a TXA dosage regimen in patients undergoing cardiac surgery on CPB based on plasma concentrations known to inhibit *in vitro* fibrinolytic activity and/or *in vitro* platelet activation. The results of the relevant studies are summarised below.

Dowd 2002

In Dowd 2002, the pharmacokinetics of TXA were assessed in 30 adult patients with normal renal function undergoing elective coronary artery bypass grafting (CABG) or valve surgery, or repair of atrial septal defect (ASD) after TXA 50 mg/kg (n=10) or TXA 100 mg/kg (n=10) as a single IV bolus infusion given over 15 minutes after induction of anaesthesia, or TXA (n=10) 10 mg/kg as an IV loading dose given over 15 minutes after induction of anaesthesia

followed by a maintenance dose of 1 mg/kg/h for 10 hours. The TXA doses were chosen based on previous efficacy data published by the study research group [Karski 1993; Karski 1995] and on published data from *Horrow 1995*. The study was undertaken at the Toronto General Hospital following Institutional Ethics Committee (IEC) approval and granting of informed consent. The authors stated that no previous study has examined the pharmacokinetics of TXA in patients undergoing cardiac surgery.

In the TXA 50 mg/kg and 100 mg/kg single dose bolus groups, arterial blood was sampled: (1) before the drug and then at 2, 4, 6, 10, 30, 60, 90, 180, 400 and 600 minutes after the bolus was completed; (2) immediately before and 5 minutes after initiation of CPB; and (3) 24 hours after the drug was given. In the TXA 10 mg/kg loading dose followed by maintenance dose of 1 mg/kg/h for 10 hours treatment group blood was sampled: (1) before giving the drug and then at 2, 4, 6, 10, 30, 60, 90 and 180 min after completion of the loading dose; (2) exactly as the maintenance infusion was stopped and then at 2, 5, 10 and 60 min after the infusion finished; and (3) 24 hours after the drug was given. Plasma concentrations of TXA were analyzed by high-performance liquid chromatography (HPLC). Concentration versus time data were fitted to compartmental models using the nonlinear mixed effects regression technique (NONMEM). The data were best fitted to a 2-compartment model and the model parameters are summarised in Table 4.

Table 4: Dowd 2002 – pharmacokinetic model parameter estimates (mean±SEM).

	Before CPB	CPB	After CPB
k_{10}	0.014 ± 0.002	0.009 ± 0.002	0.014 ± 0.002
k_{12}	0.018 ± 0.003	Unchanged	Unchanged
k_{21}	0.021 ± 0.007	Unchanged	Unchanged
V_1 (l) at 80 kg	10.3 ± 0.8	11.9 ± 1.0	11.9 ± 1.0
V_1 (l) (weight adjusted)	0.149 l/kg* – 1.61 L	0.149 l/kg*	0.149 l/kg*
ξ	0.52 ± 0.06	Unchanged	Unchanged
V_2 (l) at 80 kg	8.5 ± 1.3	9.8 ± 1.7	9.8 ± 1.7
V_2 (l) (weight adjusted)	0.13 l/kg* – 1.4 L	0.13 l/kg*	0.13 l/kg*
Cl_1 (l/min) at 80 kg	0.15 ± 0.01	0.11 ± 0.02	0.17 ± 0.02
Cl_1 (l/min) (weight adjusted)	0.0021 l · kg ⁻¹ · min ⁻¹ * – 0.023 l/min	0.0013 l · kg ⁻¹ · min ⁻¹ * – 0.015 l/min	0.0021 l · kg ⁻¹ · min ⁻¹ *
Cl_2 (l/min) at 80 kg	0.18 ± 0.03	0.21 ± 0.03	0.21 ± 0.03
Cl_2 (l/min) (weight adjusted)	0.0027 l · kg ⁻¹ · min ⁻¹ * – 0.029 l/min	0.0027 l · kg ⁻¹ · min ⁻¹ *	0.0027 l · kg ⁻¹ · min ⁻¹ *

See Results for description of pharmacokinetic parameters.

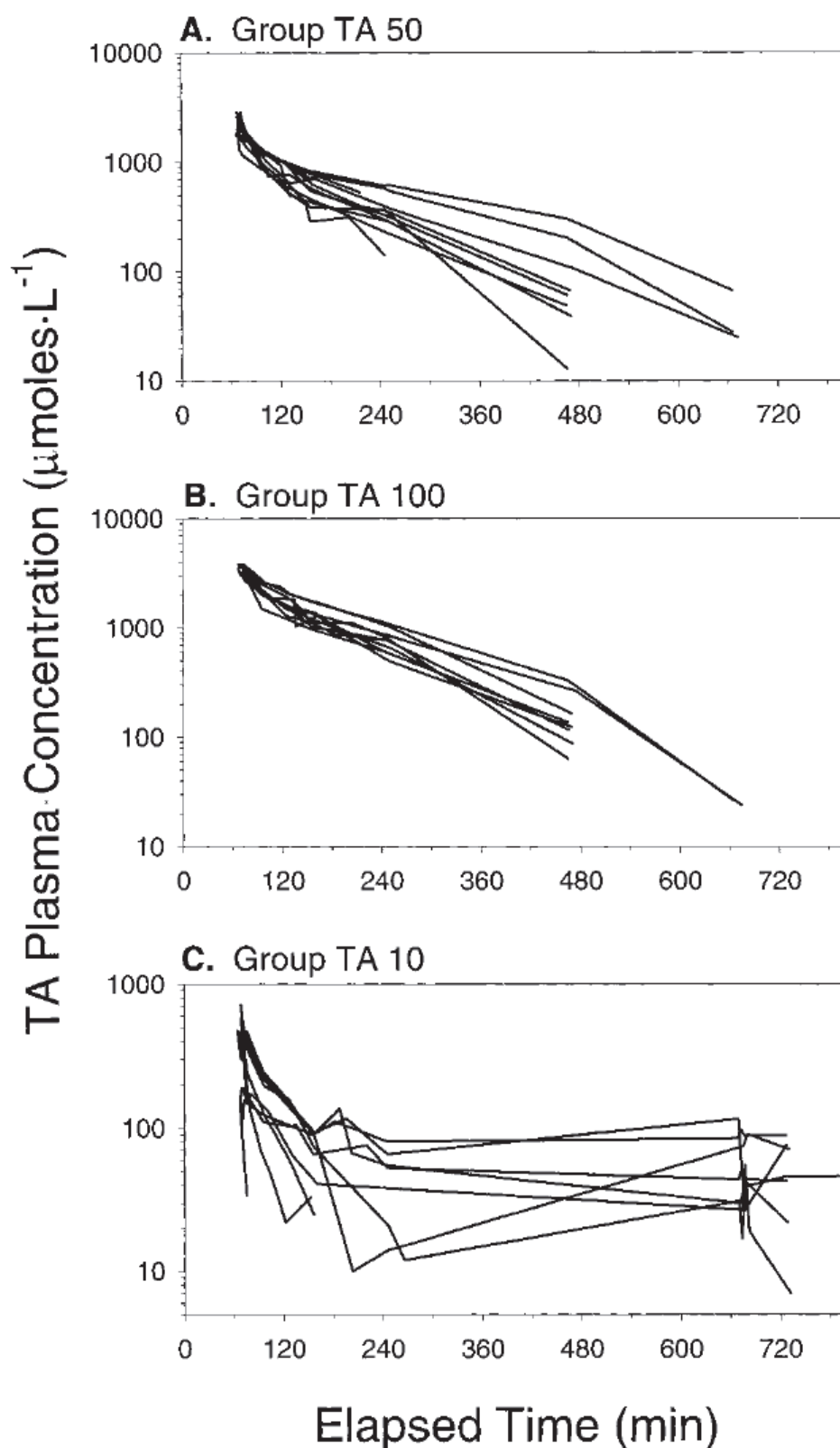
Formula used: $V_2 = k_{12}/k_{21} \cdot V_1$; $Cl_1 = V_1 \cdot k_{10}$; $Cl_2 = V_1 \cdot k_{12}$

* The weight adjusted terms containing kg⁻¹ as a unit need to be multiplied by the patient's weight in kg to calculate the parameter. For example an 80-kg patient, pre-CPB could have a V_1 (l) = 80 kg · 0.149 l · kg⁻¹ – 1.61 l = 10.3 l.

SE = standard error; CPB = cardiopulmonary bypass.

The study showed that TXA is rapidly eliminated in patients undergoing cardiac surgery when given as a bolus dose. Peak TXA plasma concentrations were much higher in the 50 mg/kg and 100 mg/kg single bolus dose groups than in 10 mg/kg initial dose followed by a maintenance infusion of 1 mg/kg/h for 10 hours and theoretically maintained longer steady state TXA concentrations within the therapeutic range (Figure 1).

CPB increased the volume of distribution of the central compartment (V_1) by 1.61 L (from 10.3 to 11.9 L in an 80 kg person) and reduced the elimination rate constant (k_{10}) by 0.005 (from 0.014 to 0.009) of the central compartment.

Figure 1. Dowd 2002 – TXA plasma concentrations following three regimens.

(A) Group TA 50: Tranexamic acid (TA) concentrations in blood after a 50 mg/kg loading dose given intravenously over 15 minutes after induction of anesthesia. (B) Group TA 100: TA concentrations in blood after a 100 mg/kg loading dose given intravenously over 15 minutes after induction of anesthesia. (C) Group TA 10: TA concentrations in blood after a 10 mg/kg loading dose given intravenously over 15 minutes after induction of anesthesia followed by 1 mg/kg/h maintenance infusion given for 10 hours.

Using mixed-effects modelling, with adjustments for CPB, three dosing regimens were calculated that targeted intra-operative steady state plasma concentration of 33 µg/mL, 52 µg/mL and 125 µg/mL (Table 5, below).

Table 5. Dowd 2002 - Dosage recommendations aimed at achieving specified CSS concentrations

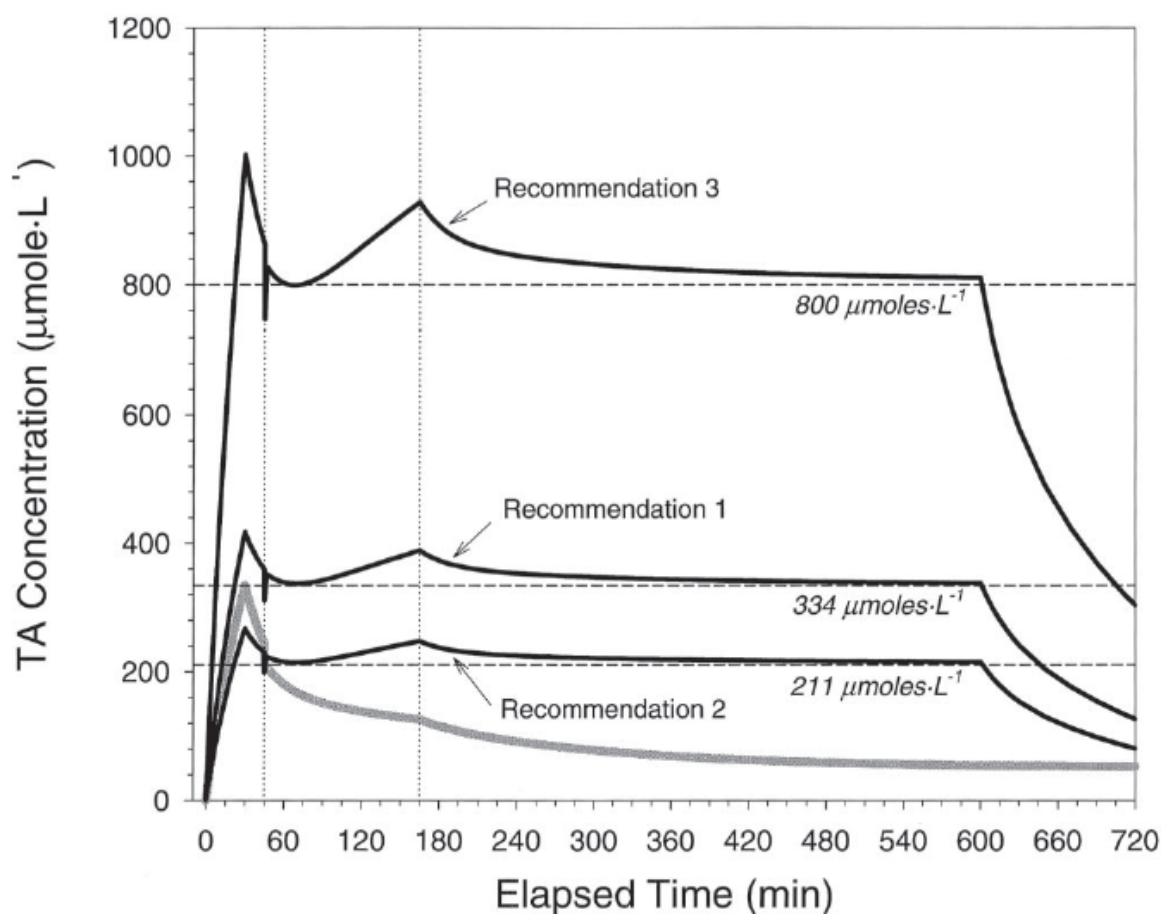
Loading	Maintenance	Pump Line	Cmax estimate	Css estimate
8 mg/kg	4 mg/kg/hour	0.6 mg/kg	42 µg/mL	33 µg/mL
12.5 mg/kg	6.5 mg/kg/hour	1 mg/kg	67 µg/mL	52 µg/mL
30 mg/kg	16 mg/kg/hour	2 mg/kg	157 µg/mL	125 µg/mL

Based on previous *in vitro* and *in vivo* studies, the authors estimated that effective control of systemic fibrinolysis appears to require a plasma concentration of 10-15 µg/mL. The authors refer to *in vitro* studies showing that a TXA concentration of 100 µg/ml reduced fibrinolytic activity in tissue extracts by 98-100% and a concentration of 10 µg/mL reduced activity by 80%. However, the authors stated that they could not, "with any confidence", determine the *in vivo* threshold TXA concentration that would completely inhibit fibrinolysis but considered it likely to be less than 52 µg/mL for the typical patient. In order to achieve a steady state plasma concentration of 52 µg/mL throughout a 4 hour procedure the authors suggested a 30 minute loading dose of 12.5 mg/kg followed by a maintenance infusion of 6.5 mg/kg/h starting immediately after the loading dose and continued for 4 hours, with an additional dose of 1 mg/kg to be added to the pump prime. If a higher plasma concentration is required in high-risk bleeding patients the authors suggested a loading dose of 30 mg/kg followed by 16 mg/kg/h plus an additional 2 mg/kg to the pump prime would maintain TXA concentration at 125 µg/mL. The simulated TXA plasma concentration versus time profiles are provided in Figure 2.

Comment

This was a good quality study. It highlighted some of the uncertainties surrounding the pharmacokinetics of TXA such as the therapeutic range and minimal effective plasma concentration. The proposed dosing regimen for cardiac surgery is a loading dose of 15 mg/kg followed by an infusion of 4.5 mg/kg/h of which 0.6 mg/kg may be added to the pump line. This gives a total TXA dose of 33.6 mg/kg for a 4 hour procedure. The total TXA doses for a 4 hour procedure for the dosage regimens recommended in *Dowd 2002* are 39.5 mg/kg for the 12.5 mg/kg loading dose followed by a 6.5 mg/kg/h maintenance dose with 1 mg/kg added to the pump line regimen and 24.6 mg/kg for the 8 mg/kg loading dose followed by a 4 mg/kg/h maintenance dose with 0.6 mg/kg added to the pump line. Assuming linear TXA pharmacokinetics, the results suggest that the TXA steady state plasma concentration for the proposed dosage regimen is likely to be about 42.5 µg/mL (that is, half-way between the concentrations for the two regimens proposed by *Dowd 2000*).

Figure 2. Dowd 2002 – Recommended dosing regimens with simulated tranexamic acid versus time profiles.



A comparison between the recommended dosing schemes and that of *Horrow 1995*. For modeling purposes, three alternatives were assumed. **Recommendation 1:** that the peak concentration achieved by the one-time dosing scheme of *Horrow 1995* should be the target concentration to be maintained as long as a TA effect is desired. For recommendation 1, the authors suggest a 30 minute loading dose of 12.5 mg/kg, a maintenance infusion of 6.5 mg/kg/h starting immediately after the loading dose and continued for 4 h after surgery and an additional dose of 1 mg/kg to be added to the CPB priming solution. **Recommendation 2:** attempted to maintain the concentration that would have been present at the start of CPB using the *Horrow 1995* technique. For recommendation 2, the authors suggest a loading dose of 8 mg/kg given over 30 min, a maintenance infusion of 4 mg/kg/h and 0.6 mg/kg in the CPB priming solution. **Recommendation 3:** attempted to maintain the peak concentration achieved after a single 100 mg/kg dose; assuming a weight of 80 kg, 45 minutes of surgery before and after 120 min of CPB and no renal or hepatic failure. For recommendation 3, to achieve and maintain TA concentration at 800 $\mu\text{M/L}$, the authors suggest a loading dose of 30 mg/kg plus 2 mg/kg added to the pump prime followed by 16 mg/kg/h continuous infusion.

Fiechtner 2001

In *Fiechtner 2001*, TXA administered as a loading dose of 10 mg/kg over 20 minutes followed by an infusion of 1 mg/kg/hour was given to 21 patients undergoing cardiac surgery on CPB in order to see if resulting plasma TXA concentrations were sufficient to inhibit fibrinolysis *in vitro* (that is, 10 $\mu\text{g/mL}$ targeted in the publication). Plasma TXA concentrations (mean \pm SD) were 37.4 \pm 16.9 $\mu\text{g/mL}$ after bolus, 27.6 \pm 7.9 $\mu\text{g/mL}$ after 5 minutes on CPB, 31.4 \pm 12.1 $\mu\text{g/mL}$ after 30 minutes on CPB, 29.2 \pm 9.0 $\mu\text{g/mL}$ after 60 minutes on CPB, 25.6 \pm 18.6 $\mu\text{g/mL}$ at discontinuation of TXA infusion and 17.7 \pm 13.1 $\mu\text{g/mL}$ at 1 hour after discontinuation of TXA. The concentrations varied throughout CPB, ranging from 14.3 to 54.4 $\mu\text{g/mL}$. All patients had plasma TXA concentrations greater than 10 $\mu\text{g/mL}$ during CPB. In addition 16 of the 19 patients had TXA concentrations above 16 $\mu\text{g/mL}$ during CPB (that is, above the IC_{50} shown to abolish plasmin induced platelet activation *in*

vitro). The data were analysed using a repeated measures analysis of variance (ANOVA) in order to see if increased pre-operative creatinine concentrations were associated with increased TXA plasma concentrations at various time points during the study. The analysis revealed a significant main effect of abnormal creatinine concentration ($p=0.02$) and time ($p<0.001$) and a significant interaction between time and creatinine concentration ($p < 0.001$). Patients with increased baseline serum creatinine concentrations had higher TXA concentrations than patients with normal baseline serum creatinine at discontinuation of TXA infusion ($p=0.003$) and at 1 hour after discontinuation of TXA infusion ($p=0.001$).

The authors recommended that in order to maintain a TXA plasma concentration of 20 µg/mL during CPB the dosing regimen in patients with normal renal function should be a loading dose of 5.4 mg/kg, a CPB prime dose of 50 mg for 2.5 L circuit or 40 mg for 2 L circuit and an infusion of 5 mg/kg/hour. The authors also recommended that for patients with renal insufficiency the infusion rate be decreased based on the pre-surgery serum creatinine concentration with the loading and prime doses remaining unchanged. The recommended regimens are summarised below in Table 6.

Table 6. Fiechtner 2001 – Reductions in TXA infusion rates for patients with impaired renal function.

Serum Creatinine		Loading	Prime	Infusion
Normal Function	Renal	5.4	0.6	
		mg/kg	mg/kg	5 mg/kg/hour
1.6 – 3.3 mg%		5.4	0.6	3.75
		mg/kg	mg/kg	mg/kg/hour
3.3 – 6.6 mg%		5.4	0.6	2.5
		mg/kg	mg/kg	mg/kg/hour
> 6.6 mg%		5.4	0.6	1.25
		mg/kg	mg/kg	mg/kg/hour

Comment

This was a good quality study. The results showed that a TXA loading dose of 10 mg/kg followed by an infusion of 10 mg/kg/hour was sufficient to maintain TXA plasma concentrations above 16 µg/mL during CPB in 16 out of 19 patients. The data also showed that TXA plasma concentrations increased in patients with elevated pre-operative serum creatinine concentrations indicating that downward TXA dosage adjustments are required in patients with renal impairment. The authors provided dosage regimens for use in patients with renal impairment undergoing cardiac surgery based on pre-operative serum creatinine concentration. The sponsor has modified the provided dosage regimens and included them in the PI for use in patients with renal impairment undergoing cardiac surgery. It is considered that the sponsor should adopt the proposed dosage regimens used in this study without modification (apart from changing the serum creatinine units to µmol/L) and include them in a separate table in the dosage and administration section of the PI.

Nuttal 2008

In *Nuttal 2008*, the effect of a "new" dosing regimen for use in cardiac surgery on CPB designed to achieve TXA plasma concentrations of 20 µg/mL was explored. The paper referred to published data which suggested that TXA concentrations of > 10 µg/mL were required to inhibit plasmin activity by 80% *in vitro* and 16 µg/mL to abolish plasmin induced platelet activation *in vitro*. The "new" dosing regimen consisted of a loading dose of 6.6 mg/kg given over 20 minutes followed by an infusion of 6 mg/kg/h and a CPB prime dose of

40 mg for a 2 L circuit. In renal insufficiency, the same loading and CPB prime doses were used but the infusion rate was decreased depending on the serum creatinine concentration. The new dosing regimen (n=11) was compared with the author's "standard" dosing regimen (n=9) of 10 mg/kg given over 20 minutes followed by an infusion of 1 mg/kg/h.

The percentage of patients with plasma TXA concentrations of 20 µg/mL at each time point for the "standard" and "new" regimens were, respectively: 44% versus 0% at 5 minutes after loading; 22% versus 9% at 5 minutes after the start of CPB; 0% versus 27% at 30 minutes after the start of CPB; 33% versus 100% at the termination of CPB; and 22% versus 100% at the discontinuation of TXA. The mean±SD post-operative blood loss collected in the chest drains at 24 hours after surgery was 955.6±1057.91 mL with the "standard" regimen and 1134±535.40 mL with the "new regimen" (p=0.12). Red blood cell (RBC) transfusions during the first 24 hours post-operatively were required by 6 (67%) of patients treated with the "standard" regimen and 8 (73%) of patients treated with the "new" regimen (p=1.0).

The authors concluded that the "new" TXA regimen did not achieve target TXA concentrations of 20 µg/mL 5 minutes after loading and 5 minutes after initiation of CPB. However, most of the patients in the study treated with both TXA dosing regimens had plasma concentrations during CPB greater than the 10 µg/mL needed to reduce *in vitro* tissue plasmin activity by 80 %. Based on the results of the study the authors suggested a revised dosing regimen consisting of a loading dose of 10 mg/kg, a pump prime dose of 50 mg for a 2.5 L circuit (assuming 1 L/kg Vd in prime fluids), 40 mg for a 2 L circuit and an infusion rate of 2 mg/kg/h for normal renal function. For patients with renal insufficiency, the authors proposed reduced infusion rates of 1.5 mg/kg/h for a serum creatinine of 1.6 to 3.3 mg/dL, 1 mg/kg/h for a serum creatinine of 3.3 to 6.6 mg/dL and 0.5 mg/kg/h for a serum creatinine of > 6.6 mg/dL.

Comment

This was a good quality study in which the authors attempted to design a TXA dosage regimen based on *in vitro* data relating to TXA concentrations known to inhibit tissue plasmin activity. The "new" dosage regimen was sufficient to achieve satisfactory TXA plasma concentrations 30 minutes after the start of CPB and at discontinuation of CPB compared with the "standard" dosage regimen. However, there was a non-statistically significant trend to greater mean reduction in chest tube blood loss with the "standard" compared with the "new" TXA treatment regimen at 12 and 24 hours post-operatively. The results suggest no direct relationship between blood loss and *in vivo* TXA plasma concentration. The authors state that "the amount of [TXA] needed to prevent fibrinolysis *in vivo* is not known".

Andersson 1978

In *Andersson 1978*, the effect of renal impairment on TXA plasma concentration was investigated in 28 patients with chronic renal disease. The TXA plasma concentrations (µg/mL) following administration of a single IV dose of 10 mg/kg are summarised below in Table 7 for patients with serum creatinine 120-249 µmol/L (Group I), 250-500 µmol/L (Group II) and > 500 µmol/L (Group III).

Table 7. TXA mean±SD plasma concentrations (µg/mL) following a dose of 10 mg/kg.

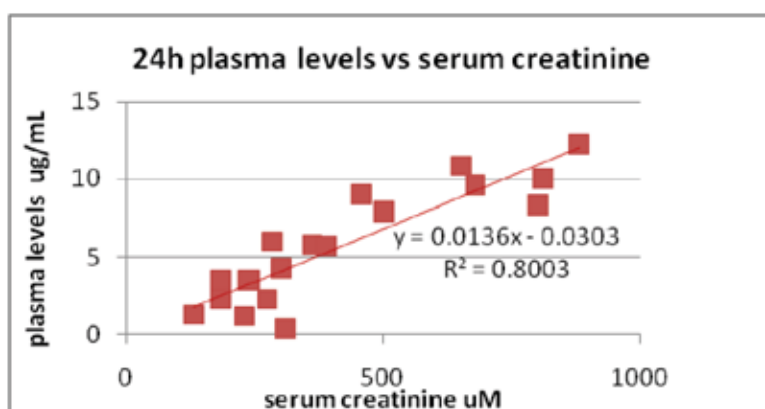
Group:	serum			0.5		3.0	5.0	8.0	24.0
creatinine	n	Dose	hours	1.0 hour	hours	hours	hours	hours	hours
GI: 120 – 249 µmol/L	6	10 mg/kg	32.3±2.9	26.5±2.7	15.3±3.3	13.1±2.7	7.3±3.1	2.4±1.0	

G2: 250 – 500 µmol/L	7	10 mg/kg	36.4±6.3	26.7±2.7	22.7±4.2	18.0±3.7	13.1±3.4	4.8±2.8
G3: > 500 µmol/L	6	10 mg/kg	31.3±4.8	26.9±5.8	23.5±2.7	20.7±3.8	16.1±2.6	9.8±1.6

Comment

The results showed that TXA elimination is impaired in patients with chronic renal disease and that dosage adjustments based on serum creatinine concentrations will be required in patients with renal impairment. The sponsor provided the following figure derived from the 24 hour data in *Andersson 1978* (Figure 3, below).

Figure 3. Plasma concentration of TXA at 24 hours versus serum creatinine concentration after a single IV dose to patients with normal and impaired renal function.



The authors note that mean total recovery of TXA from urine following IV administration to healthy volunteers has been reported to be 92.3% and 94.8% at 24 and 48 hours respectively [Erickson 1974]. In the current study, 24 hour TXA recovery in patient Groups II and III were 40.9% and 20.3%, respectively. The study reported serum concentrations of 18.3 µg/mL, 9.6 µg/mL and 5 µg/mL at 1, 3 and 5 hours, respectively, following 10 mg/kg IV to 10 healthy male volunteers. The authors commented that the half-life of TXA following IV administration has been reported to be 1.9 and 2.4 hours in two healthy subjects [Erickson 1974]. TXA plasma concentrations in these two healthy subjects were 2.0 µg/mL and 2.8 µg/mL at 8 hours after injection of TXA 1 g and it was estimated that the TXA plasma concentration at 24 hours would be about 0.5 µg/mL.

Orthopaedic Surgery

Benoni 1995 was the only study which investigated the pharmacokinetics of TXA in orthopaedic surgery (total hip replacement). The study was undertaken at the Malmö University Hospital, Malmö, Sweden. It was approved by an IEC and all patients gave informed consent. TXA at a dose of 10 mg/kg over approximately 7 minutes was administered IV shortly before surgery and repeated 3 hours later over approximately 23 minutes to 10 patients of median age 77 years [range: 51-80] with normal renal function undergoing primary hip arthroplasties. The dose was designed to provide plasma concentrations of > 10 µg/mL over 7 to 8 hours from the beginning of surgery. The authors referred to a published study [Pilbrant 1981], which calculated a median terminal half-life of 7.3 hours for TXA and data from this study were used for the simulations. Venous blood was collected for TXA concentrations before administration of the first dose and then at 3, 4, 5 and 10 hours after the first dose and then at 16-25 hours after the first dose. In all but two of the 10 patients the dosage regimen provided plasma concentrations sustained at > 10 µg/mL

for approximately 8 hours. The results suggest that the TXA dosage regimen was too low to maintain satisfactory plasma concentrations over 8 hours based on *in vitro* assumptions relating to *in vitro* therapeutic concentrations. There was no statistically significant correlation between post-operative blood loss and the concentration of TXA in the drains.

Summary Comments

The approved Cyklokapron PI includes previously evaluated information on the pharmacokinetics of TXA. The drug is cleared predominantly unchanged by the kidneys with excretion of a 10 mg/kg IV dose being about 90% at 24 hours. The calculated renal clearance is close to creatinine clearance, suggesting that TXA is eliminated by glomerular filtration [Ericksson 1974; Pilbrant 1981]. The total amount of metabolites excreted in the urine over 72 hours is less than 5%. The drug does not bind to serum albumin. Protein binding is about 3% at therapeutic levels and appears to be exclusively to plasminogen. The pharmacokinetic (PK) data from *Eriksson 1974* and *Pilbrant 1981* were examined as these two studies were frequently referred to in the submitted PK studies and appear to be the source of much of the PK information in the approved PI. These two studies were not included in the current submission but were obtained independently by the evaluator.

The current submission provided new PK information on TXA IV doses required to maintain satisfactory plasma concentrations during cardiac and orthopaedic surgery and on plasma concentrations in renal impairment. *In vitro* data have shown that tissue plasminogen activator activity is reduced by 80% at TXA concentrations of 10 µg/mL and plasmin induced platelet activation is inhibited at TXA concentrations of 16 µg/mL (half maximal inhibitory dose; IC₅₀). However, the TXA concentration needed to inhibit fibrinolysis *in vivo* is unknown. In addition, no direct association has been identified between blood loss and *in vivo* TXA plasma concentration based on concentration estimates derived from *in vitro* studies of fibrinolytic activity. The TXA treatment regimens varied among the submitted PK cardiac surgery studies. However, common features were a pre-surgery loading dose administered after induction of anaesthesia but before skin incision, followed by a maintenance infusion for the duration of the surgery with or without an additional dose added to the CPB pump prime.

The data from *Dowd 2000* suggest that TXA steady state plasma concentration for the proposed treatment regimen in cardiac surgery on CPB lasting about 4 hours is likely to be about 42.5 µg/mL. This steady state concentration is sufficient to inhibit *in vitro* fibrinolysis and plasmin induced platelet aggregation. The preferred approach to TXA dosing outlined in *Dowd 2000* is an initial loading dose followed by a maintenance infusion with an additional bolus being added to the pump line. The study proposed two basic regimens, one for "typical" patients and one for patients at high risk of bleeding. Both of these proposed regimens provide higher total TXA doses than the regimen being proposed by the sponsor: for example, for a 4 hour procedure on CPB the total TXA doses are 39.5 mg/kg (Dowd typical patient), 96 mg/kg (Dowd high risk) and 33.6 mg/kg (sponsor proposed). The sponsor proposes that only one TXA regimen be used in patients undergoing both low and high risk cardiac surgery based on similar clinical efficacy for post-operative blood loss and reduction in blood transfusion requirements. Clinical issues relating to TXA dosing regimens are discussed later in the "**Clinical Findings**" section. *Dowd 2008* showed that TXA is rapidly eliminated when given as a bolus dose in patients undergoing cardiac surgery. Despite this observation, satisfactory plasma concentrations appeared to be maintained throughout surgery provided the single bolus dose was high enough (for example, 50 mg/kg and 100 mg/kg). The data from *Dowd 2000* also showed that CPB increased the volume of distribution of the

central compartment by 1.61 L (that is, from 10.3 to 11.9 L in an 80 kg person) and reduced the elimination rate constant.

The data from *Nuttal 2008* explored two TXA treatment regimens ("standard" and "new") aimed at maintaining TXA plasma concentrations above 20 µg/mL. The new regimen administered a total TXA dose which was about 2-fold higher than the standard regimen. However, neither regimen achieved plasma TXA concentrations above 20 µg/mL in 100% of patients at all time points following initiation of treatment. Furthermore, the reduction in mean post-operative blood loss was non-statistically significantly lower with the standard compared with the new regimen. The authors conclude that the dose of TXA needed to prevent fibrinolysis is unknown. In *Andersson 1978* and *Fiechtner 2001*, the effect of increased serum creatinine concentration on plasma TXA concentration in cardiac surgery was investigated and the results showed that downward dosage adjustments are required in patients with renal impairment.

The data from *Benoni 1995*, showed that a TXA (total dose 20 mg/kg) given as an initial dose of 10 mg/kg repeated 3 hours later in patients undergoing total hip replacement was too low to maintain TXA plasma concentrations > 10 µg/mL over 8 hours in all 10 treated patients. The total TXA dose being proposed by the sponsor for use in hip and knee surgery in adults is 60 mg/kg given as an initial 15 mg/kg bolus followed by repeat 15 mg/kg bolus doses at 8 hour intervals to a maximum of time of 24 hours after surgery. There were no PK data on the proposed dosing regimen in orthopaedic surgery.

There were no PK data in patients with hepatic or cardiac impairment. There were no PK drug-drug interaction data involving TXA IV. There were no racial or sex specific PK data. There were no PK studies in children and adolescents undergoing cardiac or spinal surgery.

Drug Interactions

No data were submitted under this heading.

Pharmacodynamics

Overview

Most submitted studies reported at least one fibrinolytic parameter pre- and post-surgery. The sponsor identified 11 studies which reported fibrinolytic parameters at various time points before, during and after surgery (10 cardiac surgery studies and one total knee arthroplasty study). The relevant studies were *Benoni 1997*, *Casati 2001*, *Casati 2004*, *Kuitunen 2005*, *Kuitunen 2006*, *Matsuzaki 1999*, *Misfield 1998*, *Miyashita 2000*, *Soslau 1991*, *Uozaki 2001* and *Zabeeda 2002*. Each of the 11 studies has been evaluated and are reviewed below. The dosage regimens used in these studies are summarised in Table 8.

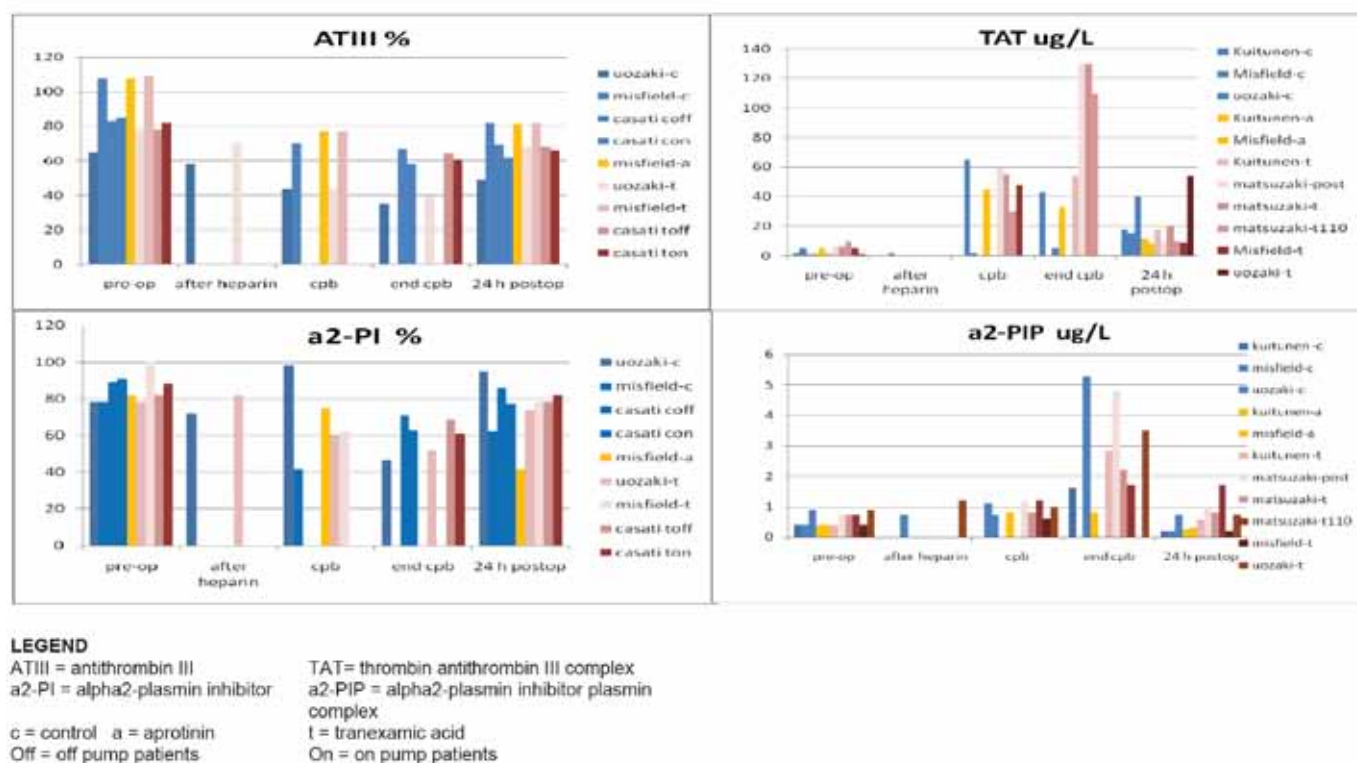
Table 8. Studies with repeat pharmacodynamic data over the duration of the study.

Study	Operation	n	Pre-Surgery	Maintenance
Benoni 1997	Knee	12	10 mg/kg	10 mg/kg at 3 hours repeat bolus
Casati 2004 off pump	Cardiac	26	14 mg/kg	5.6 mg/kg/h infusion
Casati 2004 on pump	Cardiac	26	13 mg/kg	5.2 mg/kg/h infusion
Casati 2001	Cardiac	20	14 mg/kg	5.6 mg/kg/h infusion
Kuitunen 2006	Cardiac	15	1 g	-
Kuitunen 2005	Cardiac	20	15 mg/kg	15 mg/kg/h infusion + 15 mg/kg in the pump line
Matsuzaki 1999	Cardiac	14	50 mg/kg	-
Matsuzaki 1999	Cardiac	15	50 mg/kg	10 mg/kg/h infusion
Misfeld 1998	Cardiac	14	10 mg/kg	1 mg/kg/h for 10 hours infusion
Miyashita 2000	Cardiac	12	20 mg/kg	2 mg/kg/h infusion during surgery
Soslau 1991	Cardiac	8	-	11 mg/kg/h bolus + 1 mg/kg/h infusion for 10 hours
Soslau 1991	Cardiac	7	11 mg/kg	1 mg/kg/h infusion for 10 hours
Uozaki 2001	Cardiac	6	50 mg/kg	-
Zabeeda 2002	Cardiac	25	10 mg/kg	1 mg/kg/h infusion

Cardiac Surgery Studies

Anti-Thrombin and Anti-Plasmin Parameters

The submission included studies which assessed the effects of TXA, control and aprotinin on anti-thrombin III (ATIII), thrombin-antithrombin III complex (TAT), α 2-plasmin inhibitor (α 2-PI) and α 2-plasmin inhibitor complex (α 2-PIP). Overall, the results suggested that at 24 hours after surgery the anti-fibrinolytic effects of TXA are minimal. The results are summarised in Figure 4.

Figure 4. Pharmacodynamic results.

The results for ATIII levels from *Uozaki 2001*, *Misfield 1998* and *Casati 2004* were consistent and showed similar patterns for TXA and control groups at all time points. In *Uozaki 2001*, ATIII levels were significantly lower during CPB compared with pre-operative levels in both TXA and control groups undergoing CABG. Following CPB, ATIII levels began to rise towards baseline levels over the following 24 hours. A similar pattern was observed in *Misfield 1998*, in patients undergoing CABG on CPB treated with TXA or aprotinin and in the no treatment control group. In *Casati 2004*, ATIII levels fell significantly after operation in both TXA and control groups in patients undergoing both CABG on CPB (n=51) and CABG off CPB (n=51). However, ATIII levels fell to a greater extent in patients on CPB. The $\alpha 2$ -PI (%) patterns in TXA and control groups were similar to those observed for ATIII (%) in *Uozaki 2001*, *Misfield 1998* and *Casati 2004* (CABG on and off pump).

Similar patterns in TAT concentrations in TXA and control groups were observed in *Misfield 1998*, *Kuitunen 2005* and *Matsuzaki 1999*. In *Misfield 1998*, TAT concentration increased during surgery in TXA, control and aprotinin groups and then fell post-operatively in all three groups with concentrations at 2 and 24 hours being significantly lower in the TXA and aprotinin groups compared with control. TAT concentrations in first 24 hours post-operatively were greater than pre-operative concentrations in all three treatment groups. In *Kuitunen 2005*, a similar pattern was observed with TAT concentrations peaking 2 hours after CPB in TXA, aprotinin and control groups after which concentrations declined but were still higher at 6 and 16 hours after CPB than pre-operatively. In *Matsuzaki 1999*, TAT concentrations in the TXA and control groups increased gradually during CPB reaching a peak at the end of CPB and then gradually declining to reach concentrations on the first post-operative day similar to those recorded pre-operatively. In this study there was no difference in TAT concentrations between patients who had received a continuous TXA infusion for 6 hours after CPB and those who had not received an infusion. The TAT concentration pattern

differed in *Uozaki 2001* from that observed in *Misfield 1998*, *Kuitunen 2005* and *Matsuzaki 1999*. In *Uozaki 2001*, TAT concentrations remained low throughout surgery but then significantly increased in both TXA and control groups after protamine administration peaking at 24 hours after surgery in the TXA group and 1 hour after surgery in the control group with concentrations at 24 hours post-operatively in both groups being well above pre-operative concentrations. The reasons for the difference in TAT concentration in *Uozaki 2001* compared with the other three studies are unknown.

The α 2-PI (%) patterns in TXA and control groups were similar to those observed for ATIII (%) in *Uozaki 2001*, *Misfield 1998* and *Casati 2004* (CABG on and off pump). The α 2-PIP concentrations in TXA and control groups were similar in *Uozaki 2001*, *Misfield 1998*, *Casati 2004* (CABG on and off pump) and *Kuitunen 2005* with concentrations rising gradually during surgery, peaking towards the end of CPB and then falling post-operatively to reach similar concentrations at 24 hours to those reported pre-operatively.

Fibrin Split Products and D-dimer Levels

TXA significantly reduced D-dimer levels (that is, breakdown products of cross-linked fibrin) compared with control during and up to 24 hours after surgery in *Misfield 1998*, *Kuitunen 2005*, *Casati 2004*, *Casati 2001* and *Miyashita 2000*. In *Miyashita 2000*, TXA significantly reduced fibrin degradation products (FDP) compared with control from before protamine to 30 minutes after protamine. In *Zabeeda 2002*, fibrinogen split products (FSP) increased significantly during CABG in the control group and continued to increase with duration of bypass. In contrast, in the TXA group pre-operative FSP levels did not change during bypass ($p < 0.001$ versus control). In both control and TXA groups, FSP levels were at pre-operative levels at 24 hours post-operatively.

Platelet Function

In *Soslau 1991*, the effects of TXA on platelet function were investigated both *in vivo* in patients undergoing cardiac surgery on CPB and *in vitro*. The *in vivo* results showed that TXA administered prior to initiation of CPB preserved platelet function to a greater degree than TXA administered after initiation of CPB. In 7 patients, TXA was initiated before CPB (that is, prior to skin incision) while in another 8 patients TXA was initiated after CPB and protamine administration. The group that received TXA prior to initiation of CPB experienced less bleeding (median values 420 versus 655 mL/12 h; $p = 0.024$), lower FSP concentrations ($\geq 10 \mu\text{g/mL}$: 0/7 versus 5/8; $p < 0.05$) and greater platelet adenosine diphosphate concentrations after surgery (15.47 versus 4.05 nmoles/mg protein median, $p = 0.021$).

In vitro, TXA was shown to completely inhibit plasmin induced platelet activation at clinically observed plasma concentrations. Inhibition was shown to come from specific binding of TXA to plasmin and not to the plasmin receptor on platelets. The EC_{50} of TXA required to inhibit plasmin induced platelet activation was $16 \mu\text{g/mL}$ [95% CI: 7.3, 99]. The authors noted that clinically recommended intravenous doses of TXA result in plasma concentrations of 5-10 $\mu\text{g/mL}$. TXA had no effect on collagen, adenosine diphosphate (ADP), or thrombin induced platelet aggregation in either model.

Clot Strength

In *Kuitunen 2006*, TXA 1 g administered after 15 mL/kg of 6% hydroxyethyl starch (HES) in the immediate post-operative period did not reverse the reduction in clot strength induced by HES after cardiac surgery on CPB. Clot formation time was prolonged and maximum clot firmness and shear elastic modulus were decreased after administration of HES ($p < 0.001$). These abnormalities persisted despite administration of TXA. Maximal clot lysis increased

after HES and TXA did not prevent this outcome. In addition, TXA (n=15) did not increase mean \pm SD cumulative chest tube drainage measured to the first post-operative morning compared with placebo (n=15); 1008 \pm 251 mL and 1081 \pm 654 mL, p=0.698, respectively.

Knee Surgery

In *Benoni 1997*, the effect of TXA (n=12) (10 mg/kg shortly before the release of the tourniquet and repeated 3 hours later) on fibrinolysis was compared with placebo (n=12) in patients undergoing total knee arthroplasty (TKA). Samples from peripheral venous blood were analysed for coagulation and fibrinolytic factors before surgery (after induction of anaesthesia), at the end of surgery (10-15 minutes after the release of the tourniquet) and post-surgery (3 hours after the end of surgery). There were signs of increased fibrinolysis throughout the observation period. However, no significant differences were observed between TXA and placebo at the end of surgery and post-surgery in D-dimer, plasminogen, α 2-antiplasmin, tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI-1) concentrations, apart from lower plasminogen concentrations in the TXA group at the end of surgery [p=0.03]. The coagulation factors platelet factors (PFs) 1+2 increased throughout the observation period with both TXA and placebo, but there were no significant differences between treatments. Fibrinolytic activity was greater in wound blood taken from the surgical site at the end of surgery than in peripheral venous blood. D-dimer, tPA and PAI-1 concentrations were higher in wound blood compared with venous blood, but plasminogen and α 2-antiplasmin concentrations were lower in wound than venous blood. The reduction in D-dimer concentration in wound blood was statistically significantly lower in the TXA group compared with placebo (p=0.01). The PF 1+2 concentrations were about 12 times higher in wound blood than in venous blood, but there was no significant difference between TXA and placebo. In TXA treated patients post-operative blood loss was approximately half that compared with placebo and the authors comment that the difference was "highly significant" but no values were provided. Overall, the results showed that fibrinolysis and coagulopathy were activated during knee arthroplasty, but no direct correlation was found between increased fibrinolysis and blood loss. TXA inhibited fibrinolysis in wound blood but had no effect on fibrinolysis in plasma from venous blood. The authors conclude that diminished post-operative blood loss in patients treated with TXA is "probably induced by decreased fibrinolysis in the wound".

Summary Comments

TXA is an anti-fibrinolytic agent belonging to the group of lysine analogues which competitively inhibit plasminogen activation and, at much higher concentrations, non-competitively, inhibits plasmin. TXA is about 10 times more potent *in vitro* than ϵ -aminocaproic acid (EACA), another anti-fibrinolytic lysine analogue. TXA acts as an anti-fibrinolytic agent by blocking the lysine sites of plasminogen involved in binding to fibrin. This interaction delays the conversion of plasminogen into plasmin by tissue plasminogen activator, resulting in inhibition of fibrin degradation and allowing formation of a stable clot. TXA may also displace plasminogen from the fibrin surface preventing its activation and further inhibiting fibrinolysis.

The clinical pharmacodynamic data primarily examined the *in vivo* effect of TXA on pro-thrombotic and fibrinolytic factors. In general, the cardiac surgery studies showed similar changes in anti-thrombin (ATIII & TAT) and anti-plasmin (α 2-PI & α 2-PIP) complexes in both TXA treated patients and placebo. In one study involving knee surgery arthroplasty PF 1+2 coagulation factor levels increased to a similar extent following both TXA and placebo treatment. Overall, the limited clinical pharmacodynamic data suggest that TXA does not promote *in vivo* thrombus formation.

In the cardiac surgery studies, D-dimer levels were significantly lower during and up to 24 hours after surgery in TXA treated patients compared with placebo. In one study, FSP products increased significantly in placebo controls compared with TXA treated patients. D-dimer and FSP results suggest that in cardiac surgery TXA inhibits fibrinolysis compared with non-active controls. In one study involving knee arthroplasty there was no evidence of inhibition in fibrinolysis in peripheral blood in TXA or placebo treated patients. However, there was evidence of inhibition of fibrinolysis in wound blood in TXA treated patients compared with placebo.

Efficacy

Cardiac Surgery Tranexamic Acid versus Control (Placebo or No Anti-fibrinolytic Treatment)

Overview

The sponsor identified 53, published, prospective, randomised controlled (placebo or no anti-fibrinolytic treatment) studies that examined the effects of TXA on post-operative blood loss and/or on the incidence of allogeneic blood transfusion in patients undergoing cardiac surgery. Of the 53 identified studies, 37 were included in meta-analyses of post-operative blood loss and 35 were included in meta-analyses of blood transfusion. In the 53 studies, a total of 2112 adult patients were treated with TXA of whom 755 (35.7%) received total doses of between 20 mg/kg and 50 mg/kg, 854 (40.0%) received total doses > 50 mg/kg and 501 (23.7%) received total doses > 100 mg/kg. The total dose of TXA was calculated as the sum of the bolus dose plus the product of infusion dose and time of infusion. If the time of infusion was not specified, it was assumed to have continued for 2 hours to cover the time on cardiopulmonary by-pass (CPB). The proposed dose of TXA for use in cardiac surgery in adults is a loading dose of 15 mg/kg, followed by an infusion of 4.5 mg/kg/hour for the duration of the surgery of which 0.6 mg/kg may be added in the pump line. This proposed TXA dose is equivalent to a total dose of 24 mg/kg assuming that the duration of time on CPB is 2 hours.

Of the 2025 patients in whom the type of surgery was specified, 1421 (70.2%) underwent CABG, 325 (16%) underwent valve replacement, 98 (4.8%) underwent CABG plus valve replacement and the remaining 181 (9%) underwent repeat CABG, repeat valve replacement, atrio-septal repair or aortic surgery (aneurysm, dissection). The CPB 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 undertaken with patients mildly hypothermic (approximately 32°C) except for those studies designed to study normothermic perfusion effects on post-operative blood loss and platelet preservation. CPB times were usually reported in the studies and ranged from 1 to 2 hours.

The primary outcomes in the 53 studies were the amount of post-operative blood loss and/or the number and/or type of transfusion. Transfusion protocols to correct post surgery haemoglobin and clotting parameters were reported in 31 studies. Post operative blood loss was measured until the chest drains were removed and this ranged from 12 to 39 hours post chest closure. The mean age of patients in the studies ranged between 44 and 75 years. In the 33 studies which reported patient sex, 69% were male and 31% female. In studies which reported exclusion criteria the most common factors (one or more) were: renal impairment; hepatic impairment; coagulopathy; thrombocytopaenia; anaemia; intra-aortic balloon counterpulsation; repeat cardiac surgical procedure; history of pulmonary embolism (PE), deep vein thrombosis (DVT) or cerebro-vascular accident (CVA); treatment with anticoagulants or antiplatelet agents within 10 days of surgery; and treatment with aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) within 3-7 days of surgery. Apart from

aspirin, NSAIDs and anti-coagulants, the use of medications prior to surgery was poorly described in the studies.

Post-Operative Blood Loss (Primary Efficacy Outcome)

a. Overview

Of the 53 identified studies, 37 reported post-operative blood loss as mean and standard deviation (SD) or mean and 95% confidence intervals (CIs) which allowed the results to be pooled. The 37 studies included 22 published papers in peer review journals and 15 published conference abstracts. In general, the sponsor graded the 22 published paper as Grade 0, 1 or 2 (that is, highest grades) and the 15 conference papers as Grade 4 or 5 (that is, lowest grades). All included studies were defined by the sponsor as providing Level I or II evidence. The conference abstracts are not peer reviewed publications, but their inclusion in the meta-analysis is considered acceptable as the abstracts clearly described the study results and were randomized, controlled and blinded studies. However, two conference abstracts appear to include the same group of patients and, consequently, these same patients appear to have been entered into the meta-analysis twice [Isetta 1991a; Isetta 1991b]. The 37 studies included about 1525 TXA treated patients and about 1480 control patients.

The analysis of the effect of TXA on post-operative blood loss in cardiac surgery included two meta-analyses (duplicates included and duplicates removed) and a number of subgroup meta-analyses (dose subgroups and blood loss in control group categories). The meta-analyses compared the effects of total TXA dose and control on the amount of post-operative blood loss (mL). The duplicates included meta-analysis included all comparisons from all individual studies. The duplicates removed meta-analysis removed multiple pair-wise comparisons between TXA and control reported in the same study and replaced them with one combined pair-wise comparison. Inclusion in the duplicates included meta-analysis of all pair-wise comparisons which shared the same control group resulted in the data for the control group being replicated. This had the potential to bias the pooled mean outcome estimate for the control group. However, the results were similar for the duplicates included and duplicates removed meta-analyses suggesting that no significant bias occurred in the duplicates included meta-analysis from repeated inclusions of the same control data.

Comment

The underlying methodology adopted by the sponsor for the meta-analysis is considered to be basically sound. The sponsor provided a single combined pair-wise comparison for each of these studies for inclusion in the duplicates removed meta-analysis. There were four studies which included two or more TXA pair-wise comparisons with the same control group. The sponsor also provided satisfactory information on how the combined pair-wise comparison had been calculated.

b. Post-operative Blood Loss by Total TXA Dose Subgroup

The duplicates removed meta-analysis has been chosen to represent the results for the TXA versus control comparisons by dose category as it included all TXA doses examined in the relevant studies and has not been significantly biased by inclusion of repeat control groups. In the duplicates included meta-analysis, there were about 1525 TXA treated patients and about 1480 control patients and a total of 47 pair-wise comparisons between TXA and control from 37 studies. In the duplicates included meta-analysis, TXA combined over the dose range (5.5-250 mg/kg total dose) reduced post-operative blood loss by 226 mL [95%CI: 181, 271] compared with placebo (Table 9, below). In the duplicates removed meta-analysis, TXA combined over the dose range (12-188 mg/kg total dose) reduced post-operative blood loss by 240 mL [95%CI: 188, 292] compared with placebo.

Table 9. Cardiac blood loss TXA versus control by TXA dose category - duplicates included meta-analysis.

	< 20 mg/kg	20-50 mg/kg	51-100 mg/kg	> 100 mg/kg	Overall
Pair-wise Comparisons	9	23	5	10	47
Patients (n) – TXA treated	377	487	269	392	1525
Mean TXA Total Dose (mg/kg)	13.0	28.0	82.2	145.2	67.1
WMD [95%CI] mL	-222 [-303, 141]	-218 [-264, -173]	-159 [-242, -76]	-256 [-386, -126]	-226 [-271, -181]
Heterogeneity I ² (%); p value	72.5%; p <0.001	23.7%; p=0.149	65.5%; p=0.021	92.8%; p <0.001	82.2%; p <0.001
Weight %	21.50	42.7	13.21	23.13	100.00

WMD= Weighted Mean Difference

Comment

The results of the duplicates included meta-analysis showed that TXA over the dose range (5.5-250 mg/kg total dose) significantly reduced post-operative blood loss by 226 mL [95%CI: 181, 271] compared with control. This represents a saving in post-operative blood loss due to TXA compared with control of about 31%. However, heterogeneity among the studies was statistically significant. Factors which might have contributed to heterogeneity among the studies include differences in TXA dose, TXA administration regimen, surgical procedures, repeat surgery rates, surgical expertise, expertise of surgical support teams, patient numbers and patient characteristics. Despite the significant heterogeneity among the studies the percentage of statistically significant individual pair-wise comparisons in the duplicates included meta-analyses was 68% (32/47).

Based on a 2 hour surgical procedure the proposed total TXA dose is 24 mg/kg. Consequently, the TXA 20-50 mg/kg total dose subgroup meta-analysis is considered to be the most relevant as it included the proposed dose. In the TXA 20-50 mg/kg total dose subgroup (duplicates included meta-analysis), TXA significantly reduced post-operative blood loss by 218 mL [95%CI: 173, 264] compared with control (Table 9, above). This represents a saving in post-operative blood loss due to TXA of about 33% compared with control. Heterogeneity was not significant in this subgroup. Of the 23 individual pair-wise comparisons in this subgroup, 65% (15/23) statistically significantly favoured TXA over control. The absolute difference in post-operative blood loss between TXA and control was similar for the overall meta-analysis (5.5-250 mg/kg total dose) and the subgroup meta-analysis (20-50 mg/kg total dose), as were the percentage savings in post-operative blood loss due to TXA.

In the majority of the 37 studies in the duplicates included meta-analyses the sample size for both TXA and control groups was less than 40 patients. Of the 37 studies, only 5 included an estimate of power. The sample size and power calculations from these studies suggest that an absolute difference in post-operative blood loss between TXA and control of at least 200 mL

and a saving of at least 30% due to TXA are likely to be clinically meaningful. In *Pleym 2003*, it was calculated that sample sizes of 40 patients in each of the two treatment groups would give a power of 80% to detect a clinically relevant post-operative blood loss difference of 200 mL with a SD of 300 mL and an $\alpha = 0.05$. In *Coffey 1995*, it was calculated that sample sizes of about 15 patients in each of the two treatment groups would give a power of $> 90\%$ to detect a difference of 270 mL between the groups based on an $\alpha = 5\%$. In *Karski 1995*, it was calculated that sample sizes of 50 in each of the three treatment groups would give a power of at least 80% to detect a difference in post-operative blood loss of 200 mL with a SD of 200 mL and an $\alpha = 5\%$. In *Corbeau 1995*, it was calculated that sample sizes of about 30 in each of the two groups would be needed to find a significant decrease of 40% in blood loss. In *Maddali 2007*, it was calculated that sample sizes of 74 patients in each treatment group were required to detect a reduction in post-operative blood loss of 30% (Type 1 error 0.05%, variance error of 1). In *Santos 2006*, it was calculated that a sample size of 24 patients in each group would provide a power of 80% to detect a clinically relevant blood loss difference of 250 mL (30% reduction) and a standard deviation of 300 mL, with a Type 1 error of 5%.

The results from the *Cochrane Review [Henry 2008]* meta-analysis of 17 trials showed that, on average, TXA (n=595) reduced post-operative blood loss by 262 mL [95%CI: 206, 318] per patient compared with control (n=535). Heterogeneity among the 17 trials was statistically significant: $p=0.01$; $I^2=47.9\%$. In a subgroup meta-analysis, the 17 trials were divided by total TXA dose into 9 trials of < 2 g and 8 trials of 2-10 g. In the < 2 g subgroup, TXA significantly reduced post-operative blood loss by 251 mL [95%CI: 151, 352] and heterogeneity was not statistically significant: $p=0.07$; $I^2=45.2\%$. In the 2-10 g subgroup, TXA significantly reduced post-operative blood loss by 272 mL [95%CI: 204, 340] and heterogeneity was statistically significant: $p=0.003$; $I^2=53.9\%$. The difference in blood loss of about 20 mL between the two dose subgroups is considered to be clinically insignificant. Of the 17 studies in the *Cochrane Review [Henry 2008]* meta-analysis, 16 were also included in the sponsor's meta-analysis of 37 studies. The results of the duplicates removed meta-analysis and the *Cochrane Review [Henry 2008]* meta-analysis are consistent as regards the mean difference in post-operative blood loss between TXA total dose and control. In addition, in neither meta-analysis was a dose-response relationship observed between total TXA dose and post-operative blood loss reduction compared with control.

c. Post-operative Blood Loss by Control Group Blood Loss Category

The sponsor also submitted a meta-analysis comparing TXA and control groups categorised by post-operative blood loss in the control group. The four control group blood loss categories were < 300 mL (low), 300-600 mL (low medium), 601-900 mL (medium) and > 900 mL (high). The sponsor argued that the mean post-operative blood loss for the control group is a surrogate measure of the underlying risk of the surgical procedure. The assumption is that high risk surgical procedures are associated with greater post-operative blood loss. The sponsor considered that inter-subject variability in the types of surgical procedure and the lack of information on the number of patients undergoing different procedures in some studies made a meta-analysis categorised on the basis of the actual surgical procedure unreliable.

The results from the duplicates removed meta-analysis has been chosen to represent the results for the TXA versus control comparisons categorised by control group blood loss. This meta-analysis excludes repeat counts of the same control group from studies with duplicate comparisons. The results showed that TXA significantly reduced blood loss compared with control for each of the control blood group categories (Table 10, below). Overall

heterogeneity was statistically significant, but heterogeneity in the individual meta-analyses of the three categories including more than one study was not statistically significant. The volume of blood saved by TXA increased with increasing blood loss category.

Table 10. Cardiac blood loss TXA versus control by blood loss category - duplicates removed meta-analysis.

	< 300 mL	300 – 600 mL	601 – 900 mL	> 900 mL	Overall
Pair-wise comparisons (n)	1	8	15	14	38
WMD [95%CI] (mL)	-52 [-74, -30]	-152 [-204, -100]	-230 [-274, -185]	-339 [-397, -280]	-240 [-292, -188]
Heterogeneity I^2 (%); p value	-	37.9%; p=0.127	13.6%; p=0.302	38.1%; p=0.074	84.5%; p < 0.001

The results for the TXA 20-50 mg/kg subgroup from the duplicates removed meta-analysis are summarised below in Table 11. The results showed that TXA 20-50 mg/kg statistically significantly reduced post-operative blood loss compared with control in each of the three blood loss categories and that overall and individual category heterogeneity were not statistically significant. The results showed that TXA 20-50 mg/kg significantly reduced post-operative blood loss across the range of cardiac surgical procedures from low to high risk. The volume of blood saved by TXA increased with increasing control blood loss category (that is, increased surgical risk).

Table 11. Post-operative blood loss TXA 20-50 mg/kg subgroup versus control (by control blood loss category - duplicates removed meta-analysis).

	< 300 mL	300 – 600 mL	601 – 900 mL	> 900 mL	Overall
Pair-wise comparisons	-	4	10	6	20
WMD [95%CI] mL	-	-140 [-196, -84]	-264 [-327, -200]	-308 [-410, -205]	-225 [-274, -177]
Heterogeneity I^2 (%); p value	-	0%; p=0.467	0%; p=0.837	3.0%; p=0.398	23.9%; p=0.162

Data provided by the sponsor (dated 22 September 2009).

Additional results for the duplicates removed meta-analysis for the TXA 20-50 mg/kg subgroup are summarised below in Table 12. The results were calculated by the evaluator using the Statistical Package for the Social Sciences (SPSS 17.0) from data provided in the sponsor's response of 22 September 2009 and relevant data lists provided with the original data and in the response of 10 September 2009. The tabulated results are similar to and consistent with those provided by the sponsor in the original clinical submission.

Table 12. Relevant parameters from controlled studies included in the duplicates removed meta-analysis for total TXA dose of 20-50 mg/kg across blood loss categories.

Control blood loss category	< 300 mL	300 – 600 mL	601 – 900 mL	> 900 mL
Studies (n)	-	4	10	6
Mean total TXA dose (mg/kg)	-	33	28	27
TXA dose range (mg/kg)	-	20 – 45	20 – 50	20 - 45
Patients treated TXA (n)	-	160	203	129
Mean±SD control group blood loss (mL)	-	487±45	761 ±69	1060±89
Mean±SD TXA group blood loss (mL)	-	353±38	505±116	690±83
Mean saving in blood loss (mL)	-	134	256	370
Range in blood saving loss (mL)	-	50 – 193	74 – 370	193 – 522
Mean saving in blood loss due to TXA as % [95%CI]	-	27.1 % [95%CI: 9.7, 44.6]	33.9% [95%CI: 25.3, 42.5]	34.4% [95%CI: 23.8, 45.0]

Source: Calculated by evaluator using SPSS 17.0.

Comment

The duplicates removed meta-analysis showed that TXA 20-50 mg/kg statistically significantly reduced mean post-operative blood loss compared with control in each of the control group blood loss categories. Furthermore, while the mean total TXA dose remained relatively constant in each of the control group blood loss categories the mean volume of blood saved by TXA increased with increasing control group blood loss (that is, increasing surgical risk).

The sponsor categorized the studies on the basis of the blood loss occurring in the control group. The sponsor considered that this categorization was a surrogate for the type of cardiac surgery, with higher risk surgeries (such as repeat surgery and aortic surgery) being included in the control group blood loss > 900 mL category while lower risk surgeries (such as CABG off pump) being included mainly in the control group blood loss category < 300 mL. This assumption appears reasonable. However, it was noted that a simple descriptive comparison of total TXA dose and surgical procedure showed that total TXA dose increased with surgical complexity (Table 13, below). This might reflect surgical practice in which higher TXA doses were selected for higher risk procedures. However, the control blood loss category meta-analysis showed that the dose of TXA does not need to be increased with high risk surgical procedures. Consequently, as proposed by the sponsor the same TXA dose can be used irrespective of the risk of blood loss associated with the surgical procedure.

Table 13. Distribution of studies and patients by surgical categories in controlled studies.

Surgical Categories	Categories	TXA (mg/kg)	Patients (n)	Studies (n)
1. CABG (s & m)*, ASD**.	CABG off pump	28 [range 18-45]	127	4
	CABG on pump	49 [range 12-140]	467	15
	CPB	56 [range 5.5-133]	174	8
	Total	-	768	27
2. Valve (s & m)*, CABG+Valve.	-	56 [range 20-150]	399	13
3. Repeat Surgery, Aortic Surgery.	-	130 [range 24-250]	220	4
4. Not Stated.	-	25 [range 15-30]	138	3

Note: Some studies contributed to more than one category. * (s & m) = single and multiple; ** ASD = Atrial Septal Defect.

The submission included two meta-regressions which explored the effect of different risk factors on the summary estimate of mean difference in blood loss (TXA – control). These meta-regressions showed that the control blood loss category was a more significant risk factor for post-operative blood loss than the specified type of surgery. In one of the meta-regressions, risk factors of type of surgery, treatment regimen, dose category and study quality were included and the results showed that only the type of surgery ($p=0.005$) significantly affected blood loss reduction. However, in the other meta-regression, risk factors of surgery type, control group blood loss category, treatment regimen, anticoagulant use and study quality were included and the results showed that surgery type ($p=0.047$) and control group blood loss category ($p<0.001$) both significantly affected blood loss reduction. The results from this meta-regression showed that control group blood loss category was a more significant predictor of TXA blood loss reduction than specified surgery type. The results of the meta-regression support the use of control blood loss as a surrogate measure of surgical risk.

d. Dosage Regimens

The effect of dosage regimen on blood loss was also examined in the 37 key studies included in the post-operative blood loss meta-analysis (Table 14, below).

Table 14. Dosage regimens used in the 37 studies in the post-operative blood loss meta-analysis.

Dosage Regimen	Single pre-surgery dose	Pre-surgery dose + repeat post-surgery dose	Pre-surgery dose + infusion \pm pump line dose
Mean total TXA dose (mg/kg)	89	33	22
Dose range (TXA mg/kg)	12 – 140	30 – 45	12 – 45
Number of patients treated (n)	793	142	544 *
Number of studies (n)	16	5	18
Mean saving in blood loss (mL)	231	299	262
Range in blood saving (mL)	52 – 432	160 -149	50 – 522

Note: *Corbeau 1995* and *Yau 1991* each included two TXA treatments each compared with a separate control group and each comparison from both studies was included. * 46 patients excluded from *Horrow 1995* as lower dose study arms were not as effective as higher dose study arms.

Comment

The results showed that although the single-dose pre-surgery regimens used higher total TXA doses than the other two regimens the mean saving in blood loss (mL) was lower. The pre-surgery + repeat post-surgery regimens used higher total TXA doses and obtained a higher mean saving in blood loss (mL) than pre-surgery dose + infusion \pm pump line dose regimens. However, pre-surgery dose + infusion \pm pump line dose regimens were the most commonly used regimens. In these regimens the mean total TXA dose (22 mg/kg) was lower than that for the other two regimens and the mean saving in blood loss (262 mL) was clinically meaningful. The mean total dose used in the dose + infusion \pm pump regimens (22 mg/kg) was the one closest to the proposed total TXA dose (24 mg/kg). There were 10 studies which used a total TXA dose of 20-29 mg/kg (pre-surgery doses ranging from 6.6-20 mg/kg, dose in, infusion doses ranging from 1-6 mg/kg/h and dose in CPB line 0.5 mg/kg). The data are considered to support the proposed treatment dose and regimen.

e. Comparison between Included and Excluded Studies

The meta-analysis included 37 studies which reported mean and standard deviation or 95% confidence intervals for post-operative blood loss which allowed pooling of the results. There were 16 identified studies which only reported median and interquartile range or range for post-operative blood loss and, consequently, were omitted from the meta-analysis. In order to see whether the excluded studies biased the results of the meta-analyses, the sponsor calculated the inter-quartile range of the included studies and a visual comparison was made of these results with those excluded from the meta-analysis. Visual inspection suggests no significant difference between the inter-quartile post-operative blood loss ranges for included and excluded studies.

The report also included a comparison of the proportion of studies with statistically significant results for post-operative blood loss (TXA versus control) for the included and excluded studies. This comparison showed that the percentage of studies with statistically significant positive results was 83% of the 37 included studies and 94% of the 16 excluded studies, with no studies in either group having statistically significant negative results. The comparative data showed that the results of the meta-analysis have not been biased by excluding identified studies on the basis of the descriptive method of reporting post-operative blood loss.

Allogeneic Blood Transfusion (Secondary Efficacy Outcome)

The submission included a meta-analysis of 35 studies with allogeneic blood transfusion data from about 1300 patients treated with TXA and about the same number of control patients who received packed red blood cells or whole blood during post-operative recovery. The 35 studies included 25 studies from the meta-analysis of post-operative blood loss in the TXA versus control studies.

In the meta-analysis grouped by TXA total dose, TXA 12-150 mg/kg statistically significantly reduced the relative risk of blood transfusion by 29% compared with control: RR = 0.71 [95% CI: 0.63, 0.80]; heterogeneity not statistically significant ($p=0.123$; $I^2 = 21.2\%$) (Table 15 below). Of the 39 individual relative risk estimates included in the TXA 12-150 mg/kg meta-analysis, 32 favoured TXA over control but in only 7 (17.9%) was the relative risk statistically significant. TXA 20-50 mg/kg statistically significantly reduced the relative risk of blood transfusion by 28% compared with control: RR = 0.72 [95%: 0.62, 0.83]; heterogeneity not statistically significant ($p=0.492$, $I^2 = 0\%$). The TXA 20-50 mg/kg subgroup meta-analysis contributed 23 (65.7%) studies to the overall relative risk meta-analysis by dose group and the weight given to these 23 studies was 49.1%. Of these 23 studies, TXA 20-50 mg/kg reduced the relative risk of blood transfusion compared with placebo in 19 (82.7%) but in only 4 (21.0%) were the results statistically significant [Shore-Lesserson 1996; Isetta 1991a; Isetta 1991b; Cassati 2002].

Table 15. Relative risk (RR) of allogeneic blood transfusion – TXA versus control by dose subgroup.

	< 20 mg/kg	20-50 mg/kg	51-100 mg/kg	> 100 mg/kg	Overall
Pair-wise Comparisons	6	23	3	7	39
RR [95%CI] TXA:	0.53 [0.40,	0.72 [0.62,	0.59 [0.45,	0.86 [0.69,	0.71 [0.63,
Control	0.70]	0.83]	0.77]	1.09]	0.80]
Heterogeneity I^2 (%);	0%;	0%;	0%;	37.7%;	21.2%;
p value	$p=0.950$	$p=0.492$	$p=0.454$	$p=0.141$	$p=0.123$

In the meta-analysis categorised by control group blood loss, TXA 12-140 mg total dose reduced the risk of blood transfusion by: 19% in the < 300 mL category (RR = 0.81 [95%CI: 0.48, 1.38]); 32% in the 300-600 mL category (RR = 0.68 [95%CI: 0.50, 0.93]); 27% in the 601-900 mL category (RR = 0.73 [95%CI: 0.60, 0.87]); and 23% in the > 900 mL category (RR = 0.67 [95%CI: 0.55, 0.81]). Heterogeneity was not statistically significant in the three categories which included more than one study (that is, all apart from the < 300 mL category). The overall risk reduction due to TXA 12-140 mg/kg total dose across the 4 control group blood loss categories was 29% (RR = 0.71 [95%CI: 0.63, 0.80]; heterogeneity

not statistically significant ($p=0.123$; $I^2=21.2\%$). The risk difference between TXA 12-140 mg and control across the 4 control blood loss categories was 12.9% [95%CI: 9.2, 16.7].

In the TXA dose subgroup meta-analysis categorised by control blood loss, TXA 20-50 mg/kg total dose reduced the risk of blood transfusion by: 17% in the 300-600 mL category (RR = 0.83 [95%CI: 0.58, 1.18]); 32% in the 601-900 mL category (RR = 0.68 [95%: 0.54, 0.87]); and 33% in the > 900 mL category (RR = 0.67 [95%CI: 0.50, 0.89]). Heterogeneity was not statistically significant in these three categories. There were no studies in the < 300 mL category. The overall risk reduction due to TXA 20-50 mg/kg total dose across the three control blood loss categories was 28% (RR = 0.72 [95%CI: 0.62, 0.83]; heterogeneity not statistically significant ($p=0.492$; $I^2=0\%$). The risk difference between TXA 20-50 mg/kg and control across the three control blood loss categories was 11.8% [95% CI: 6.6, 17.0].

Comment

The results showed that both TXA 12-150 mg/kg total dose and TXA 20-50 mg/kg total dose statistically significantly reduced the relative risk of blood transfusion by 29% and 28%, respectively. These results were consistent with those in the *Cochrane Review* [Henry 2008] meta-analysis of relative risk of allogeneic blood transfusion. The Cochrane Review meta-analysis included results from 28 cardiac surgery studies and showed that TXA ($n=1322$) reduced the risk of allogeneic blood transfusion by 30% compared with control ($n=1220$): RR = 0.70 [95%CI: 0.61, 0.80]; heterogeneity was statistically significant ($p<0.03$; $I^2=36.7\%$). In a subgroup meta-analysis of 16 of these 30 trials, TXA at a total dose of < 2 g ($n=495$) significantly reduced the risk of allogeneic blood transfusion by 28% compared with control ($n=431$): RR = 0.72 [95%CI: 0.59, 0.88]; heterogeneity statistically significant ($p=0.05$; $I^2=39.9\%$). In a subgroup meta-analysis of 14 of these 30 trials, TXA at a total dose of 2-10 g ($n=827$) significantly reduced the risk of allogeneic blood transfusion by 33% compared with control ($n=789$): RR = 0.67 [95%CI: 0.55, 0.83]; heterogeneity not statistically significant ($p=0.09$; $I^2=37.2\%$). The *Cochrane Review* [Henry 2008] and the sponsor's meta-analyses of relative risk of allogeneic blood transfusion shared 25 studies. The high proportion of shared studies in the two meta-analyses accounts for the similarity of the relative risk estimates. TXA 20-50 mg/kg statistically significantly reduced the risk of blood transfusion in the two highest control blood loss categories (601-900 mL & > 900 mL), but not the lowest control blood loss category (>300 mL). This suggests that TXA 20-50 mg/kg can significantly reduce blood transfusion requirement in high risk surgical procedures but not in low risk surgical procedures. However, this observation might simply reflect the fact that blood transfusion requirements are likely to be lower in low risk cardiac surgical procedures than higher risk cardiac surgical procedures.

Tranexamic Acid versus Active Comparator

The submission included meta-analyses comparing the effects of TXA, aprotinin, ϵ -aminocaproic acid [EACA], desmopressin and dipyridamole on both post-operative blood loss and the risk of allogeneic blood transfusion. Aprotinin, EACA and dipyridamole are not available for this indication in Australia, while desmopressin is registered for patients undergoing cardiac surgery complicated by platelet function defects sufficient to prolong bleeding time despite a relatively normal platelet count. However, desmopressin is considered to offer no benefit as routine therapy for patients undergoing uncomplicated CPB.

Aprotinin was withdrawn in Australia due to an increased risk of death compared with EACA and TXA in patients treated to control bleeding during high risk cardiac surgery [Fergusson 2008]. It was approved for the "prophylactic reduction of perioperative blood loss and reduction in the need for blood transfusion in adult patients undergoing [CPB] in the course

of [CABG], where the risk of bleeding is high (impaired haemostasis for example, presence of aspirin) or when transfusion is unavailable or unacceptable". As there were no concerns regarding the efficacy of aprotinin for use in cardiac surgery it is considered reasonable to briefly review the submitted efficacy data comparing aprotinin with TXA. The submitted efficacy data comparing TXA with EACA, desmopressin and dipyridamole are not considered to be directly relevant to the submission and will not be considered further.

The mean dose [range] of TXA was 44 mg/kg [12-154] in 2624 patients and the mean dose [range] of aprotinin was 3.7 million kallikrein inhibitory units (MKIU) [0.25-7.00] in 2607 patients in 34 studies comparing the two treatments. The reduction in post-operative blood loss in a meta-analysis of 26 studies was 65 mL [95%: 34, 95] greater with aprotinin compared with TXA: heterogeneity statistically significant ($p < 0.001$; $I^2 = 57.3\%$). The risk of allogeneic blood transfusion requirement in a meta-analysis of 22 studies was 13% greater with TXA compared with aprotinin: RR = 1.13 [95%CI: 0.99, 1.30]; heterogeneity statistically significant ($p < 0.009$; $I^2 = 46.5\%$). The risk difference of allogeneic blood transfusion between TXA and aprotinin in a meta-analysis of 22 studies was 6.4% [95%CI: 1.2, 11.5]. The risk of excessive blood loss in the meta-analysis of 22 studies was 21% greater with TXA compared with aprotinin: RR = 1.21 [95%CI: 1.01, 1.46]; heterogeneity not statistically significant ($p = 0.308$; $I^2 = 11.4\%$). The risk difference of excessive blood loss between TXA and aprotinin in a meta-analysis of 32 studies was 2.2% [95%CI: -0.4, 4.8]; heterogeneity statistically significant ($p < 0.001$; $I^2 = 84.5\%$).

Comment

The results suggest that aprotinin is marginally more efficacious than TXA as regards reducing post-operative blood loss. While aprotinin reduces the risk of blood transfusion requirements to a greater extent than TXA neither the risk reduction nor the risk difference were statistically significant. Aprotinin statistically significantly reduced the risk of excessive blood loss compared with TXA and while the risk difference for this outcome favoured aprotinin over TXA the result was not statistically significant.

Re-operation for Uncontrolled Bleeding

The submission included a meta-analysis of 22 studies comparing the effects of TXA and control on re-operation for uncontrolled bleeding based on the control blood loss categories (Table 16, below). In the highest control blood loss group (> 900 mL), TXA significantly reduced the relative risk of re-operation by 71% compared with placebo: RR = 0.29 [95%CI: 0.10, 0.89]. However, the risk difference between the two treatments was relatively small at 3.2% [95%CI: 0.5, 5.9]. In the 300-600 mL and 601-900 mL control blood loss categories, the relative risks for TXA and control and the absolute risk difference between the two treatments were not statistically significant.

Table 16. Cardiac Surgery – Re-operation for uncontrolled bleeding, distribution of patients and studies in the controlled studies blood loss categories.

Control Group Blood Loss	< 300mL	300- 600 mL	601 – 900 mL	> 900 mL
Mean total TXA dose	-	21 mg/kg	49 mg/kg	87 mg/kg
Mean total TXA dose range	-	19-22 mg/kg	12-154 mg/kg	19-250 mg/kg
Patients treated with TXA (n)	-	59	561	303
Total number of studies (n)	-	2	14	7
% of TXA patients re-operated	-	3.3	2.7	0.7
Relative Risk [95%CI] TXA versus Control	-	1.16 [0.17, 7.98]	0.66 [0.35, 1.22]	0.29 [0.10, 0.89]
% Risk difference TXA versus Control [95%CI]	-	+0.5 [-5.4, +6.3]	-1.1 [-2.9, +0.6]	-3.2 [-5.9, -0.5]
p = 0.982				
Heterogeneity: p value and [I ²]	-	[0%]	p = 0.868 [0%]	p = 0.996 [0%]

Comment

The results of this meta-analysis showed that there was a small, statistically significant risk difference of re-operation for uncontrolled bleeding in favour of TXA compared with control in high risk cardiac surgery (control > 900 mL). The risk difference in these high risk procedures of approximately 3% represents a number needed to treat (NNT) of about 33 patients (that is, on average, TXA will abolish the need for re-operation for uncontrolled bleeding in one patient out of every 33 treated). The mean total TXA dose in the > 900 mL category was 87 mg/kg. There was a favourable trend towards a benefit in TXA treated patients in the 601-900 mL category, but the absolute risk difference was small (about 1%) and was not statistically significant. In the 300-600 mL category there was a small trend away from a benefit with TXA, but there were only two studies involving 21 TXA treated patients included in the meta-analysis for this low risk category.

Orthopaedic Surgery - Knee Surgery (Total Knee Arthroplasty)

Tranexamic Acid versus Control (Placebo or No Anti-fibrinolytics)

Overview

The sponsor identified 16, prospective, randomized, controlled studies from the published literature involving 502 adult patients treated with TXA undergoing single total knee arthroplasty (TKA). Of these 502 patients, 301 (60.0%) received total TXA doses between 20 and 50 mg/kg and 92 (18.3%) received total TXA doses > 100 mg/kg. The mean age of patients in the studies ranged from 65 to 77 years and in the 14 studies which reported the sex of the patients 65.9% (n=431) were female. The surgical procedure was relatively standard among the studies and included a tourniquet and exsanguination of the operation site resulting in a bloodless surgical field. Both cemented and none cemented prostheses were

used. Anaesthetic procedures included both spinal and general. In all studies patients were instructed to stop taking aspirin from 1 to 14 days prior to surgery. In 11 of the 16 studies patients received oral low molecular weight heparin (LMWH) or aspirin post surgery for prophylaxis against thrombosis and in three of the 16 studies patients received physiotherapy from Day 1 post surgery. Post-operative blood loss was measured until the drains were removed which ranged from 12 to 48 hours post surgery. Transfusion protocols based on haematocrit were reported in 14 of the 16 studies. The submission included two knee surgery studies in which TXA was compared with an active control: aprotinin [Engel 2001 and EACA [Camarasa 2006]. The results of TXA versus active control in knee surgery from these two studies have not been discussed in the clinical evaluation as they are considered not to be relevant to the submission to register TXA for use in patients undergoing TKA.

Post-Operative Blood Loss (Primary Efficacy Outcome)

a. Overview

Of the 16 relevant studies identified by the sponsor, 11 were included in a meta-analysis of post-operative blood loss. In these studies, post-operative blood loss was reported as mean \pm SD or mean with 95% CI which allowed for pooling of the results. The methodology was similar to that used in the meta-analysis of blood loss in cardiac surgery, apart from the absence of a duplicates removed meta-analysis. One of the 11 studies, *Zohar 2004* included three pair-wise comparisons in which three different TXA treatment regimens were compared with the same control of 20 patients. Consequently, this same group of 20 patients has been included three times in the meta-analysis. Of the 11 studies, the sponsor graded the quality of 10 as 1 or 2 and the quality of 1 as 4 [Sorin 1999].

The primary efficacy endpoint of the meta-analysis was post-operative blood loss. The meta-analysis included 365 patients treated with TXA at a total dose ranging from 14 to 150 mg/kg administered by four different regimens and 390 control patients. The included studies were small with the average sample size being about 30 patients for both the TXA and control groups. The surgical procedure was similar for all studies (tourniquet with bloodless field) and surgery was carried out under general or spinal anaesthesia. All patients received prophylactic LMWH to reduce the risk of thromboembolic events. The mean age of patients in the studies was mid 70s and more females were included than males. The predominant reason for surgery was osteoarthritis. The main differences among the studies were TXA doses and treatment regimens. It is likely that these differences were the source of the marked overall and subgroup heterogeneity seen in the meta-analysis.

b. Post-operative Blood Loss by Total TXA Dose Subgroup

The total TXA dose was calculated as the sum of the bolus dose administered before release of the tourniquet and a repeat bolus dose or infusion administered after surgery. The sponsor's proposed dose in total knee arthroplasty is TXA 15 mg/kg prior to the release of the tourniquet followed by repeat bolus injection of 15 mg/kg at 8 hour intervals after the initial dose to a maximum of 24 hours. Therefore, the proposed total TXA dose in the first 24 hours after surgery is 60 mg/kg (that is, initial bolus followed by three further bolus injections at 8 hour intervals). The overall reduction in post-operative blood due to TXA (14-150 mg/kg) was 331 mL [95%CI: 246, 416]. No subgroup included the proposed 60 mg/kg TXA total dose. However, as can be seen below in Table 17 the reduction in post-operative blood loss due to TXA was similar in the 20-50 mg/kg and > 100 mg/kg subgroups. These results suggest that the proposed TXA dose should be able to significantly reduce post-operative blood loss.

Table 17. Post-operative blood loss TXA versus control by TXA dose category.

	< 20 mg/kg	20-50 mg/kg	> 100 mg/kg	Overall
Pair-wise comparisons	4	5	4	13
WMD [95%CI] mL	-304 [-486, -122]	-345 [-510, -179]	-359 [-518, -200]	-331 [-416, -246]
Heterogeneity I ² (%); p value	84.7%; p < 0.001	91.9%; p < 0.001	85.6%; p < 0.001	86.7%; p < 0.001

Note: 11 individual studies included in the meta-analysis with one studies having three pair-wise comparisons [Zohar 2004].

The key features of the 11 studies included in the meta-analysis are summarised below in Table 18. The results showed that mean saving in blood loss as a percentage of mean blood loss in the control group was similar for the TXA 20-50 mg/kg and TXA > 100 mg/kg subgroups. This suggests similar effectiveness of these two subgroups even though the mean dose in the > 100 mg/kg dose subgroup was about 4.5 fold higher than in the 20-50 mg/kg subgroup. There were no studies with TXA in the dose range 51-100 mg/kg.

There were four treatment regimens identified numerically (1-4) and descriptively as: 1 – single pre-surgery or pre-tourniquet release dose (mean total dose 15 mg/kg and 2 pair-wise comparisons); 2 - single pre-surgery or pre-tourniquet release followed by post-surgery dose (mean total dose 74 mg/kg [range: 14-150] and 5 pair-wise comparisons); 3 - single pre-surgery or pre-tourniquet release followed by post-surgery repeat bolus or infusion dose (mean total dose 63 mg/kg [range: 28-135] and 4 pair-wise comparisons); 4 - single pre-surgery oral dose followed by repeat oral doses after surgery (mean total dose 32 mg/kg [range: 28-35] and 2 pair-wise comparisons). The sponsor's proposed regimen is number 3 and the mean total TXA dose of the studies in this regimen (63 mg/kg) was similar to that being proposed (60 mg/kg).

Table 18. Post-operative blood loss, key features of the 11 studies included in the meta-analysis by TXA dose subgroup.

Dose subgroups	< 20 mg/kg	20-50 mg/kg	> 100 mg/kg
Mean TXA dose [range] mg/kg	15 [14 – 16]	32 [20 – 40]	143 [135 – 50]
Number of TXA treated patients	126	157	82
Number of Control Treated Patients	126	181	82
Number of pair-wise comparisons	4	5	4
Mean blood loss in control group	1012 mL	784 mL	842 mL
Mean saving in blood loss as % [95%CI] of mean blood loss in control group.	30 [12.1, 48.0]	43.9 [22.8, 65.1]	42.6 [23.6, 61.3%]

Note: 11 individual studies included in the meta-analysis with one studies having three pair-wise comparisons [Zohar 2004].

Comment

The results showed that TXA (14-150 mg/kg) statistically significantly reduced post-operative blood loss compared with control. In addition, post-operative blood loss due to TXA was also statistically significantly lower than control in each of the dose subgroup meta-analyses. The reduction in post-operative blood loss was similar for the 20-50 mg/kg and > 100 mg subgroups and the observed difference in this outcome between these two subgroups is unlikely to be clinically significant. It is likely that the significant heterogeneity observed in the overall and dose subgroup meta-analyses resulted primarily from the differences in total TXA dose and treatment regimens among the 11 studies. None of the dose subgroup analyses included the proposed total TXA dose of 60 mg/kg. However, the submitted data suggest that this dose should be effective. Meta-regression showed that the blood loss category was the only factor which significantly ($p=0.012$) affected the difference in mean blood loss between TA and control with both dose and treatment regimen being statistically non-significant.

There were some methodological problems noted with the meta-analysis, but these are unlikely to have invalidated the conclusions. In *Hiippala 1995*, the reported weighted mean difference (WMD) given in the meta-analysis (-702 mL) is the difference in total peri-operative blood loss (that is, surgery + recovery room + ward) and not the post-operative blood loss (that is, recovery room + ward). From the data reported in the study it can be calculated that the mean difference in post-operative blood loss (that is, recovery room + ward) was -714 mL (TXA 420 mL, Control 1134 mL). In *Hiippala 1997*, the reported WMD given in the meta-analysis (-272 mL) is the difference in blood loss measured in the ward and not the post-operative difference (that is, recovery room + ward). From the data reported in the study it can be calculated that the mean difference in post-operative blood loss (that is, recovery room + ward) was -785 mL (TXA 1191 mL, control 406). The difference in total post-operative blood loss and ward blood loss is 513 mL and this difference might have

biased the results towards control as the meta-analysis underestimated the actual difference in post-operative blood loss. The effect of TXA was “Duplicates included” meta-analysis as a control group of 20 patients in one study (Zohar 2004) were included three times in the meta-analysis.

c. Post-operative Blood Loss by Control Group Blood Loss Category

The submission also included a meta-analysis comparing TXA and control treatments by control blood loss categories of 300-600 mL and > 900 mL (Table 19, below). There were no studies in control blood loss categories < 300 mL or 601-900 mL.

Table 19. Distribution of controlled studies included in the meta-analysis by blood loss categories.

Control blood loss category	< 300 mL	300 – 600 mL	601 – 900 mL	> 900 mL
Studies/Pairwise comparisons (n)	-	5/7	-	6/6
Mean total TXA dose (mg/kg)	-	57	-	65
TXA dose range (mg/kg)	-	15 - 135	-	14 – 150
Patients treated TXA (n)	-	180	-	185
Mean control group blood loss	-	448 mL	-	1329 mL
% Mean saving in blood loss	-	47.5 mL	-	41.9 mL
Range in blood saving loss (mL)	-	34.6 – 61.0	-	27.6 – 56.3

In the 300-600 mL category, TXA significantly reduced post-operative blood loss by 214 mL [155, 273] compared with control and heterogeneity was statistically significant ($p=0.001$; $I^2=74.0\%$). In the > 900 mL category, TXA significantly reduced post-operative blood loss by 557 mL [95%CI: 367, 748] compared with control and heterogeneity was statistically significant ($p=0.001$; $I^2=76.3\%$). The difference in blood loss between TXA and control was statistically significant in all 13 pairwise comparisons from the 11 studies included in the meta-analysis.

Comment

The results showed that TXA was effective in both control blood group categories, with greater savings in the higher control group blood loss group with similar mean doses. The blood loss categories were surrogate measures of the "intrinsic" risk of bleeding in cardiac surgical procedures rather than in TKA.

d. Comparison with Studies Not Included

The sponsor compared the inter-quartile ranges of the 11 studies included in the post-operative blood loss meta-analysis with the 5 excluded studies. Visual inspection suggests no significant differences in the inter-quartile post-operative blood loss ranges for the included and excluded studies. The sponsor also compared the proportion of included and excluded studies with statistically significant results for post-operative blood loss (TXA versus control). This comparison showed that the percentage of studies with statistically significant results was 91% (10/11) in the included studies and 67% (4/6) in the excluded studies, with

no studies in either group having statistically significant negative results. Overall, the data showed that the results of the meta-analysis are unlikely to have been biased by excluding identified studies.

Allogeneic Blood Transfusion (Secondary Efficacy Outcome)

The sponsor submitted a meta-analysis of 15 studies with transfusion data from patients treated with TXA (n=487) or control (n=514) who received packed red blood cells or whole blood. Of the 15 studies, 10 were also included in the meta-analysis of post-operative blood loss. Overall, the results showed that TXA over the total dose range (14-150 mg/kg total dose) significantly reduced the risk of receiving a blood transfusion by 64% [95%CI: 50, 70 %] (Table 20, below).

The relative risk in the four dose regimen categories are summarised below in Table 21. The results showed that the risk difference was similar in Regimens 2 and 3, although the mean dose was about two fold higher in Regimen 3 compared with Regimen 2. The greatest risk difference was seen with Regimen 4, which also had a lower mean dose than both Regimen 2 and 3. However, the summary data for Regimen 4 are based on only two pair-wise comparisons.

Table 20. Risk of blood transfusion - TXA versus control by TXA dose subgroup.

	< 20 mg/kg	20-50 mg/kg	> 100 mg/kg	Overall
Mean TXA dose [range]	15 [14 – 16]	37 [20 – 135]	122 [39 – 150]	55 [14-150]
Pairwise comparisons (n)	3	11	5	19
TXA treated patients (n)	111	284	92	487
TXA patients transfused	14.4 %	29.2%	9.8%	22.2%
Relative Risk [95%CI]	0.53 [0.25, 1.41]	0.43 [0.30, 0.62]	0.16 [0.08, 0.29]	0.36 [0.25, 0.50]
Heterogeneity I ² (%); p value	48.9%; p=0.141	74.8%; p<0.001]	0%; p = 1.000	75.8%; p<0.001
Risk Difference % [95%CI]	-11.9 [-4.0, 19.8]	-35.4[-28.6, -42.1]	-53.3[-41.8, -64.9]	-35.7 [-43.8, -27.6]
Heterogeneity I ² (%); p value	0%; p=0.572	19.5%; p=0.258	0%; p=0.993	67.6%; p<0.001

Note: 15 individual studies included in the meta-analysis with two studies having three pairwise comparisons [Tanaka 2006; Zohar 2004].

Comment

The results showed that TXA (14-150 mg/kg total dose) significantly reduced the relative risk of receiving a blood transfusion by 64% [95%CI: 50, 75] compared with control, with the risk difference in favour of TXA being 36% [95%CI: [28, 44]. Overall, the mean [range] of the TXA dose was 55 mg/kg [14-150]. This mean value is similar to the proposed total TXA dose of 60 mg/kg. Of the three dose subgroups, relative risk reduction and risk difference

compared with control were greatest in the > 100 mg/kg subgroup. Of the four treatment regimens, the greatest risk reduction occurred with Regimen 4. However, this regimen included only two pairwise comparisons from one study [Zohar 2004]. Consequently, little weight can be given to the results from this regimen. Regimen 2 included the most pairwise comparisons (10 from 9 studies) and resulted in a similar relative risk reduction to Regimen 3, but with about half the TXA total dose.

There are some methodological issues with the meta-analysis. Two studies in the meta-analysis each included three TXA pairwise comparisons with the same control group [Tanaka 2001 and Zohar 2004]. Examination of the results from the control groups from these two studies suggests that their repeated inclusion might have biased the pooled results away from placebo. In addition, the TXA 20-50 mg/kg dose subgroup meta-analysis included the 135 mg/kg dose TXA regimen from *Zohar 2004* and the TXA > 100 mg/kg dose subgroup meta-analysis included the 39 mg/kg dose TXA regimen from *Zohar 2004*. No explanations for these apparent classification anomalies were provided. However, it is unlikely that these problems have invalidated the conclusions of the meta-analysis.

Table 21. Relative risk and risk difference for total knee arthroplasty TXA versus control by treatment regimen.

	Regimen 1	Regimen 2	Regimen 3	Regimen 4
Mean Dose mg/kg [range]	17.5 [15-20]	49 [14-150]	92 [16-135]	33.5 [28-39]
Patients treated with TXA				
(n)	37	279	131	40
Pairwise comparisons (n)	2	10	5	2
Relative Risk TXA versus CTR [95%CI]	0.76 [0.62, 0.93]	0.41 [0.29, 0.57]	0.17 [0.09, 0.34]	0.27 [0.12, 0.58]
Patients Transfused (%)	73.0	24.0	6.1	15.0
Risk Difference % [95%CI]	-23.6 [-8.4, -38.3]	-35.8 [-25.4, -46.2]	-38.6 [-17.3, -59.9]	-45.8 [-26.8, -64.1]

Regimen: 1 = Single pre-surgery or pre-tourniquet release; 2 = Pre-surgery of pre-tourniquet release dose followed by post-surgery dose; 3 = Pre-surgery or pre-tourniquet release dose followed by post-surgery repeat bolus or infusion; 4 = Pre-surgery or pre-tourniquet release dose followed by oral maintenance dose.

Orthopaedic Surgery – Hip Surgery (Total Hip Arthroplasty)

Tranexamic Acid versus Control (Placebo or No Anti-fibrinolytics)

Overview

The sponsor identified 12 studies involving the use of TXA in total hip arthroplasty (THA). Of these 12 studies, the sponsor included 11 in a meta-analysis evaluating post-operative blood loss. The study excluded from the meta-analysis [Benoni 2000] assessed the effect of TXA administered after surgery on post-operative blood loss and its exclusion from the meta-analysis is unlikely to have biased the results.

Of the 11 studies, the majority were randomized, placebo-controlled (normal saline) and double-blinded. One of the studies was cross-over in design with 21 patients scheduled for

staged bilateral THA having one hip operated on with TXA and the other hip operated on without TXA [Yamasaki 2005]. The sponsor rated the quality of 9 of the studies as 1, while one study was rated as 2 and one study as 5. Of the 11 studies included in the meta-analysis, 10 were THAs undertaken predominantly for the treatment of osteoarthritis or osteonecrosis and one was undertaken to repair hip fracture. There were no hip surgery studies comparing TXA with aprotinin or other anti-fibrinolytic agents.

Total patient numbers in the 11 studies ranged from about 40 to 100 and the studies included 262 patients treated with TXA and 274 control patients. The mean age of the patients in most studies was in the mid 60s and the number of males and females appeared to be about even. In most of the studies the surgical procedure was similar (lateral position with postero-lateral approach) and all were undertaken using spinal anaesthesia with general anaesthesia (GA) being used for only a small number of patients. In 6 of the studies it was reported that non-steroidal anti-inflammatory drugs (NSAID) or aspirin use was discontinued 0-14 days prior to surgery. In 7 of the studies, standard LMWH regimens were used for thromboprophylaxis, while in three of the studies it was expressly stated that no LMWH regimen was employed and in one study (hip fracture) no information was provided.

Post-operative blood loss was measured until the drains were removed which ranged from 1 to 4 days. The meta-analysis included post-operative blood loss data at 24 hours, or 48 hours if 24 hour data were not provided. As the majority of post-operative bleeding occurred in the first 12 hours it is unlikely that inclusion in the meta-analysis of a small amount of blood loss from 24 to 48 hours has biased the results. Of the 262 patients treated with TXA, 203 were treated with a total TXA dose of 10-19 mg/kg and the remainder with a total TXA dose of 20-30 mg/kg. Of the 11 studies, 7 used a single bolus dose prior to surgery regimen, two used a single bolus dose prior to surgery followed by an infusion, one used a single bolus dose prior to surgery followed by an infusion plus repeat bolus dose post surgery and one study used a single bolus dose prior to surgery followed by repeat bolus doses post surgery.

Post-operative Blood Loss (Primary Efficacy Outcome)

Overall, TXA 10-30 mg/kg statistically significantly reduced post operative blood loss by 159 mL [95%CI: 101, 216] compared with control. The TXA 10-19 mg/kg subgroup reduced post-operative blood loss by 144 mL [95%CI: 80, 208] and the TXA 20-30 mg/kg subgroup reduced post-operative blood loss by 239 mL [95%CI: 60, 417]. Heterogeneity was significant in both the TXA 10-30 mg/kg and TXA 10-19 mg/kg subgroup meta-analyses. The percentage blood saving due to TXA was 22.9% in the 10-19 mg/kg subgroup and 39.2% in the 20-30 mg/kg subgroup (Table 22, below). The sponsor considered that total doses of < 20 mg/kg are too low to maintain TXA plasma concentrations > 16 µg/mL for 24 hours (that is, > IC₅₀ for platelet aggregation *in vitro*). There were no studies in the meta-analysis which used TXA at the proposed total dose for hip surgery of 60 mg/kg (that is, 15 mg/kg initially followed by 15 mg/kg at 8 hour intervals to a maximum of 24 hours after surgery).

Table 22. Studies in the meta-analysis of post-operative blood loss.

Dose (mg/kg)	10-19	20-30	Overall (10-30)
Studies (n)	8	3	11
TXA treated patients (n)	203	59	262
TXA mean total dose (mg/kg)	14.4	23.3	16.8
Mean difference control versus TXA [95%CI] (mL)	144 [80, 208]	239 [60, 417]	159 [101, 206]
Mean control group blood loss (mL)	630	610	624
Saving in blood loss (%)	22.9%	39.2%	25.5%

Reductions in post operative blood with TXA were greater in the control blood loss categories 601-900 mL and > 900 mL compared with the 300-600 mL category (Tables 23 and 24, below). The percentage mean saving due to TXA was $\geq 30\%$ in the two high control group blood loss categories and < 30% in the low control group blood loss category. The mean TXA dose was higher in the two high control blood loss categories (19 and 23 mg/kg, respectively) than the low control group blood loss category (14 mg/kg).

Table 23. Distribution of controlled studies included in the meta-analysis by blood loss categories.

Control blood loss category (mL)	<300	300 – 600	601 – 900	> 900
Studies)/Pairwise comparisons (n)	-	6/6	3/3	2/2
TXA mean total dose (mg/kg)	-	14	19	23
TXA dose range (mg/kg)	-	10-20	19-20	15-30
Patients treated TXA (n)	-	161	61	40
Mean difference control versus TXA[95%CI] (mL)	-	119 [63, 174]	269 [128, 410]	292 [155, 429]
Mean control group blood loss	-	425 mL	789 mL	974 mL
Saving in blood loss due to TXA	-	28.0%	34.1%	30.0%

The mean percentage saving in post-operative blood loss due to TXA was: 23.5% in 183 patients treated with a single pre-surgery dose administered before the skin incision (Regimen 1); 46.8% in 19 patients treated with a single pre-surgery dose administered before the skin incision with repeat bolus injections being administered after surgery (Regimen 2); and 33.3% in 60 patients treated with a single pre-surgery dose administered before the skin incision followed by a continuous infusion for a maximum of 10 hours with or without a second bolus dose after surgery (Regimen 3). The respective mean total TXA doses for regimens 1, 2 and 3, were 15, 20 and 21 mg/kg. Patient numbers for Regimen 2 come from

one study only and are considered too small to allow meaningful conclusions to be made about this regimen.

Comment

The meta-analysis appeared to be methodologically sound. No "duplicates" were included with all studies having only one relevant pairwise comparison. The *Sadeghi 2007* study differed from the other studies as it assessed TXA used in emergency surgery to repair hip fracture rather than in planned elective THA surgery. Of the 11 studies included in the total TXA dose subgroup meta-analysis, 10 resulted in a reduction in post-operative blood loss with TXA compared with control and of these 10 studies the results in 7 were statistically significant. There was one study in which the post-operative blood loss reported with TXA was statistically significantly higher than control [Garneti, 2004].

Overall, TXA 10-30 mg/kg reduced mean post-operative blood loss by 159 mL [95%CI: 101, 216] compared with control. However, while the result was statistically significant it is of doubtful clinical significance. Similarly, while the reduction in mean post-operative blood loss in the TXA 10-19 mg/kg subgroup was statistically significant it is also of doubtful clinical significance (144 mL [95%CI: 80, 208]). The reduction in mean post-operative blood loss in the TXA 20-30 mg/kg subgroup was 239 mL [95%CI: 60, 417] which was statistically significant and clinically meaningful. However, the TXA 20-30 mg/kg subgroup meta-analysis included only three studies [Niskanen 2005; Husted 2003; Ekback 2000] and the reduction in mean blood loss was statistically significant in only two of these studies [Niskanen 2005; Ekback 2000]. In one of the two statistically significant studies the mean reduction in post-operative blood loss due to TXA was 146 mL [95%CI: 57, 235] which is considered to be not clinically meaningful [Niskanen 2005]. Therefore, in only one of the studies included in the TXA 20-30 mg/kg subgroup meta-analysis [Ekback 2000] can the mean reduction in post-operative blood loss due to TXA be considered to be both statistically significant and clinically meaningful (381 mL [95%CI: 170, 592]). However, this study included only 40 patients (20 patients in both the TXA and control groups). The reduction in post-operative blood loss data for TXA based on control group blood loss category suggests that TXA is likely to be more effective in patients at higher risk of blood loss (> 600 mL) than patients at lower risk (\leq 600 mL). No studies in the meta-analysis used total TXA doses similar to that being proposed for total hip arthroplasty (60 mg/kg). Overall, it is considered that the submitted data have not satisfactorily demonstrated the efficacy of TXA as regards reducing post-operative blood loss in total hip arthroplasty. Meta-regression showed no statistically significant association between reduction in post-operative blood loss due to TXA and dose subgroup, treatment regimen or control group blood loss category.

Allogeneic Blood Transfusion (Secondary Efficacy Outcome)

The sponsor included 10 studies in a meta-analysis evaluating the effects of TXA compared with placebo on allogeneic blood transfusion requirements. This meta-analysis included 9 of the 11 studies included in the post-operative blood loss meta-analysis plus *Benoni 2000*, a study in which TXA was given after surgery. Two studies (Yamasaki 2004 and 2005) were excluded from the meta-analysis as no TXA or control patients required allogeneic blood transfusion in these studies. Exclusion of these results from the relative risk meta-analysis is considered acceptable. Of the 10 studies, two reported transfusion protocols, 5 did not use protocols but gave transfusions on a case by case basis and three did not report transfusion criteria.

Overall, TXA 10-30 mg/kg significantly reduced the risk of allogeneic blood transfusion by 40% compared with control: RR: 0.60 [0.44, 0.82]. Heterogeneity in the overall meta-

analysis was not statistically significant: $p=0.157$; $I^2=31.4\%$. The overall risk difference favoured TXA (10-30 mg/kg) over control: 17.6% [95%CI: 8.1, 27.2]. Both the TXA 10-19 mg/kg and 20-30 mg/kg subgroups significantly reduced the risk of allogeneic blood transfusion compared with control by 41% [95%CI: 7, 63] and 42% [95%CI: 10, 63], respectively. The risk difference between TXA 10-19 mg/kg and control was statistically significant: 20.7% [95%CI: 9.7, 31.7]. The risk difference between TXA 20-30 mg/kg and control was not statistically significant: 15% [95%CI: -3.2, 33.2].

Comment

The meta-analysis evaluating the relative risk of allogeneic blood transfusion between TXA and control was generally sound. However, it is considered that *Benoni 2000* should not have been included as in this study TXA was administered after surgery. Overall, TXA 10-30 mg/kg significantly reduced the risk of allogeneic blood transfusion by 40% compared with control. In addition, the risk difference between TXA 10-30 mg/kg and control was statistically significant. Risk reductions with TXA in the 10-19 mg/kg and 20-30 mg/kg subgroups were similar and both were statistically significant. However, while the risk difference between the TXA 10-19 mg/kg subgroup and control was statistically significant the risk difference between the TXA 20-30 mg/kg subgroup and control was not statistically significant. While TXA 10-30 mg/kg significantly reduced the risk of allogeneic blood transfusion compared with control, in only two of the 10 individual studies included in the meta-analysis was the result statistically significant. This suggests that the individual studies are likely to have been underpowered to detect significant differences in risk of allogeneic blood transfusion between TXA and control. None of the studies were powered on reduction in relative risk of allogeneic blood transfusion.

Cochrane Review [Henry 2008] – Orthopaedic Surgery Studies.

The *Cochrane Review* [Henry 2008] included a meta-analysis of 6 orthopaedic surgery studies in which post-operative blood loss associated with TXA was compared with control. The six studies included four THA studies [Benoni 2001; Yamasaki 2004; Lemay 2004; Garneti 2004] and two TKA studies [Benoni 1996; Zohar 2004]. The meta-analysis pooled the data from the 6 orthopaedic studies rather than analysing them separately for hip and knee surgery. All 6 of these studies were also included in the submitted sponsor's meta-analyses of hip and knee surgery. The 6 studies included a total of 293 patients, of whom 146 had been randomised to TXA and 147 to control. The review concluded that "TXA treatment in orthopaedic surgery appeared to be only marginally effective in reducing post-operative blood loss". The reduction in post-operative blood loss due to TXA was 209.7 mL [95%CI: 35.2, 384.3] compared with control and heterogeneity was statistically significant ($p<0.00001$; $I^2=90.5\%$).

The *Cochrane Review* [Henry 2008] also included a meta-analysis of 21 orthopaedic studies in which the risk of allogeneic blood transfusion associated with treatment with TXA was compared with control. The meta-analysis pooled data from hip and knee orthopaedic surgery studies. The 21 studies included in the meta-analysis were all included in the sponsor's hip and knee meta-analyses. The 21 studies included a total of 993 patients, of whom 520 had been randomized to TXA and 473 to control. The relative risk reduction due to TXA was 56%: RR 0.44 [95%CI: 0.33, 0.60] and heterogeneity was statistically significant ($p<0.00001$; $I^2=64.5\%$).

Paediatric Cardiac Surgery

Overview

The sponsor identified 6 cardiac surgical studies which assessed the effect of TXA on post-operative blood loss in children aged from 2 months to 15 years. Of these 6 studies, 5 included a placebo or no treatment control group (and one of these did not include patient numbers), while one study did not include a relevant control group. The 6 studies included about 247 patients treated with TXA of whom 130 (52.6%) received doses in the range 20-50 mg/kg. The sex of the patients was reported in only two studies and of these patients 74.2% (121/163) were male. In all 6 studies, surgery was conducted using CPB, but the actual surgical procedure was not well described in three of the 6 studies. Those studies which adequately described the surgical procedure used heparinisation during surgery and reversed it with protamine on chest closure. Transfusion protocols were reported in two studies, two studies expressly reported not using protocols and two studies did not comment on whether transfusion protocols were used. Post-operative blood loss was reported in units of mL/kg. Transfusion requirements were reported, but the outcome measures differed among studies with most reporting reduction in RBC transfusion in mL/kg.

Post-operative Blood Loss

Studies (n=3) Included in the Meta-analysis

Of the 6 identified studies, the sponsor included three prospective, randomized, controlled, double-blind studies in a meta-analysis of post-operative blood loss [Chauhan 2004; Zonis 1996; Reid 1995]. The three studies included in the meta-analyses represented 66.8% (165/247) of the paediatric cardiac surgery patients treated with TXA. *Chauhan 2004* included four pairwise comparisons in which four different TXA dose and treatment regimens were compared with the same control group. *Zonis 1996* included three pairwise comparisons in which TXA was compared with placebo in children with cyanosis, children without cyanosis and in a combined group of children with or without cyanosis. *Reid 1995* was a small pilot study in 9 patients which compared TXA with placebo in children undergoing repeat sternotomy for congenital cardiac defects (that is, high risk procedures). In a duplicates included meta-analysis, reduction in post-operative blood loss due to TXA (18-220 mg/kg) compared with control was 10.6 mL/kg [95%CI: 6.2, 14.9]; heterogeneity $p < 0.188$, $I^2 = 31.5\%$. In a duplicates combined meta-analysis, reduction in post-operative blood loss due to TXA (40-220 mg/kg) compared with control was 9.0 mL/kg [95%CI: 4.0, 14.0]; heterogeneity $p = 0.514$, $I^2 = 0\%$.

In meta-analyses of age sub-groups, reduction in post-operative blood loss due to TXA compared with control was: 14.0 mL/kg [95%CI: 12.6, 40.8] in the < 2 years subgroup; 10.7 mL/kg [95%CI: 4.3, 17.0] in the 2-4 years subgroup; and 10.8 mL/kg [95%CI: 1.0, 20.6] in the > 4 years subgroup. The results from the age subgroup meta-analyses should be interpreted cautiously as the lowest age subgroup (< 2 years) included only one study involving only 9 patients. In an analysis of the three studies by total TXA dose subgroup, blood saving due to TXA was: 22.2% with a dose < 20 mg/kg ($n=30$); 30.9% with a dose 20-50 mg/kg ($n=138$); and 37.2% with a dose > 100 mg/kg ($n=5$). In an analysis of the studies by treatment regimen, blood saving due to TXA was: 37.8% in 96 patients (mean age 3.8 years) from three studies with a single pre-surgery dose (mean dose 50 mg/kg); 29.7% in 60 patients (mean age 3.6 years) from two studies with pre-surgery and post-surgery doses (mean dose 35 mg/kg); and 29.2% in 35 patients (mean age 2.4 years) from two studies with a pre-surgery dose followed by a maintenance infusion (mean dose 139 mg/kg). There was a meta-regression which showed that dose subgroup, age, treatment regimen and mean control post-

operative blood loss category were not significantly associated with mean post-operative blood loss difference between TXA and control.

The submission included a study purported to be a meta-analysis of blood transfusion requirements in TXA and control groups assessed by packed RBC use in 24 hours (mL/kg). However, this "meta-analysis" simply combined the results from the different TXA treatments regimens in *Chauhan 2004* and found that, overall, TXA 18-50 mg/kg reduced packed RBC use in 24 hours by 5.0 mL/kg [95%CI: 2.2, 7.9] compared with placebo. There was no meta-analysis examining the relative risk of blood transfusion in TXA and control patients.

Studies (n=3) Not Included in the Meta-analysis

Of the 6 identified paediatric surgery studies, three were not included in the meta-analysis. Two studies were not included as post-operative blood loss was not reported as mean \pm SD and/or mean with 95%CI [Reid 1997; Shore-Lesserson 2002] and one study was not included due to the absence of a true control group comparison [Vacharaska 2002]. The three excluded studies are briefly reviewed below.

Reid 1997 was a prospective, randomized, controlled study, undertaken at the Children's Hospital, Boston, USA. In this study, 41 children undergoing repeat sternotomy for repair of congenital heart defects were randomized to TXA (n=21) or saline placebo (n=20). There were no statistically significant differences between the two treatment groups with respect to age, weight, height, pre-operative haematocrit, platelet count or arterial oxygen saturation. The mean \pm SD age was 3.1 \pm 1.8 years in the TXA group and 3.2 \pm 2.2 years in the placebo group. The median duration of CPB was 18 minutes longer in the placebo group than in the TXA group (p=0.01). The aortic cross-clamp time and total heparin dose administered prior to and during CPB bypass were similar for the two treatment groups. The total TXA dose was 216 mg/kg administered as an initial bolus dose of 100 mg/kg given after anaesthetic induction and prior to skin incision, followed by an infusion of 10 mg/kg/hour and a second bolus dose of 100 mg/kg given at the onset of CPB. The median \pm quartile deviation post-operative blood loss was 26 \pm 17 mL/kg with TXA and 34 \pm 17 mL/kg with placebo (p=0.03). The total RBC transfusion volume (mL/kg) and total red cell exposure (units) were both statistically significantly lower in TXA treated patients compared with placebo.

Shore-Lesserson 2002 was a conference abstract reporting the results from a prospective, randomized, placebo controlled study in an undefined number of children weighing < 15 kg undergoing undefined cardiac surgical procedures. The two groups were similar with regard to demographic variables, CPB time and aortic cross-clamp time. Patients randomized to TXA were given an initial 20 mg/kg bolus, followed by an infusion of 2 mg/kg/hour with addition of 200 mg to the pump prime. The post-operative blood loss was 19.1 mL/kg [0.8-381] in the TXA group and 26.9 mL/kg [3.3-151.8] in the control group; p=0.046. Transfusion of packed cells was greater in the TXA group than in the placebo group: 24.6 mL/kg [0-133] mL/kg versus 0 mL/kg [0-116]; p=0.04. The units of measurement were not stated in the abstract. The authors comment that "the lack of a transfusion sparing effect of [TXA] in the current study suggests that the drug is ineffective in small paediatric patients or that a higher dose is needed to achieve efficacy". No information was provided on important variables such as patient numbers and the units used to summarise the outcome values.

Vacharaska 2002 compared TXA 15 mg/kg administered after induction of anaesthesia followed by saline at the end of CPB with TXA 15 mg/kg administered after induction followed by TXA 15 mg/kg at the end of CPB. There was no placebo treated third arm

control group (that is, placebo administered after induction of anaesthesia followed by placebo at the end of CPB). Consequently, this study will not be considered further.

Comment

The proposed TXA treatment regimen in children and adolescents undergoing cardiac surgery is "10 mg/kg before surgery followed by a repeat dose of 10 mg/kg during surgery or as an infusion during surgery". The sponsor proposes restricting use of TXA in paediatric surgery to children aged > 2 years. The results from the submitted meta-analyses of post-operative blood loss should be interpreted cautiously as they included only three studies, one of which was a conference abstract in only 9 patients. The results from the duplicates combined meta-analysis of three studies showed that TXA 40-220 mg/kg reduced post-operative blood loss by 9.0 mL/kg [95%CI: 4.0, 14.0] compared with placebo. However, the post-operative blood loss results for both *Reid 1995* (20 mg/kg) and *Zonis 1996* (50 mg/kg) were not statistically significant. Only the post-operative blood loss result for *Chauhan 2004* (40 mg/kg) was statistically significant, with the reduction in post-operative blood loss due to TXA being 11.7 mL/kg [95%CI: 4.4, 18.9]. The proposed total TXA dose of 20 mg/kg was less than the lowest dose in the duplicates combined meta-analysis (40-220 mg/kg). The results of the TXA duplicates combined meta-analysis of post-operative blood loss suggest that the optimal total dose might be in the range 40-220 mg/kg. The submitted data also suggest that the optimal regimen might be a single pre-surgery dose (that is, after induction of anaesthesia and before skin incision). This treatment regimen was the only one of the three treatment regimens examined in which TXA resulted in an overall saving of > 30% in post-operative blood loss compared with control (mean dose 50 mg/kg).

In view of the uncertainties concerning the validity of the meta-analysis of the effect of TXA on post-operative blood loss in paediatric surgery, it is considered that examination of the results from individual studies is likely to be more informative. There are three key studies [*Chauhan 2004*, *Zonis 1996* and *Reid 1997*] and one supportive study [*Shore-Lesserson 2002*]. The results from *Reid 2005* and *Vacharaska 2002* (which were not included in the meta-analysis) are considered to carry no evidentiary weight as the first was a pilot study in 9 patients reported as a conference abstract and the second did not include a control arm. Data from the 4 relevant studies are summarised below in Table 24.

Table 24. Summary results for the 4 relevant studies of TXA versus control in paediatric surgery.

Study	Age	n	* Load	Infusion/Bolus	Prime	Difference	Saving	p-value	TFN
Chauhan 2004	2m – 5y	60	50 mg/kg	-	-	- 5 mL/kg	14%	NS	NS
Chauhan 2004		60	10 mg/kg	1 mg/kg/h ivi	-	- 8 mL/kg	22%	< 0.05	SS
Chauhan 2004		60	10 mg/kg	2x10 mg/kg bol	-	- 16 mL/kg	44%	< 0.05	SS
Chauhan 2004		60	20 mg/kg	20 mg/kg bol.	-	- 14 mL/kg	39%	< 0.05	SS
Zonis 1996 CO	1d – 14y	82	50 mg/kg	-	-	- 6 mL/kg	22%	NS	N/A
Zonis 1996 CY		18	50 mg/kg	-	-	- 25 mL/kg	52%	0.02	SS
Zonis 1996 AC		64	50 mg/kg	-	-	- 0	0%	NS	N/A
Reid 1997	6m – 12y	41	100 mg/kg	10 mg/kg/h ivi	10 mg/kg	- 8 mL/kg	24%	0.03	SS
S-Lesserson									
2002	< 15 kg	?	20 mg/kg	2 mg/kg/h ivi	200 mg	- 8 mL/kg	29%	0.046	SS *

* n = Total number of patients in the study (that is, TXA plus control). m=months, d=day, y=years old. Bol-bolus, ivi-IV infusion. Difference = TXA post-operative blood loss minus control post-operative blood loss (mL/kg) [mean values for *Chauhan 2004*, *Zonis 1995*, *Shore-Lesserson 2002* and median for *Reid 1997*]; Saving = % saving in post-operative blood loss due to TXA; TFN = transfusion requirements; SS* = transfusion requirement was statistically significantly (SS) greater with TXA than with placebo.

The data showed that TXA administered as a single 50 mg/kg bolus dose prior to surgery did not significantly reduce post-operative blood loss in two studies involving children with mixed cardiac defects [*Chauhan 2004*; *Zonis 1996 CO*], but was effective in a small subgroup analysis of cyanotic patients [*Zonis 1996 (CY)*]. TXA reduced the requirement for packed RBC transfusion in the cyanotic subgroup in *Zonis 1996 [CY]*: 1/8 versus 7/10; p=0.02. In *Reid 1997*, a large dose of TXA administered as a pre-surgery bolus of 100 mg/kg, followed by an infusion of 10 mg/kg/h and a further bolus dose of 100 mg/kg added in the pump prime, resulted in a significant 24% reduction in post-operative blood loss in children undergoing elective repeat cardiac surgery via sternotomy with CPB (that is, high-risk procedures). TXA also reduced total RBC transfusion compared with placebo (39±20 versus 24±5 mL/kg; p=0.04). The authors state that it "may be particularly important to administer [a] second [TXA] bolus after onset of bypass in children because of the large alteration in circulating blood volume when the bypass circuit is introduced". In *Shore-Lesserson 2002*, TXA administered as a pre-surgery bolus of 20 mg/kg, followed by an infusion of 2 mg/kg/h and an additional bolus of 200 mg to the pump prime, significantly reduced post-operative blood loss by 29% in children weighing < 15 kg, but packed RBC transfusion requirement was significantly greater with TXA compared with placebo. The authors commented that "the lack of a transfusion sparing effect of [TXA] suggests that the drug is ineffective in small paediatric patients or that a higher dose is needed to achieve efficacy".

The only study which showed significant reduction in post-operative blood loss with TXA at doses similar to that being proposed by the sponsor for children > 2 years of age undergoing mixed risk surgical procedures was *Chauhan 2004*. In this study, two repeat dose TXA regimens resulted in significant reductions in post-operative blood loss of 44% (10 mg/kg

pre-surgery, 10 mg/kg on CPB, 10 mg/kg after protamine) and 39% (20 mg/kg pre-surgery, 20 mg/kg after protamine). In addition, these two TXA regimens significantly reduced packed RBC requirements. However, the regimens in both of these studies (30 and 40 mg/kg total dose) were different from that being proposed (20 mg/kg total dose) and the age of the patient population was broader (2 months – 5 year) than that being proposed (>2 years). The sub-group meta-analysis based on age showed no significant difference between TXA and control in post-operative blood loss in children < 2 years of age, but this subgroup only included one small pilot study of 9 children undergoing high risk surgical procedures.

Safety

Cardiac Surgery in Adults

Exposure

The submission included 5736 TXA treated patients. Of these 5736 patients, 2917 (51%) received TXA doses within the range 20-50 mg/kg (mean 30 mg/kg), 697 (12.2%) received doses within the range 5.5-19 mg/kg (mean 13 mg/kg), 740 (12.9%) received doses within the range 51-100 mg/kg (mean 76 mg/kg) and 1382 (24.1%) received doses > 100 mg/kg (mean 142 mg/kg). In the 72 studies there were a total of 105 separate TXA treatment arms. The most commonly used TXA treatment regimen was pre-surgery bolus followed by infusion which was used 56 times (that is, 53% of 105 regimens) and the most commonly used TXA dose in this regimen was 20-50 mg/kg which was used 37 times (that is, 35% of 105 treatments). The second most commonly used TXA treatment regimen was a single bolus dose which was used 35 times pre-surgery (that is, 33% of 105 treatments) and the most commonly used TXA dose in this regimen was > 100 mg/kg which was used 14 times (that is, 13% of 105 treatments) followed by 20-50 mg/kg which was used 10 times (that is, 10% of 105 treatments).

The submission included a safety summary which included pooled safety information on 3852 (67%) of the 5736 TXA treated patients undergoing cardiac surgery (not all studies including TXA treated patients included safety information). The safety summary also included pooled safety information on 1822 patients treated with aprotinin, 953 patients treated with EACA and 1247 non-active controls (that is, placebo or no anti-fibrinolytic treatment).

Low and High Risk Cardiac Surgery

The pooled safety population included 2797 TXA treated low risk patients (mostly undergoing primary CABG, valve surgery or multiple procedures) recruited from 19 studies (8 of which included more than 100 patients per treatment arm). The majority of these low risk patients (56%; 1565/2797) were treated with TXA at a total dose of 20-50 mg/kg and 8.6% of patients were treated with total doses > 100 mg/kg. The pooled safety summary also included 1055 TXA treated high risk patients (mainly repeat surgery or aortic surgery) recruited from 9 studies (most of which included < 50 patients per treatment arm). The majority of these high risk patients (91%; 963/1055) were treated with TXA > 100 mg/kg (mean 114 mg/kg) as a single bolus dose at the start of surgery. The safety data for the majority of high risk patients were accounted for by one study, *Fergusson 2008* (74% TXA, 90% aprotinin and 100% EACA). The safety data in *Fergusson 2008* and *Murkin 1995* differed from that in the other submitted studies as they collected detailed information on adverse events. Consequently, the incidence of adverse events reported in *Fergusson 2008* and *Murkin 1995* was substantially higher than in all other submitted studies and for this reason the sponsor considered the safety data from these two studies separately from the other studies.

Adverse Events, Serious Adverse Events and Deaths

The safety summary included only serious adverse events (SAEs) as "only serious adverse events were reported" in the published studies. Neither the safety summary nor individual studies provided a definition of serious adverse events. In general, the published studies simply reported "adverse events". The safety summary included information on deaths occurring in the individual studies. Not all studies in which deaths occurred provided the cause.

Adverse Events (Serious)

The safety summary referred to all adverse events occurring in the cardiac surgery studies as serious. Overall adverse event results are summarised below in Table 26. Adverse events occurred in a greater percentage of patients treated with the three active treatments compared with control with the risk being about 2.4 fold greater with TXA than with control. In low risk procedures, adverse events occurred in a similar percentage of patients in all four treatment groups. However, in high risk procedures adverse events occurred in a greater percentage of patients in each of the three active treatment groups compared with non-active control. In high risk procedures the risk of patients experiencing an adverse event was about 3.1 fold greater with TXA than with non-active control. In the safety summary, the most commonly occurring adverse events reported with TXA were *renal* (7.5% versus 0.8% in non-active control patients). The second most commonly occurring adverse events reported with TXA were *cardiac* (6.1% versus 4.4% in non-active control treated patients). These were followed by *respiratory, thoracic and mediastinal* (2.8% TXA versus 0.24% non-active control), *death* (1.7% TXA versus 1.8% active control) and *central nervous system* (1.4% TXA versus 0.56% non-active control).

Table 26. Total incidence of adverse events in the treated patients.

	Low Risk		High Risk		Total	
Control ^a	66/1040	6.4%	37/207	17.9%	103/1247	8.3%
APR ^b	74/915	8.1%	581/907	64.1%	655/1822	36.0%
EACA ^c	9/173	5.2%	529/780	67.8%	538/953	56.5%
TXA ^d	174/2797	6.2%	588/1055	55.7%	762/3852	19.8%

Source: Adapted from sponsor Tables. ^a Control = Placebo or no-anti-fibrinolytics. ^b APR = Aprotinin. ^c EACA = Epsilon aminocaproic acid. ^d TXA = Tranexamic acid.

The marked difference in the percentage of high risk patients with adverse events between non-active control and the three active treatment groups is being driven primarily by the results from *Fergusson 2008* and, to a lesser extent, from *Murkin 1995* (see results for TXA in high risk patients in Table 27).

Table 27. Adverse events reported in the literature for adult patients undergoing cardiac surgery. Results expressed as number patients (%).

Surgical Risk	Control ^a			Aprotinin			EACA			TXA				
	Low	High	Total	Low	High	Total	Low	High	Total	Low	High *	High #	High Tot	Total
Patients (n)	n=1040	n=207	n=1247	n=915	n=907	n=1822	n=173	n=780	n=953	n=2797	n=273	n=782	n=1055	n=3852
Death	8 (0.77)	14 (6.76)	22 (1.76)	14 (1.53)	55 (6.06)	69 (3.79)	3 (1.73)	31 (3.97)	34 (3.57)	26 (0.93)	6 (2.20)	32 (4.10)	38 (3.50)	64 (1.66)
Cardiac	45 (4.33)	10 (4.83)	55 (4.41)	27 (2.95)	160 (17.64)	187 (10.26)	5 (2.89)	139 (17.82)	144 (15.11)	73 (2.61)	15 (5.49)	148 (18.93)	163 (15.45)	236 (6.13)
<i>Arrhythmia</i>	<i>6 (0.58)</i>	<i>-</i>	<i>6 (0.48)</i>	<i>-</i>	<i>6 (0.66)</i>	<i>6 (0.33)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>4 (0.14)</i>	<i>4 (1.47)</i>	<i>-</i>	<i>4 (0.38)</i>	<i>8 (0.21)</i>
<i>Atrial Fibrillation.</i>	<i>23 (2.21)</i>	<i>5 (2.42)</i>	<i>28 (2.25)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>22 (0.79)</i>	<i>2 (0.73)</i>	<i>4 (0.51)</i>	<i>6 (0.57)</i>	<i>28 (0.73)</i>
<i>Cardiac Ischemia.</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>3 (0.33)</i>	<i>-</i>	<i>3 (0.16)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>3 (0.11)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>3 (0.08)</i>
<i>Cardiogenic Shock</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>112 (12.35)</i>	<i>112 (6.15)</i>	<i>-</i>	<i>119 (15.26)</i>	<i>119 (12.25)</i>	<i>3 (0.11)</i>	<i>-</i>	<i>112 (14.32)</i>	<i>112 (10.62)</i>	<i>112 (2.91)</i>
<i>Heart Block</i>	<i>-</i>	<i>2 (0.97)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>1 (0.37)</i>	<i>-</i>	<i>1 (0.09)</i>	<i>1 (0.03)</i>
<i>Myocardial Inf.</i>	<i>16 (1.54)</i>	<i>3 (1.45)</i>	<i>19 (1.52)</i>	<i>24 (2.62)</i>	<i>42 (4.63)</i>	<i>66 (3.62)</i>	<i>5 (2.89)</i>	<i>20 (2.56)</i>	<i>25 (2.62)</i>	<i>40 (1.43)</i>	<i>7 (2.56)</i>	<i>32 (4.10)</i>	<i>39 (3.70)</i>	<i>79 (2.05)</i>
<i>Ventricular Arrhy.</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>1 (0.37)</i>	<i>-</i>	<i>1 (0.09)</i>	<i>1 (0.03)</i>
<i>Ventricular Dysft.</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>
<i>Ventricular Tachy</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>1 (0.04)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>1 (0.03)</i>
CNS	3 (0.29)	4 (1.93)	7 (0.56)	8 (0.87)	23 (2.54)	31 (1.70)	-	22 (2.82)	22 (2.31)	17 (0.61)	7 (2.56)	28 (3.58)	35 (3.32)	52 (1.35)
<i>Aphasia</i>	<i>-</i>	<i>1 (0.48)</i>	<i>1 (0.08)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>
<i>Cerebral Haem.</i>	<i>1 (0.1)</i>	<i>-</i>	<i>1 (0.08)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>
<i>Hemiparesis (left)</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>1 (0.37)</i>	<i>-</i>	<i>1 (0.09)</i>	<i>1 (0.03)</i>

<i>Weakness (left)</i>	-	-	-	-	-	-	-	-	-	-	1 (0.37)	-	1 (0.09)	1 (0.03)
<i>Neurol Dysfunct</i>	-	-	-	6 (0.66)	-	6 (0.33)	-	-	-	11 (0.39)	-	-	-	11 (0.29)
<i>Neurol Complics.</i>	-	-	-	1 ((0.11)	-	1 (0.05)	-	-	-	1 (0.04)	-	-	-	1 (0.03)
<i>Stroke</i>	2 (0.19)	3 (1.45)	5 (0.40)	1 (0.11)	23 (2.54)	24 (1.32)	-	22 (2.82)	22 (2.31)	5 (0.18)	5 (1.83)	28 (3.58)	33 (3.13)	38 (0.97)
Eye Disorders	-	1 (0.48)	1 (0.08)	-	-	-	-	-	-	-	1 (0.37)	-	1 (0.09)	1 (0.03)
<i>Blindness</i>	-	1	1 (0.08)	-	-	-	-	-	-	-	-	-	-	-
<i>Retinal Artery Emb</i>	-	-	-	-	-	-	-	-	-	-	1 (0.37)	-	1 (0.09)	1 (0.03)
Gastrointestinal	-	-	-	-	-	-	-	-	-	1 (0.04)	-	-	-	1 (0.03)
<i>Bowel Infarction</i>	-	-	-	-	-	-	-	-	-	1 (0.04)	-	-	-	1 (0.03)
	Control ^a			Aprotinin			EACA			TXA				
Surgical Risk	Low	High	Total	Low	High	Total	Low	High	Total	Low	High *	High #	High Tot	Total
Patients (n)	n=1040	n=207	n=1247	n=915	n=907	n=1822	n=173	n=780	n=953	n=2797	n=273	n=782	n=1055	n=3852
Immune System	-	-	-	-	-	-	-	-	-	-	1 (0.37)	-	-	1 (0.03)
<i>Anaphylactic Shk</i>	-	-	-	-	-	-	-	-	-	-	1 (0.37)	-	-	1 (0.03)
Infect/Infest	3 (0.29)	-	3 (0.24)	-	-	-	-	-	-	3 (0.11)	-	-	-	3 (0.08)
<i>Infections</i>	3 (0.29)	-	3 (0.24)	-	-	-	-	-	-	3 (0.11)	-	-	-	3 (0.11)
Renal	3 (0.29)	7 (3.38)	10 (0.80)	24 (2.62)	238 (26.24)	262 (14.38)	-	232 (29.74)	232 (24.34)	50 (1.79)	6 (2.20)	234 (29.92)	240 (22.75)	290 (7.53)
<i>Renal Dysfunction</i>	3 (0.29)	-	3 (0.24)	-	109 (12.02)	109 (5.98)	-	100 (12.82)	100 (10.49)	2 (0.07)	-	97 (12.40)	97 (9.19)	99 (2.57)
<i>Renal Failure</i>	-	6 (2.90)	6 (0.48)	7 (0.77)	129 (14.22)	136 (7.46)	-	132 (16.92)	132 (13.85)	12 (0.43)	6 (2.20)	137 (17.52)	143 (13.55)	155 (4.02)

<i>Renal Impairment</i>	-	1 (0.48)	1(0.08)	-	-	-	-	-	-	-	-	-	-	-
<i>Renal Insufficiency</i>	-	-	-	17 (1.86)	-	17 (0.93)	-	-	-	36 (1.29)	-	-	-	36 (0.93)
Resp, Tho, Med	3 (0.29)	-	3 (0.24)	1 (0.11)	96 (10.58)	97 (5.32)	1 (0.58)	98 (12.56)	99 (10.39)	4 (0.14)	2 (0.73)	100 (12.79)	102 (9.67)	106 (2.75)
<i>Pul Complications</i>	-	-	-	-	-	-	-	-	-	-	2 (0.73)	-	-	2 (0.05)
<i>Pul Embolism</i>	1(0.10)	-	1(0.08)	-	-	-	1(0.58)	-	1 (0.10)	2 (0.07)	-	-	-	2 (0.05)
<i>Pul Oedema</i>	-	-	-	-	-	-	-	-	-	1 (0.04)	-	-	-	1 (0.03)
<i>Resp Dysfunction</i>	2 (0.19)	-	2 (0.16)	1 (0.11)	-	1 (0.05)	-	-	-	1 (0.04)	-	-	-	1 (0.03)
<i>Resp Failure</i>	-	-	-	-	96 (10.58)	96 (5.27)	-	98 (12.56)	98 (10.28)	-	-	100 (12.79)	100 (9.48)	100 (2.60)
Vascular	1 (0.10)	1 (0.48)	2 (0.16)	-	9 (0.99)	9 (0.49)	-	7 (0.90)	7 (0.73)	1 (0.37)	8 (1.02)	9 (0.85)	9 (0.23)	
<i>DVT</i>	1 (0.10)	1 (0.48)	2 (0.16)	-	-	-	-	-	-	-	-	-	-	-
<i>DVT or Pul Emb</i>	-	-	-	-	9 (0.99)	9 (0.49)	-	7 (0.90)	7 (0.73)	-	-	8 (1.02)	8 (0.76)	8 (0.21)
<i>Carotid Plaque</i>	-	-	-	-	-	-	-	-	-	-	1 (0.37)	-	1 (0.09)	1 (0.03)
TOTAL	66 (6.35)	37 (17.87)	103 (8.26)	74 (8.09)	581 (64.06)	655 (35.95)	9 (5.20)	529 (67.82)	538 (56.45)	174 (6.22)	38 (13.92)	550 (70.33)	588 (55.73)	762 (19.78)

Control ^a = Placebo or no anti-fibrinolytic treatment.

TXA High * = High risk patients excluding *Fergusson 2008* and *Murkin 1995*.

TXA High # = High risk patients including *Fergusson 2008* and *Murkin 1995*.

In the TXA group, the incidence of adverse events in the high risk patients excluding *Fergusson 2008* and *Murkin 1995* was 13.9% (38/273) compared with 70.3% (550/782) in high risk patients including *Fergusson 2008* and *Murkin 1995*. Of the 1055 high risk patients treated with TXA, 769 came from *Fergusson 2008*. Of the 780 high risk patients treated with EACA and 781 (of the 907) high risk patients treated with aprotinin also came from this study. The interpretation of the significance of the safety results for the three active treatments from *Fergusson 2008* are complicated by the absence of a non-active control group in this study. The safety data from *Fergusson 2008* are summarised below in Table 28. In this study all patients underwent one of the following elective or urgent high risk cardiac surgical procedures on CPB: repeat cardiac surgery; isolated mitral-valve replacement; combined valve and CABG surgery; multiple valve replacement or repair; and surgery of the ascending aorta or aortic arch. The study excluded patients undergoing low risk operations such as isolated primary CABG with or without CPB, isolated mitral-valve repair or aortic-valve replacement and infrequent procedures such as heart transplantation, implantation of a left ventricular assist device and surgery to repair congenital heart defects. The safety data from *Murkin 1995* were presented in abstract form and included only 38 high risk patients undergoing repeat surgery for CABG and/or valve replacement randomized to high dose aprotinin (n=12), low dose aprotinin (n=16) or single dose TXA 10 g (n=12) prior to the skin incision.

Death

The overall mortality rate in TXA treated patients was 1.7% (64/3852) which compared with 1.8% (22/1247) in non-active control patients. The mortality rate in high risk patients was lower in TXA treated patients compared with non-active control patients (3.6% [38/1055] versus 6.8% [14/207], respectively). The mortality rate in low risk patients was similar in TXA treated patients and non-active control patients (0.9% [26/2797] versus 0.8% [8/1040], respectively). The total, low risk and high risk mortality rates were all lower in TXA treated patients than in both aprotinin and EACA treated patients. The reported causes of death as percent of total reported deaths for each treatment are summarised below in Table 29. The most common cause of death was due to cardiac or cardiac related causes (for example, multi-organ failure due to low cardiac output). The cause of death was not reported in a number of studies. The "other" reported causes of death included wound infection, haemorrhage and multi-organ failure. The risk difference in mortality between TXA and control was 0.2% [95%CI: -0.4, 0.8] in low risk patients and -3.2% [95%CI: -6.7, 0.4] in high risk patients. The risk difference between aprotinin and control was 0.8% [95%CI: -0.2, 1.7] in high risk patients and -0.7% [95%CI: -4.5, 3.1] in low risk patients. The risk differences were not statistically significant for any of the comparisons.

Table 28. Fergusson 2008 – Safety data.

Adverse Event	Aprotinin		Tranexamic Acid		E-aminocaproic acid		APR versus TXA		APR versus EACA	
	n	Events	n	Events	n	Events	RR [95% CI]		RR [95% CI]	
Stroke	759	22 (2.9)	753	28 (3.7)	768	22 (2.9)	0.78	[0.45, 1.35]	1.01	[0.57, 1.81]
Myocardial. Infarction	717	33 (4.6)	727	28 (3.9)	735	20 (2.7)	1.19	[0.73, 1.95]	1.69	[0.98, 2.92]
DVT of PE	712	9 (1.3)	718	8 (1.1)	729	7 (1.0)	1.00	[0.99, 1.01]	1.00	[0.97, 1.01]
Respiratory. Failure	771	96 (12.5)	769	100 (13.0)	776	98 (12.6)	0.96	[0.74, 1.24]	0.99	[0.76, 1.28]
Cardiac Shock	772	112 (14.5)	769	112 (14.6)	778	119 (15.3)	1.00	[0.78, 1.27]	0.95	[0.75, 1.20]
Renal Failure										
Pre-existing condition										
Any	770	129 (16.8)	766	137 (17.9)	774	132 (17.1)	0.94	[0.75, 1.17]	0.98	[0.79, 1.23]
Cr increase bl > 2 fold	772	49 (6.3)	766	34 (4.4)	773	38 (4.9)	1.43	[0.93, 2.19]	1.29	[0.86, 1.95]
Cr increase >150 µmol/L	772	119 (15.4)	767	125 (16.3)	775	124 (16.0)	0.95	[0.75, 1.19]	0.96	[0.76, 1.21]
Post-operative Dialysis	773	24 (3.1)	769	24 (3.1)	778	21 (2.7)	0.99	[0.57, 1.74]	1.15	[0.65, 2.05]
New Condition Any	770	102 (13.2)	766	97 (12.7)	774	100 (12.9)	1.05	[0.81, 1.36]	1.03	[0.79, 1.33]
Cr increase bl> 2 fold	772	47 (6.1)	766	31 (4.0)	773	35 (4.5)	1.50	[0.97, 2.34]	1.34	[0.88, 2.06]
Cr increase >150 µmol/L	772	92 (11.9)	767	86 (11.2)	775	93 (12.0)	1.06	[0.81, 1.40]	0.99	[0.76, 1.30]
Post-operative Dialysis	773	16 (2.1)	769	19 (2.5)	778	11 (11.4)	0.84	[0.43, 1.62]	1.46	[0.68, 3.13]

bl=baseline. DVT=deep vein thrombosis. PE=pulmonary embolus. Cr=creatinine.

Table 29. Reported causes of death as percent of total reported deaths for each treatment

Treatment	CTR ^a			APR ^b			EACA ^c			TXA ^d		
Risk	Low	High	Total	Low	High	Total	Low	High	Total	Low	High	Total
Patients	1040	207	1247	915	907	1822	173	780	953	2797	1055	3852
Deaths	8 (0.77)	14 (6.76)	22 (1.76)	14 (1.53)	55 (6.06)	69 (3.7)	3 (1.73)	31 (3.9)	34 (3.57)	26 (0.93)	38 (3.60)	64 (1.66)
Cardiac	37.5%	28.6%		-	50.9%		33.3%	41.9%		3.8%	35.1%	
Cereb/vasc	25.0%	-		7.1%	1.8%		-	16.1%		3.8%	10.8%	
Respir	-	28.6%		-	-		33.3%	-		7.7%	-	
Other	12.5%	28.6%		-	38.2%		-	41.9%		-	51.4%	
Not Rep.	25.0%	14.3%		92.9%	9.1%		33.3%	-		88.5%	5.4%	

^a CTR = Placebo or no-anti-fibrinolytics. ^b APR = Aprotinin. ^c EACA = Epsilon aminocaproic acid. ^d TXA = Tranexamic acid. Cereb=cerebral, vasc=vascular, respir=respiratory and not rep=not reported.

The mortality results are dominated by *Fergusson 2008*. It was the preliminary results from this study which precipitated the regulatory action leading to worldwide marketing withdrawal of aprotinin. The study was terminated early because of the observed higher risk of death in patients treated with aprotinin compared with TXA and EACA. The study compared the effects of aprotinin (n=781), EACA (n=780) and TXA (n=770) on massive post-operative bleeding (the primary outcome) and secondary outcomes including death from any cause at 30 days in patients undergoing high risk cardiac surgery. The primary cause of death in patients from this study are summarised below in Table 30. At 30 days, the death rate for any cause was 6.0% (47/779) in the aprotinin group compared with 3.9% (30/769) in the TXA group (RR [APR: TXA] = 1.55 [95%CI: 0.99, 2.42]) and 4.0% (31/780) in the EACA group (RR [APR: EACA] = 1.52 [95%CI: 0.98, 2.36]). The risk of death due to any cardiac cause was statistically significantly greater with aprotinin than with TXA (RR = 2.47 [95%CI: 1.19, 5.10]).

Table 30. Fergusson 2008: Adjudicated primary cause of death in 108 patients.

Primary Cause of Death	Overall (n=2328) *	APR (n=779)	TXA (n=769)	EACA (n=780)	APR versus TXA	APR versus EACA
Cardiac Causes						
Any	48 (2.1%)	25 (3.2%)	10 (1.3%)	13 (1.7%)	2.47 (1.19, 5.10)	1.93 (0.99, 3.74)
Congestive Heart Failure	5 (0.2%)	1 (0.1%)	2 (0.3%)	2 (0.3%)	0.49 (0.04, 5.43)	0.50 (0.05, 5.51)
Cardiogenic Shock	19 (0.8%)	9 (1.2%)	3 (0.4%)	7 (0.9%)	2.96 (0.80, 10.90)	1.29 (0.48, 3.44)
Myocardial Infarction	14 (0.6%)	8 (1.0%)	3 (0.4%)	3 (0.4%)	2.63 (0.70, 9.89)	2.67 (0.71, 10.03)
Right Ventricular Failure	10 (0.4%)	7 (0.9%)	2 (0.3%)	1 (0.1%)	3.46 (0.72, 16.58)	7.01 (0.86, 56.83)
Noncardiac Causes						
Any	60 (2.6%)	22 (2.8%)	20 (2.6%)	18 (2.3%)	1.09 (0.60, 1.97)	1.22 (0.66, 2.26)
Haemorrhage	20 (0.9%)	8 (1.0%)	8 (1.0%)	4 (0.5%)	0.99 (0.37, 2.62)	2.00 (0.61, 6.62)
Stroke	10 (0.4%)	1 (0.1%)	4 (0.5%)	5 (0.6%)	0.25 (0.03, 2.21)	0.20 (0.02, 1.71)
Sepsis or multiorgan failure	17 (0.7%)	6 (0.8%)	5 (0.7%)	6 (0.8%)	1.18 (0.36, 3.87)	1.00 (0.32, 3.09)
Other or unknown	13 (0.6%)	7 (0.9%)	3 (0.4%)	3 (0.4%)	2.30 (0.60, 8.87)	2.34 (0.61, 9.00)

* = Of the 2331 patients in the intention-to-treat analysis, three were not evaluated for cause of death because they withdrew consent and were discharged from hospital before 30 days (2 in the APR group and one in the TXA group). APR = Aprotinin; TXA = Tranexamic Acid; EACA = Epsilon Aminocaproic Acid; APR versus TXA = Relative Risk (95%CI); APR versus EACA = Relative Risk (95%CI).

In *Murkin 1995*, the mortality rate in patients undergoing repeat surgery for CABG and/or valve replacement was 33.3% (4/12) in patients treated with high dose aprotinin (6 MKIU), 6.3% (1/16) in patients treated with low dose aprotinin (2 MKIU) and 16.7% (2/12) in patients treated with TXA (10 g). In *Armellin 2001*, a large placebo controlled study in

patients undergoing primary elective aortic valve replacement, there were 4 peri-operative deaths. These 4 deaths included 3 [2.1%] in 140 patients in the placebo group and 1 [0.7%] in 143 patients in the TXA [72 mg/kg] group. The death in the TXA group occurred on the 5th post-operative day in a patient who developed cardiogenic shock on the day after a myocardial infarction. In *Katsaros 1996*, another large placebo controlled study in patients undergoing CPB for first time CABG, valve replacement, or re-operation, there were two (1.9%) deaths in 106 patients in the control group and no (0%) deaths in 104 patients in the TXA group (total dose 120 mg/kg). In *Maddali 2007*, another large placebo controlled study in patients undergoing CABG on CPB there were no reports of death in 111 control patients and 111 TXA treated patients (total dose 12 mg/kg).

In the *Cochrane Review [Henry 2008]*, data from 18 cardiac surgery studies showed that TXA was not associated with an increased risk of death compared with non-active control: RR [CTR:TXA] = 0.55 [95%CI: 0.24, 1.25]. Similarly, neither aprotinin (RR [CTR: APR] = 0.95 [95%CI: 0.70, 1.28]), nor EACA (RR [CTR: EACA] = 1.65 [95%CI: 0.50, 5.43]) statistically significantly increased the risk of death compared with non-active control in patients undergoing cardiac surgery.

Cardiac Disorders

The incidence of cardiac adverse events in low risk patients was lower in the three active treatments compared with non-active control, but higher than non-active control in high risk patients. The most common cardiac adverse event reported with active treatments was cardiogenic shock followed by myocardial infarction. Cardiogenic shock occurred in 2.9% (112/3852) of TXA treated patients and in no non-active controls. Myocardial infarction occurred in 2.1% (79/3852) of TXA treated patients and 1.5% (19/1247) of non-active controls. All other cardiac adverse events apart from cardiogenic shock and myocardial infarction occurred in < 1% of TXA treated patients in both high and low risk groups. Cardiac adverse events generally occurred less frequently in TXA treated patients than in aprotinin and EACA treated patients. The distribution of cardiac adverse events is summarised below in Table 31.

In *Fergusson 2008*, the incidence of cardiogenic shock in high risk patients treated with aprotinin was 14.5% (n=112), compared with 14.6% (n=112) for TXA (RR = 1.00 [95%CI: 0.78, 1.27]) and 15.3% (n=119) for EACA (RR = 0.95 [95%CI: 0.75, 1.20]). This study contributed all cases of cardiogenic shock reported with aprotinin, EACA and TXA in high risk patients. In *Fergusson 2008*, the incidence of MI in high risk patients treated with aprotinin was 4.6% (n=33), compared with 3.9% (n=28) for TXA (RR = 1.19 [95%CI: 0.73, 1.19]) and 2.7% (n=20) for EACA (RR = 1.69 [95%CI: 0.98, 2.92]). This study contributed all cases of MI reported with EACA in high risk patients, 33 of the 42 reported with aprotinin and 28 of the 39 reported with TXA. In *Murkin 1995*, the incidence of MI in high risk patients was 33.3% (4/12) for high dose aprotinin (6 MKIU), 6.25% (1/16) for low dose aprotinin (2 MKIU) and 33.3% (4/12) for TXA (10 g).

In the *Cochrane Review [Henry 2008]*, data from 15 cardiac surgery studies were pooled and showed that TXA did not increase the risk of MI compared with control (RR = 0.91 [95%CI: 0.44, 1.88]). Similarly, neither aprotinin (RR = 0.95 [95%CI: 0.74, 1.22]), nor EACA (RR = 0.89 [95%CI: 0.37, 2.18]) statistically significantly increased the risk of MI compared with control.

Table 31. Incidence of cardiac disorders as percentage of patients treated.

Treatment	Control (Non-Active)		Aprotinin		E-aminocaproic acid		Tranexamic Acid	
Surgical Risk	Low	High	Low	High	Low	High	Low	High
Number	1040	207	915	907	173	780	2797	1055
Cardiac Disorders	45 (4.3%)	10 (4.8%)	27 (3.0%)	160 (17.6%)	5 (2.9%)	139 (17.8%)	73 (2.6%)	163 (15.5%)
Patients - n (%)	Total = 55/1247 (4.4%)		Total = 187/1822 (10.3%)		Total = 144/953 (15.1%)		Total = 236/3852 (6.1%)	
Arrhythmia	6 (0.5%)	-	-	6 (0.7%)	-	-	4 (0.1%)	4 (0.4%)
Atrial Fibrillation	23 (2.2%)	5 (2.4%)	-	-	-	-	22 (0.8%)	6 (0.6%)
Cardiac Ischaemia	-	-	3 (0.3%)	-	-	-	3 (0.1%)	--
Cardiogenic Shock	-	-	-	112 (12.3%)	-	119 (15.3%)	3 (0.1%)	112 (10.6%)
Heart Block	-	2 (1.0%)	-	-	-	-	-	1 (0.09%)
Myocardial Inf.	16 (1.5%)	3 (1.4%)	24 (2.6%)	42 (4.6%)	5 (2.9%)	20 (2.6%)	40 (1.4%)	39 (3.7%)
Vent Arrhythmia	-	-	-	-	-	-	-	1 (0.09%)
Vent Tachycardia	-	-	-	-	-	-	1 (0.04%)	-

Renal Disorders

The majority of renal disorders in the three active treatment groups were renal dysfunction and renal failure. These disorders occurred more frequently in aprotinin and EACA treated patients than in TXA treated patients. Renal disorders occurred more frequently in patients undergoing high risk procedures than low risk procedures in the three active treatment groups. Renal disorders were reported more frequently in patients in the three active treatment groups than in non-active controls. The distribution of renal adverse events is summarised below in Table 32.

Table 32. Incidence of renal disorders as percentage of patients treated.

Treatment	CTR		APR		EACA		TXA	
Risk	Low	High	Low	High	Low	High	Low	High
Number	1040	207	915	907	173	780	2797	1055
Renal Disorders	3 (0.3%)	7 (3.4%)	24 (2.6%)	238 (26.2%)	232 (29.7%)		50 (1.8%)	240 (22.7%)
Patients – n (%)	Total = 10 (0.80%)		Total = 262 (14.4%)		Total = 232 (24.3%)		Total = 290 (7.5%)	
Renal Dysfunction	3 (0.3%)	-	-	109 (12.0%)	-	100 (12.8%)	2 (0.07%)	97 (9.2%)
Renal Failure	-	6 (2.9%)	7 (0.8%)	129 (14.2%)	-	132 (16.9%)	12 (0.4%)	143 (13.6%)
Renal Impairment	-	1 (0.5%)	-	-	-	-	-	-
Renal Insufficiency	-	-	17 (1.9%)	-	-	-	36 (1.3%)	-

In the *Cochrane Review [Henry 2008]*, pooled data from 5 cardiac surgery studies showed that TXA did not increase the risk of renal failure or renal dysfunction compared with control: RR = 0.73 [95%CI: 0.16, 3.32]. The data showed a trend towards renal failure or renal dysfunction with aprotinin in cardiac surgery compared with control, but the difference was not statistically significant (RR = 1.12 [95%CI: 0.74, 1.67]).

Central Nervous System (CNS) Disorders

In non-active control patients the incidence of CNS disorders was 0.3% (n=3) in low risk patients, 1.9% (n=4) in high risk patients and 0.6% (n=7) overall. In TXA treated patients the corresponding figures were 0.6% (n=17), 3.3% (n=35) and 1.4% (n=52). The most commonly reported CNS disorder in patients in all four treatment groups was stroke. The incidence of stroke in TXA treated patients and non-active controls was, respectively, 0.18% [n=5] versus 0.19 % [n=2] in low risk patients, 3.1% [n=33] versus 1.6% [n=3] in high risk patients and 0.97 % [n=38] versus 0.40% [n=5] overall. The incidence of all other reported CNS disorders was small (generally < 0.5%) in all four treatment groups.

In *Fergusson 2008*, the incidence of stroke in high risk patients was 2.9% (n=22) with aprotinin, compared with 3.7% (n=28) for TXA (RR = 0.78 [95%CI: 0.45, 1.35]) and 2.9% (n=22) for EACA (RR = 1.01 [95%CI: 0.57, 1.81]). This study contributed all cases of stroke in high risk patients reported with EACA, 22 of the 23 reported with aprotinin and 28 of the 33 reported with TXA.

In the *Cochrane Review [Henry 2008]*, pooled data from 14 cardiac surgery studies showed that TXA non-statistically significantly increased the risk of stroke compared with control by 52%: RR = 1.52 [95%CI: 0.52, 4.41]. In this review, aprotinin was associated with a non-

statistically significant 24% reduction in the risk of stroke compared with control: RR = 0.76 [95%CI: 0.30, 1.91]. Similarly, the use of EACA in cardiac surgery was associated with a non-statistically significant 41% reduction in the risk of stroke compared with control: RR = 0.59 [95%CI: 0.10, 3.44].

Respiratory, Thoracic and Mediastinal Disorders

In non-active control patients the incidence of respiratory, thoracic and mediastinal disorders was 0.3% (n=3) in low risk patients, 0% in high risk patients and 0.2% (n=3) overall. In TXA treated patients the corresponding figures were 0.1% (n=4), 9.7% (n=102) and 2.8% (n=106). The most commonly reported respiratory, thoracic and mediastinal adverse event in the three active treatment groups was respiratory failure which occurred only in high risk patients. The incidence of respiratory failure in TXA treated patients was 2.6% (n=100) compared with 0% in non-active controls. Respiratory failure was reported more frequently with aprotinin (5.3%) and EACA (10.3%) than with TXA (2.8%). Pulmonary embolism was reported infrequently in all four treatment groups with the overall incidence being 0.05% (n=2) in TXA treated patients and 0.08% (n=1) in non-active controls. In *Fergusson 2008*, the incidence of respiratory failure in high risk patients in the three anti-fibrinolytic treatment groups was similar and varied from 12.5% to 13.0%.

Vascular Disorders

In non-active control patients the incidence of vascular disorders was 0.10% (n=1) in low risk patients, 0.48% (n=1) in high risk patients and 0.16 (n=2) overall. The corresponding figures in TXA treated patients were 0%, 0.85% (n=9) and 0.23% (n=9). There were only a small number of reports of deep vein thrombosis (DVT) and DVT or pulmonary embolism (PE) in all four treatment groups. In *Fergusson 2008*, the incidence of DVT/PE in high risk patients was 1.3% (n=9) with aprotinin, compared with 1.1% (n=8) with TXA (RR = 1.00 [95%CI: 0.99, 1.01]) and 1.0% (n=7) with EACA (RR = 1.00 [95%CI: 0.97, 1.01]). In the *Cochrane Review [Henry 2008]*, data from 6 cardiac surgery trials showed that only two control patients developed a pulmonary embolus (PE) and data from 4 cardiac surgery trials showed that only two control patients developed a deep vein thrombosis (DVT).

Other Disorders

There were a small number of reports of visual, gastro-intestinal and infections/infestations adverse events in some but not all of the treatment groups with no particular patterns being demonstrated. The only report of anaphylactic shock occurred in a high dose TXA treated patient (n=1; 0.09%).

Safety in High Quality (Grade 0 or 1), Large (>40 patients/treatment), Controlled Studies.

In *Armellin 2001*, TXA (n=143) at a total dose of 72 mg/kg was compared with placebo (n=140) in patients undergoing elective primary aortic valve replacement. Reasons for withdrawal in patients treated with TXA were re-exploration for bleeding (2.8%, n=4), death due to myocardial infarction (0.7%; n=1), profuse gastric haemorrhage (0.7%; n=1) and profuse haemorrhage from left sub-clavian artery (0.7%; n=1). Reasons for withdrawal in patients treated with placebo were re-exploration for bleeding (4.8%; n=5), replacement of ascending aorta (1.4%; n=2), death due to ischaemic stroke (0.7%; n=1), death due to cerebral haemorrhage (0.7%; n=1) and death due to low cardiac output (0.7%; n=1).

In *Diprose 2005*, TXA (n=62) at a total dose of 60 mg/kg was compared with placebo (n=61) and aprotinin (n=63) at a total dose of 5 MKIU in patients undergoing CABG or single valve replacement. In the TXA group, 5 (8.1%) patients experienced a myocardial infarction

compared with 4 (6.6%) in the placebo group and three (4.8%) in the aprotinin group. There was one death in the placebo group due to pulmonary sepsis. Prolonged ventilation for respiratory failure was required by one aprotinin treated patient and one placebo treated patient. Sternal dehiscence occurred in one placebo treated patient. Renal failure requiring temporary dialysis occurred in one placebo treated patient.

In *Hardy 1998*, TXA (n=43) at a total dose of 133 mg/kg was compared with placebo (n=43) and EACA (n=45) at a total dose of 17 g in patients undergoing primary CABG on CPB. The safety results for placebo versus TXA versus EACA were, respectively: surgical re-exploration 1 (2.2%) versus 3 (7.0%) versus 1 (2.2%); myocardial infarction 2 (4.2%) versus 1 (2.3%) versus 2 (4.2%); cerebrovascular accident 0 versus 1 (2.3%) versus 0; and death 0 versus 0 versus 2 (4.2%), respectively.

In *Katsaros 2003*, TXA (n=104) at a total dose of 120 mg/kg was compared with placebo (n=106) in patients undergoing cardiac surgery. There were two (1.9%) deaths in the control group and none in the TXA group. There was one (1.0%) patient in the TXA group re-explored for bleeding compared with 5 (4.7%) in the placebo group. Cerebrovascular events were reported in three (2.9%) patients in the TXA group and two (1.9%) in the placebo group. CNS events were reported in two (1.9%) patients in the placebo group. Renal failure occurred in one (1.0%) patient in the TXA group and 0 in the placebo group. DVT occurred in one (1.0%) patient in the control group and 0 in the TXA group and PE occurred in one (1.0%) patient in the placebo group and 0 in the TXA group. Supraventricular arrhythmias were seen with equal frequency in both groups and one (1.0%) patient in the TXA group had a refractory ventricular arrhythmia requiring implantable cardioverter-defibrillator placement.

In *Maddali 2007*, TXA (n=111) at a total dose of 12 mg/kg was compared with placebo (n=111) in patients undergoing elective CABG on CPB. There were three (2.7%) patients in each group re-explored for bleeding. In the TXA group, 7 (6.3%) patients showed electrocardiogram (ECG) ST-segment elevation compared with 6 (5.4%) in the placebo group with an additional three (2.7%) in this group showing ST-segment depression. All ECG changes were short-lived and were not associated with haemodynamic changes. There were no myocardial infarctions reported in either group.

In *Murphy 2006*, TXA (n=50) at a total dose of 28 mg/kg was compared with placebo (n=50) in patients undergoing CABG off pump. The adverse events (TXA versus placebo) were: arrhythmia 6 (12%) versus two (4%); infective complication one (3%) versus two (7%); renal complication 0 versus one (2%); myocardial infarction one (2%) versus 0; pulmonary complication 0 versus 0; and stroke 0 versus 0, respectively.

In *Pleym 2003*, TXA (n=40) at a total dose of 30 mg/kg was compared with placebo (n=40) in patients undergoing first time CABG on CPB. In the placebo group, one (2.5%) patient had a pulmonary embolism in the post-operative phase. No other thromboembolic complications were reported, nor were any other major complications reported.

Discontinuations

The safety summary provided no information on discontinuations. There was limited reporting of discontinuations in the individual cardiac surgical studies.

Clinical Laboratory Results

The safety summary provided no information on clinical laboratory results. There was no systematic reporting in individual studies of changes in biochemical parameters (blood or urine) associated with treatment. In most but not all studies there were blood transfusion protocols in place which provided haemoglobin and/or haematocrit levels needed to trigger

transfusion. In some studies protocols were provided for platelet and/or fresh frozen plasma transfusions.

Electrocardiographic Results

There was no systematic reporting of ECG changes (for example, QT interval changes) in individual studies or in the safety summary. However, continuous ECG monitoring would have been part of standard intra and post-operative management of patients undergoing cardiac surgery. Reported cardiac disorder adverse events included information on events which presumably were diagnosed by ECG. Compared with non-active controls, TXA treated patients had a lower incidence of arrhythmia, atrial fibrillation and heart block and a higher incidence of cardiac ischaemia, myocardial infarction and ventricular tachycardia.

Vital Signs

There was no information on vital sign changes.

Summary Comments

The submission provided a comprehensive summary of serious adverse events associated with TXA from the published literature. The major problem with the safety summary is the imbalance in serious adverse events between TXA and non-active control in patients undergoing high risk cardiac surgical procedures (that is, high risk patients) due to the inclusion of the data from *Fergusson 2008*. This study provided the majority of the safety data in high risk patients treated with TXA, aprotinin and EACA as it was designed specifically to collect such data. In contrast, nearly all the other submitted studies were primarily designed to investigate the efficacy of TXA and reporting of safety in these studies (where it occurred) was generally limited to serious adverse events. Furthermore, interpretation of the safety data in *Fergusson 2008* was complicated by the absence of a non-active control group. The other problem with the safety information relates to the absence of data on non-serious adverse events, biochemical laboratory changes and systematic assessment of ECG changes. No summary of the effect of dose on safety could be identified in the submission. However, the comparative safety data in the larger cardiac surgery studies suggests that there is no apparent relationship between serious adverse events and dose as these studies used a variety of total TXA doses ranging from 12 mg/kg to 133 mg/kg. Safety conclusions have been further summarised below (see *Safety-Cardiac surgery*).

Orthopaedic Surgery, Exposure

The safety summary included information on 492 TXA treated patients and 406 non-active controls that underwent knee arthroplasty and 261 TXA treated patients and 273 non-active controls that underwent hip arthroplasty. Of the 492 TXA treated patients who underwent knee arthroplasty, 284 (57.7%) received total doses in the range 20-50 mg (mean 28 mg/kg), 126 (25.6%) received total doses < 20 mg/kg (mean 15 mg/kg) and 82 (16.7%) received total doses > 100 mg/kg (mean 143 mg/kg). Of the 261 TXA treated patients who underwent hip arthroplasty, 182 (69.7%) received total doses < 20 mg/kg (mean dose 14 mg/kg) and 79 (30.3%) received total doses 20-50 mg/kg (mean 23 mg/kg). The proposed total TXA dose for adult orthopaedic surgery is 60 mg/kg. Only 82 patients (all knee arthroplasty) received total TXA doses \geq 60 mg/kg (all > 100 mg/kg). Therefore, of the 753 TXA treated patients included in the orthopaedic surgery safety summary only 82 (10.9%) received total doses \geq 60 mg/kg (all > 100 mg/kg). The duration of the follow-up period for the patients undergoing orthopaedic surgery was not provided.

Adverse Events, Serious Adverse Events and Deaths

The safety summary reported only serious adverse events including deaths. In general, the published studies simply reported adverse events including deaths.

Adverse Events (Serious)

In both hip and knee surgery, serious adverse events were reported more frequently in TXA treated patients than in non-active controls and adverse events occurred more frequently in knee than in hip surgery. The most commonly reported adverse event in the orthopaedic surgery studies was DVT. This event occurred in both hip and knee surgery more frequently in TXA treated patients than non-active controls and more frequently in knee than in hip surgery. All other adverse events occurred infrequently. Most of the DVTs reported in knee surgery came from one study [Tanaka 2001]. In *Tanaka 2001*, positive findings on venography at 7 to 14 days after surgery were observed in 46% (12/26) of patients in the non-active control group, 46% (11/24) of patients in the TXA pre-operative treatment group, 45% (10/22) of patients in the intra-operative TXA treatment group and 48% (13/27) of patients in the TXA pre- and intra-operative treatment group. In *Tanaka 2001*, the incidence of DVT was similar in the TXA treated groups and the non-active control group and none of the patients had positive findings of PE on lung scanning. The number of aprotinin treated patients (n=12) in the safety summary was too small to make meaningful comparisons with TXA and there were no safety data in EACA treated patients. The serious adverse events occurring in the hip and knee surgery studies are summarised below in Table 33.

Excluding the DVT adverse events reported in *Tanaka 2001*, total potential thrombotic related adverse events in the knee and hip studies are summarised below in Table 34. In the hip surgery studies, there was a statistically non significant greater incidence of potential thrombotic adverse events in TXA treated patients compared with non-active controls primarily due to DVT. In the knee surgery studies, the incidence of potential thrombotic adverse events (primarily DVT) was similar in both TXA treated patients and non-active controls

Table 33. Frequency of all adverse events as a percent of the number of patients treated.

	Hip Surgery		Knee Surgery	
	Control	TXA	Control	TXA
Patients Numbers	273	261	406	492
Total Events n (%)	8 (2.9%)	13 (5.0%)	31 (7.6%)	66 (13.4%)
Fatal	-	-	1 (0.25%)	-
DVT	4 (1.5%)	7 (2.7%)	25 (6.2%)	58 (11.8%)
Nausea	-	-	-	3 (0.6%)
Myocardial Infarction	-	-	-	1 (0.2%)
Chest pain	-	1 (0.4%)	-	-
Infection	2 (0.7%)	1 (0.4%)	2 (0.5%)	2 (0.4%)
Pyelonephritis	-	1 (0.4%)	-	-
Dyspnoea	-	1 (0.4%)	-	-
Pulmonary Embolism	1 (0.4%)	2 (0.8%)	2 (0.5%)	-
Cardiac Problems	-	-	-	1 (0.2%)
Pneumonia	-	-	1 (0.25%)	1 (0.2%)
Eczema	1 (0.4%)	-	-	-

Control (non-active).

Table 34. Frequency of potential thrombotic adverse events as a percent of the number of patients treated.

	Hip Surgery		Knee Surgery	
	Control	TXA	Control	TXA
Patients Numbers	273	261	406	492
DVT	1.5%	2.7%	3.2%	2.4%
	95% Risk Difference : -1.2%, +3.6%		95% Risk Difference: -3.0%, +1.4%	
Myocardial Infarction	-	-	-	0.2%
Cardiac problems	-	-	-	0.2%
Chest Pain	-	0.4%	-	-
Dyspnoea	-	0.4%	-	-
Pulmonary Embolism	0.4%	0.8%	0.5%	-
Total	1.8%	4.2%	3.7%	2.8%
	Risk Difference [95%CI] = 2.4 [-5.3, 5.3]		Risk Difference [95%CI] = -0.8 [-3.2, 1.5]	

Control (non-active).

Deaths

There was only one death reported in the orthopaedic studies. This occurred in a patient in a control group in a total knee arthroplasty study who died following a PE on the 15th post-

operative day [Hiippala 1997]. There were no deaths reported in TXA treated patients in the orthopaedic surgery studies.

Discontinuations

There was no information on discontinuations

Clinical Laboratory Results

There was no information on clinical biochemical laboratory parameters.

Electrocardiograph Results

There was no information on ECG changes.

Vital Signs

There was no information on vital sign changes.

Summary Comments

The submitted safety data in orthopaedic studies in adults showed an increased risk of adverse events in TXA treated patients compared with non-active controls in both knee and hip surgery. The increased risk was predominantly due to DVT adverse events. In knee surgery, most of the DVT adverse events came from one study [Tanaka 2001]. When the DVT adverse events from this study were excluded from the analysis, the risk of DVT adverse events in TXA treated patients was lower than in non-active controls. The studies included only a limited number of patients exposed to the proposed dose for knee and hip surgery. Conclusions regarding the safety of TXA in orthopaedic surgery in adults are provided below under *Safety-Orthopaedic surgery (adults)*.

Paediatric Cardiac Surgery

No summary safety data from the paediatric cardiac surgery studies were submitted. The 6 paediatric cardiac surgery studies included 247 TXA treated patients with total doses ranging from < 20 mg/kg to > 100 mg/kg. There was limited reporting of serious adverse events in the 6 individual studies with no other safety data being reported. The safety data were briefly described in each of the studies. In *Chauhan 2004*, it was reported that "no complications in the form of renal problems or cerebral events were noted in any of the children studied" [that is, 120 TXA treated patients and 30 control patients]. In *Reid 1995*, the conference abstract reported that "[N]o adverse drug reactions were observed in any patient [that is, 5 patients] who received tranexamic acid". In *Reid 1997*, it was stated that "no thrombotic complications or other adverse effects were detected" in 20 TXA treated patients and 21 placebo treated patients. In *Zonis 1996*, it was stated that "no patients died and no side effects were attributed to the treatment group" in 40 patients treated with TXA and 40 control patients. In *Vacharaska 2002*, it was stated that "no patients died and no adverse effects were attributed to the administration of tranexamic acid" to 52 patients. In *Shore-Lesserson 2002*, no safety data were reported.

Post-Marketing Data

Overview – Summary Bridging Report (SBR)

Tranexamic acid was first approved in Austria in 1966. Since then the 500 mg film coated tablet has been approved in 40 countries and the 100 mg/mL solution for injection in 30 countries. Tranexamic acid tablets (500 mg) have been marketed in Australia since 1981 for the treatment of hereditary oedema and menorrhagia. The submission included a Summary Bridging Report (SBR) of spontaneous adverse event reports which integrated the Periodic Safety Update Reports (PSURs) covering the period from 1 February 2000 to 31 July 2008.

During this period there were no regulatory actions taken by any regulatory agencies relating to the safety of tranexamic acid. The Australian usage of the tranexamic acid IV formulation via the SAS has increased significantly since the cancellation of the registration of aprotinin.

Over the period of the SBR there were 324 cases of spontaneous adverse event reports. The following information focuses on the spontaneous adverse event reports relating to TXA IV. There were 6 cases associated with TXA IV with a fatal outcome (total number of events = 26). The most common events associated with a fatal outcome were renal and urinary disorders (2) and pulmonary embolism (2). No other adverse events with a fatal outcome were reported more than once. There were 24 serious (non fatal) cases associated with TXA IV reporting 41 serious adverse events. The most common serious spontaneous adverse event reports were vascular disorders (9), deep vein thrombosis (3), ineffective drug (2) and chylothorax (2). There were a wide variety of other serious adverse events reported and none of these events was reported more than once. There were 9 non-serious cases associated with TXA IV reporting 16 non-serious adverse events. No non-serious adverse event was reported more than once. Overall, the spontaneous adverse event reports for TXA IV do not give rise to particular safety concerns relating to the drug.

SBR - Fatalities

There were 6 fatal cases (26 events) occurring in 790 patient-years of treatment with TXA IV (an incidence of 0.8%). In addition, there were 11 fatal cases (31 events) occurring in 5250 patient years of treatment with TXA oral (that is, incidence 0.2%) and 4 fatal cases (10 events) via "other" routes of administration. Of the 21 medically confirmed fatal cases, the most commonly involved organ systems were *respiratory, thoracic and mediastinal disorders* (12 events, 18.2%), *vascular disorders* (11 events, 16.7%) and *nervous system disorders* (10, 15.2%). The most common of the 12 *respiratory, thoracic and mediastinal disorders* events was pulmonary embolism (7) and all of the other events occurred only once (Cheyne-Stokes respiration, haemoptysis, laryngeal oedema, rales, respiratory arrest). The most common of the 11 *vascular disorders* were DVT (2) and hypertension (2) with all other events occurring once (arterial thrombosis limb, embolism, haemorrhage, hypotension, ischaemia, peripheral ischaemia, superficial thrombophlebitis). The most common of the nervous system disorders were cerebrovascular accident (3), cerebral infarction (2) and convulsion (2) with all others occurring once (brain stem syndrome, hydrocephalus, precerebral artery occlusion). The only other adverse events in all other organ systems occurring more than once were pyrexia (2) and haemoglobin decreased (2).

SBR – Serious Adverse Events Other than Fatalities

TXA IV was associated with 24 non-fatal cases involving 41 serious adverse events (790 patient-years of treatment [incidence 3.0%]). TXA oral was associated with 91 non-fatal cases involving 172 serious adverse events (5250 patient-years of treatment [incidence 1.7%]). The organ systems which included the most non-fatal, serious adverse events associated with TXA IV were – *vascular disorders* ($n=9$) consisting of three DVTs and one each of haemorrhage, phlebitis, shock, thrombophlebitis, thrombosis, wound haemorrhage; *general disorders and administration site conditions* ($n=6$) consisting of two drug ineffective and one each of extravasation, face oedema, hypothermia, malaise; *respiratory, thoracic and mediastinal disorders* ($n=6$) consisting of two chylothorax and one each of bronchospasm, cough, dyspnoea, pulmonary haemorrhage; *nervous system disorder* ($n=4$) consisting of one each of cerebrovascular accident, convulsion, dizziness, grand mal convulsion. All other systems had one or two events. Other noteworthy serious adverse events were *immune system disorders* ($n=2$) consisting of one of anaphylaxis and one of hypersensitivity.

SBR – Non-Serious Adverse Events

TXA IV was associated with 9 cases involving 16 non-serious adverse events (790 patient-years of treatment [incidence 1.1%]). TXA oral was associated with 140 cases involving 213 non-serious adverse events (5250 patient-years of treatment [incidence 2.7%]). None of the non-serious AEs reported with TXA IV occurred more than once.

SBR – Adverse Events in Children Aged < 12 years.

There were 10 cases (12 adverse events) in children aged < 12 years occurring with TXA IV and/or oral. None of the 12 events occurred more than once.

Clinical Summary and Conclusions

Efficacy - Cardiac Surgery (Adults)

Post-operative Blood Loss (Primary Efficacy Outcome)

a. It is considered that the efficacy of TXA to reduce post-operative blood loss in cardiac surgery has been satisfactorily established. The data from the TXA 20-50 mg/kg total dose subgroup is considered to be the most relevant as it includes the proposed total doses most likely to be used in cardiac surgery. The sponsor's clinical expert, who is an Australian cardiothoracic surgeon, comments that elective CABG involving one or two arteries may take 2 hours including approximately 60 minutes on CPB. He notes that as the complexity of the surgery increases the overall duration of the procedure can increase to 6 to 8 hours, with over 4 hours on CPB. Therefore, as the proposed TXA dose for cardiac surgery is a loading dose of 15 mg/kg followed by an infusion of 4.5 mg/kg/hour of which 0.6 mg/kg may be added in the pump line it can be estimated that in surgery lasting 2 hours the total TXA dose will be 24 mg/kg while in surgery lasting from 6 to 8 hours the total TXA dose will be 42 to 51 mg/kg.

b. The TXA versus control duplicates included meta-analysis showed that the TXA 20-50 mg/kg subgroup statistically significantly reduced post-operative blood loss by 218 mL [95%: 173, 264] (Table 9). This reduction in post-operative blood loss is considered to be clinically meaningful. Heterogeneity among the studies included in the TXA 20-50 mg/kg meta-analysis was not statistically significant: $p=0.149$; $I^2=23.7\%$.] The mean TXA total dose in the 20-50 mg/kg subgroup was 28.0 mg/kg in 487 patients (Table 9). In the duplicates included meta-analysis, the overall reduction in blood loss due to TXA across the dose range 5.5-250 mg/kg total dose was 226 mL [95%CI: 181, 271] compared with control and the mean TXA dose was 67.1 mg/kg in 1525 patients (Table 9). Heterogeneity in the overall meta-analysis was statistically significant: $p<0.001$; $I^2=82.2\%$. It is considered that the submitted meta-analyses support the approval of the proposed TXA treatment regimen for the reduction of post-operative blood loss in cardiac surgery in adults.

c. The duplicates removed meta-analysis of TXA versus control in control blood loss categories showed that the TXA 20-50 mg/kg subgroup statistically significantly reduced post-operative blood loss in the 300-600 mL, 601-900 mL and > 900 mL control blood loss categories (that is, surrogate for risk of cardiac surgery). The overall reduction in post-operative blood loss for the three categories for the TXA 20-50 mg/kg subgroup compared with control was 225 mL [95%CI: 177, 274] and heterogeneity was not statistically significant ($p=0.162$; $I^2=23.9\%$). TXA 20-50 mg/kg reduced post-operative blood loss by 140 mL, 264 mL and 308 mL compared with control in the 300-600 mL, 601-900 mL and > 900 mL categories, respectively (Table 11). The absolute difference in post-operative blood loss increased over the three control blood loss categories. However, the mean reduction in percentage terms in blood loss due to TXA was similar for the categories being 27.1% with 300-600 mL, 33.9% with 601-900 mL and 34.4% with > 900 mL (Table 11). It is considered

that the submitted meta-analyses support the approval of the proposed TXA treatment regimen for the reduction of post-operative blood loss in both low and high risk cardiac surgery in adults.

d. The *Cochrane Review [Henry 2008]* meta-analysis of post-operative blood loss showed that TXA (n=595) significantly reduced post-operative blood loss by 262 mL [95%CI: 206, 318] compared with control (n=535). TXA at a total dose of < 2 g (n=154) significantly reduced post-operative blood loss by 251 mL [95%CI: 151, 352] compared with control (n=148). Similarly, TXA at a total dose of 2-10 g (n=441) significantly reduced post-operative blood loss by 272 mL [95%CI: 204, 340] compared with control (n=387). The results of the Cochrane Review meta-analyses are considered to support the sponsor's meta-analyses showing a clinically meaningful reduction in post-operative blood loss in adult patients undergoing cardiac surgery treated with TXA compared with control.

Allogeneic Blood Transfusion (Secondary Efficacy Outcome)

a. In the meta-analysis of the relative risk of allogeneic blood product transfusion (whole blood or packed red blood cells) in TXA and control treated patients the TXA 20-50 mg/kg total dose subgroup statistically significantly reduced the relative risk of transfusion by 28%: RR = 0.72 [95%: 0.62, 0.83] (Table 15). Heterogeneity in the TXA 20-50 mg/kg subgroup analysis was not statistically significant: $p=0.492$; $I^2 = 0\%$. TXA reduced the relative risk of transfusion in 19 (82.7%) of the 23 studies included in the TXA 20-50 mg/kg subgroup analysis, but in only 4 (21.0%) of these was the relative risk reduction statistically significant. Nevertheless, it is considered that the meta-analysis has satisfactorily established the efficacy of the proposed TXA regimen as regards reduction in requirement for allogeneic blood transfusion in the post-operative period in adult patients undergoing cardiac surgery.

b. TXA 20-50 mg/kg, statistically significantly reduced the risk of allogeneic blood transfusion compared with control by 32% (RR = 0.68 [95%CI: 0.54, 0.87] in the 601-900 mL category and by 33% (RR = 0.67 [95%CI: 0.50, 0.89]) in the > 900 mL category. However, the reduction of 17% due to TXA in the 300-600 mL category was not statistically significant (RR = 0.83 [95%CI: 0.58, 1.18]). Heterogeneity was not statistically significant in the three categories. There were no relevant studies in the < 300 mL category. The overall risk reduction for blood transfusion due to TXA across the three control blood loss categories was 28% (RR = 0.72 [95%CI: 0.62, 0.83] and the heterogeneity was not statistically significant ($p=0.492$; $I^2=0\%$). The overall risk difference for blood transfusion between the TXA 20-50 mg/kg subgroup and control across the three control blood loss categories was 12% [95%CI: 6.6, 17], a small but statistically significant reduction.

c. The *Cochrane Review [Henry 2008]* meta-analysis of relative risk of allogeneic blood product transfusion showed that TXA (n=1322) significantly reduced the relative risk of blood transfusion by 30% compared with control (1220): RR = 0.70 [95%CI: 0.61, 0.80]. TXA at a total dose of < 2 g (n=495) significantly reduced the relative risk of blood transfusion by 28% (RR = 0.72 [95%CI: 0.59, 0.88]) compared with control (n=431). Similarly, TXA at a total dose of 2-10 g (n=827) significantly reduced the relative risk of blood transfusion by 33% (RR = 0.67 [95%CI: 0.55, 0.83]) compared with control (n=789). The results of Cochrane Review meta-analyses are considered to support the sponsor's meta-analyses showing a clinically meaningful reduction in the risk of allogeneic blood transfusion in adult patients undergoing cardiac treated with TXA compared with control.

Dosage Regimen in Cardiac Surgery

a. The most notable feature of the cardiac surgery meta-analyses was the wide variety of effective doses used in the studies. The submitted data are considered to have satisfactorily

established the efficacy of TXA in the total dose range of 20-50 mg/kg to reduce both post-operative blood loss and blood transfusion requirements. However, determination of the optimal dose from the submitted data is more problematical. The sponsor submitted three pharmacokinetic studies which attempted to derive dosage regimens for use in cardiac surgery capable of maintaining plasma TXA concentrations at or above levels known to inhibit *in vitro* fibrinolysis (10 µg/mL) and/or platelet activation ($IC_{50} = 16$ µg/mL). In order to achieve concentrations ≥ 52 µg/mL (levels considered to inhibit fibrinolysis *in vivo*), Dowd 2002 suggested a TXA dosage regimen for typical patients of 12.5 mg/kg loading followed by a maintenance infusion 6.5 mg/kg/h for 4 hours with an additional dose of 1 mg/kg to be added to the pump prime (THAT IS, total dose of 39.5 mg/kg for 4 hour surgery). In high risk surgical patients, Dowd 2002 suggested that the TXA regimen to maintain a plasma concentration of 125 µg/mL was a loading dose of 30 mg/kg, a maintenance dose of 16 mg/kg/h and an additional dose of 2 mg/kg to the pump prime (that is, total dose of 96 mg/kg for 4 hour surgery). In Nuttal 2008, the suggested TXA regimen was a loading dose of 10 mg/kg, an infusion rate of 2 mg/kg/hour and an additional dose of 40-50 mg to the pump prime depending on the volume of the CPB circuit (that is, total dose of 30-31 mg/kg for 4 hours of surgery). In Fiechtner 2001, the TXA regimen was a loading dose of 10 mg/kg followed by a maintenance dose of 1 mg/kg/hour (that is, total dose of 14 mg/kg for 4 hour surgery). Overall, the total dose of the proposed regimen is consistent with the total dose and regimens in the pharmacokinetic studies found to produce TXA plasma concentrations known to inhibit *in vitro* fibrinolysis and platelet aggregation [Dowd 2002; Nuttal 2008]. On the basis of the results of the meta-analysis grouped by baseline control blood group loss (that is, a surrogate for risk of bleeding) it is considered that there is no reason to modify the TXA treatment regimen for different cardiac surgical procedures.

b. In the meta-analysis of post-operative blood loss the most commonly used total TXA dose was 20-50 mg/kg (23 of 47 pairwise comparisons in the duplicates included meta-analysis). The TXA 20-50 mg/kg subgroup contributed 48.9% of the pairwise comparisons, which was more than twice the contribution of the next highest dose subgroup (> 100 mg/kg; 21.3% [10/47]). The most common TXA regimen was a pre-surgery dose, generally given after induction of anaesthesia but before the skin incision, followed by a maintenance infusion with or without an additional pump line dose (46% [18/39] of studies). The second most common TXA regimen was a single pre-surgery dose generally given after induction of anaesthesia but before incision of the skin (41% [16/39] of studies). Overall, the submitted data are considered to support the efficacy of the proposed TXA dosage regimen for all cardiac surgery procedures in adults. Interestingly, in the ongoing *Australasian Aspirin and Tranexamic Acid for Coronary Artery Surgery* (ATACAS) trial in elective CABG on and off pump the TXA dose chosen for investigation was 100 mg/kg administered after induction of anaesthesia but before CPB [Myles 2008]. Myles 2008, references Dowd 2002 as being the source supporting the single 100 mg/kg dose and states that the dose "has been shown to be effective, with an onset of time of < 1 hour and with a suitable side effect profile".

Efficacy - Orthopaedic Surgery - Total Knee Arthroplasty (TKA)

Post-operative Blood Loss (Primary Efficacy Outcome)

a. In TKA, the sponsor is proposing a TXA loading dose of 15 mg/kg prior to release of the tourniquet followed by repeat bolus injection of 15 mg/kg at 8 hour intervals after the initial dose to a maximum of 24 hours (that is, maximum total TXA dose of 60 mg/kg). The overall results for the meta-analysis of post-operative blood loss showed that TXA (14-150 mg/kg) statistically significantly reduced blood loss by 331 mL [95%CI: 246, 416] compared with control: heterogeneity $p < 0.001$; $I^2 = 86.7\%$ (Table 17). There was no TXA 50-100 mg/kg

dose group in the meta-analysis. The TXA 20-50 mg/kg subgroup statistically significantly reduced post-operative blood loss by 345 mL [95%CI: 179, 510] compared with control: heterogeneity $p < 0.001$; $I^2 = 91.9\%$ (Table 17). The mean TXA total dose in the 20-50 mg/kg subgroup was 32 mg/kg and the mean saving in post-operative blood loss due to TXA was 43.9% in 157 patients (Table 18). The reduction in post-operative blood loss in the TXA > 100 mg total dose subgroup due to TXA was 359 mL [95%CI: 200, 518]; heterogeneity $p < 0.001$; $I^2 = 85.6\%$ (Table 17). The mean TXA total dose in the > 100 mg/kg subgroup was 143 mg/kg and the mean saving in post-operative blood loss due to TXA was 42.6% in 82 patients (see Table 18). The reductions in post-operative blood loss observed with the 20-50 mg/kg and > 100 mg/kg subgroups are considered to be clinically meaningful. No convincing dose response was observed between these two dosage subgroups. It is considered that the meta-analyses have satisfactorily demonstrated the efficacy of the proposed TXA dose to reduce post-operative blood loss in TKA.

b. There were only two control blood loss categories (Table 19). In the 300-600 mL category, TXA at a mean dose of 57 mg/kg [range 15-135] statistically significantly reduced mean post-operative blood loss by 214 mL [95%CI: 155, 273] compared with control with a mean saving of 47.5%. In the > 900 mL category, TXA at a mean dose of 65 mg/kg [range 14-150] statistically significantly reduced mean post-operative blood loss by 557 mL [95%CI: 367.748] compared with control with a mean saving of 41.9%. The overall mean saving with TXA (14-150 mg/kg) was 331 mL [95%CI: 246, 416] compared with control. It is considered that the meta-analyses based on control blood loss categories support the efficacy of the proposed TXA dose to reduce post-operative blood loss in TKA.

Allogeneic Blood Transfusion (Secondary Efficacy Outcome)

a. In the overall meta-analysis, the mean dose of TXA was 55 mg/kg [range 14-150] in 487 patients. This mean dose is similar to the total dose being proposed for use in TKA. The overall results showed that TXA (14-150 mg/kg) statistically significantly reduced the risk of blood transfusion by 64% compared with control (RR = 0.36 [95%CI: 0.25, 0.50]; heterogeneity $p < 0.001$; $I^2 = 75.8\%$ (Table 20). The risk difference between TXA (14-150 mg/kg) and control was 36% [95%CI: 28, 44]; heterogeneity $p < 0.001$; $I^2 = 67.6\%$. There was no TXA 50-100 mg/kg dose group in the meta-analysis. It is considered that the meta-analyses have satisfactorily demonstrated the efficacy of the proposed TXA dose to reduce the risk of blood transfusion requirement.

Proposed Dosage Regimen in Total Knee Arthroplasty

a. The most notable feature of the orthopaedic surgery (TKA) meta-analyses was the wide variety of effective doses used in the studies. This makes determination of the optimal dosage regimen difficult. A common feature of the regimens was the use of a bolus dose of 10-15 mg/kg prior to release of the tourniquet with the most common initial dose being 15 mg/kg. Following the initial bolus dose the regimens were characterised by either repeat bolus doses or continuous infusions. The sponsor is proposing an initial dose of 15 mg/kg followed by 15 mg/kg every 8 hours to a maximum of 24 hours. There were two studies with similar regimens to that being proposed [Jansen 1999; Sorin 1999]. However, in both of these studies TXA was continued at 8 hourly intervals for three days instead of 24 hours. In *Sorin 1999* (total dose 150 mg/kg), the mean reduction in post-operative blood loss was 744 mL [95%CI: 433, 1055] with a mean saving due to TXA of 52%. In *Jansen 1999* (total dose 150 mg/kg), the mean reduction in post-operative blood loss was 642 mL [362, 922] with a mean saving due to TXA of 58%. The sponsor is proposing an initial dose of 15 mg/kg followed by 15 mg/kg every 8 hours to a maximum of 24 hours. In *Janssen 1999*, the meta-analysis for post-operative blood loss at 24 hours showed an 1110 mL loss for control which was 78% of the

total control blood loss over three days and 468 mL for TXA which was 69% of the total TXA blood loss over three days. There was a similar pattern in *Sorin 1999* where the difference in total blood loss was stated to be "primarily due to blood loss during the first 24 hours after surgery". Consequently, it is considered reasonable to recommend approval of the proposed 8 hourly repeat bolus regimen for a maximum of 24 hours.

Efficacy - Orthopaedic Surgery – Total Hip Arthroplasty (THA)

Post-operative Blood Loss (Primary Efficacy Outcome)

a. It is considered that the submitted data have not satisfactorily established the efficacy of TXA to reduce post-operative in patients undergoing total hip arthroplasty (THA). In the overall meta-analysis, TXA 10-30 mg/kg reduced post-operative blood loss by 159 mL [95%CI: 101, 206] compared with control (Table 22). While the 159 mL reduction was statistically significant it is considered to be of doubtful clinical significance. In the TXA 20-30 mg/kg subgroup meta-analysis the reduction in post-operative blood loss due to TXA was 239 mL [95%: 60, 417] compared with control. The 239 mL reduction was statistically significant and is considered to be clinically meaningful. However, there were only three studies in the 20-30 mg/kg subgroup meta-analysis and individual results were statistically significant for two of the three studies [Niskanen 2005; Ekback 2000]. Furthermore, although the reduction in mean post-operative blood loss in *Niskanen 2005* was statistically significant it is considered to be clinically insignificant as it was only 146 mL [95%CI: 57, 235]. The mean difference in post-operative blood loss in *Ekback 2000* was clinically and statistically significant (381 mL [95%CI: 170, 592]), but the study included only 20 patients in each of the TXA and control groups. Post-operative blood loss due to TXA based on the control blood loss categories suggests that TXA is likely to be effective in patients at higher risk of blood loss (> 600 mL), but not in patients at lower risk of blood loss (\leq 600 mL) (Table 23).

Risk of Allogeneic Blood Transfusion (Secondary Efficacy Outcome)

a. Overall, the meta-analysis of the risk of allogeneic blood transfusion showed that TXA 10-30 mg/kg statistically significantly reduced the requirement for blood transfusion by 40% [95%CI: 18, 56] compared with control. However, the results were statistically significant for only two of the 10 individual studies included in the meta-analysis. The TXA 20-30 mg/kg subgroup (n=62) significantly reduced the risk of allogeneic blood transfusion by 41% [95%CI: 7, 63] compared with control. However, the risk difference between control and the TXA 20-30 mg/kg subgroup was not statistically significant: 15.0% [95%CI: -3.2, 33.2]. Furthermore, in none of the 4 studies in the TXA 20-30 mg/kg subgroup meta-analysis was the individual relative risk reduction statistically significant and in only two of the 4 studies was the individual risk difference statistically significant. It is considered that the results for the TXA 20-30 mg/kg subgroup meta-analysis do not satisfactorily establish the efficacy of TXA compared with control as regards reduction in requirement for blood transfusion.

Proposed Dosage Regimen in Total Hip Arthroplasty

a. There are no total hip arthroplasty studies using the total proposed dose of 60 mg/kg (that is, an initial dose of 15 mg/kg followed by 15 mg/kg every 8 hours to a maximum of 24 hours). The studies in the meta-analyses used total TXA doses less than that being proposed. Of the 11 studies in the meta-analysis, 6 used a single pre-surgery dose of 10 mg/kg or 15 mg/kg. The maximum total TXA dose was 30 mg/kg in *Ekback 2000*. In this study, TXA 30 mg/kg significantly reduced post-operative blood loss by 381 mL [95%CI: 170, 592] compared with control, but did not significantly reduce the requirement for blood transfusion (RR = 1.0 [95%CI: 0.07, 14.90]). It is considered that there are no satisfactory data in the submission establishing the efficacy of TXA at the proposed dose for use in total hip

arthroplasty. The TXA doses used in the studies appear to be too low to satisfactorily reduce post-operative blood loss and reduce blood transfusion requirement in patients undergoing total hip arthroplasty.

Cochrane Review [Henry 2008] – Orthopaedic Surgery

a. In the *Cochrane Review [Henry 2008]*, pooled data from 6 orthopaedic surgery studies (knee and hip combined) showed that TXA significantly reduced post-operative blood loss by 209.7 mL [95% CI: -384.3, -35.2] compared with placebo. The authors concluded that "TXA treatment in orthopaedic surgery appeared to be only marginally effective in reducing post-operative blood loss". TXA significantly reduced the relative risk of post-operative blood transfusion compared with control in 21 pooled orthopaedic surgery studies: RR = 0.44 [95% CI: 0.33, 0.60].

Efficacy - Paediatric Surgery

a. It is considered that the efficacy data supporting the use of TXA in paediatric cardiac surgery are inconclusive and do not support approval in this patient group. The submission included a meta-analysis of post-operative blood loss in paediatric cardiac surgery which pooled data from three studies. However, *Reid 1995* was a conference abstract which included only 9 patients undergoing high-risk surgery and used a total TXA dose of 220 mg/kg which is much higher than that being proposed. Of the other two studies, four pairwise comparisons were included from *Chauhan 2004* and two pairwise comparisons from *Zonis 1996*. One of the pairwise comparisons from *Zonis 1996* was a small subgroup analysis of children with cyanotic heart disease. In view of the methodological concerns associated with the meta-analysis the individual results from the relevant studies were evaluated separately. None of the studies used the dose regimen being proposed by the sponsor. Two dose regimens in *Chauhan 2004* used similar total TXA doses to those being proposed in children aged 2 months to 5 years with mean ages of about 4 years. These two regimens found that TXA significantly reduced post-operative blood loss and blood transfusion requirements compared with placebo. Each of the two regimens included 30 TXA patients while the shared control included 30 patients. The surgical procedures in all patients included CPB and were predominantly tetralogy of Fallot repairs. The TXA total dose in *Reid 1997* was about 10 times greater than that being proposed and was efficacious in children undergoing high risk repeat procedures. The total TXA dose in *Shore-Lesserson 2002* is comparable with that being proposed, but only children < 15 mg/kg were treated and although TXA significantly reduced post-operative blood loss, transfusion requirements increased with TXA compared with control. The TXA regimen (n=40) in *Zonis 1996* was a pre-surgery single bolus (50 mg/kg) and did not significantly reduce post-operative blood loss compared with placebo (n=42) in a combined group of patients with cyanotic and acyanotic heart disease. The sponsor is not seeking approval of TXA for use in paediatric spinal (scoliosis) surgery.

Safety – Cardiac Surgery (Adults)

a. The submission included summary safety data on 3825 TXA treated patients and 1247 non-active controls. The overall incidence of serious adverse events in TXA treated patients was 19.8% (6.2% in low and 56.5% in high risk patients). This compared with an overall incidence of 8.3% in non-active controls (6.4% low and 17.9% high risk patients). The interpretation of the adverse event data in high risk patients has been complicated by the results from *Fergusson 2008*. This study specifically collected adverse event data (including mortality) in patients undergoing high risk surgical treatments and treated with TXA, EACA, or aprotinin. The incidence of adverse events in all three active treatment groups was high but there was no non-active control group which complicates interpretation of the results. The

incidence of adverse events in high risk patients in this study was greater than in high risk patients from other studies. The inclusion of the large amount of non-active controlled data from *Fergusson 2008* in the integrated safety data might have biased the overall results against TXA.

c. The most commonly reported adverse events in TXA treated patients were renal disorders (7.5% [n=290] versus 0.80% [n=10] in non-active controls). The majority of the renal disorders reported with TXA were renal dysfunction and renal failure. The reason for the increased incidence of renal disorders in TXA treated patients compared with non-active controls is unknown. There are no data in the submission comparing the effects of TXA and non-active control on renal function in patients undergoing cardiac surgery (for example, serum creatinine, creatinine clearance, serum electrolytes, urinalysis and renal ultrasound). The data from *Fergusson 2008* suggest that renal failure is more common in TXA treated patients with pre-existing renal disease. In contrast to the data in the safety summary, the *Cochrane Review [Henry 2008]* showed that TXA did not increase the risk of renal failure or renal dysfunction compared with non-active control (5 studies, only one of which was high risk). TXA is primarily renally cleared and the PK data show that downward dosage adjustments are indicated in patients with renal impairment. The non-clinical overview states that renal toxicity has been reported in rats following long-term oral administration of TXA with the lesion being described as "progressive accumulation of concrement in the renal pelvis, distal tubules and renal papilla with hyperplasia of the renal pelvic epithelium". Overall, the aetiology of the observed clinical renal toxicity associated with TXA is not understood and there appears to be risk of renal dysfunction/failure in patients with and without pre-existing renal disease undergoing cardiac surgery and treated with TXA.

d. Cardiac disorders were reported more frequently in TXA treated patients than in non-active controls (6.1% [n=236] versus 4.4% [n=55]). The most common cardiac disorder in TXA treated patients was cardiogenic shock which occurred in 2.9% of TXA treated patients (10.6% in high risk and 0.1% in low risk patients). The high incidence of cardiogenic shock in high risk TXA treated patients was driven primarily by the results from *Fergusson 2008* and similar patterns were seen with EACA and aprotinin. There were no reports of cardiogenic shock in non-active treatment controls. The reason for the increased risk of cardiogenic shock with TXA compared with non-active controls is unknown. The second most commonly reported cardiac disorder in TXA treated patients was myocardial infarction (2.1% versus 1.5% in non-active controls). There was no marked difference in the incidence of myocardial infarction between high and low risk TXA treated patients. All other cardiac disorders occurred infrequently in TXA treated patients.

e. CNS disorders were reported infrequently in TXA treated patients. The most commonly reported CNS disorder in TXA treated patients was stroke which occurred in 0.97% [n=38] of patients (overall). In non-active controls the overall incidence of stroke was 0.40% [n=5]. In both TXA treated patients and non-active controls the incidence of stroke was greater in high risk patients than in low risk patients. The underlying causes of the reported "stroke" were not provided. In *Fergusson 2008*, the risk of stroke in high risk patients was 3.7% for TXA compared with 2.9% for both aprotinin and EACA. In the *Cochrane Review [Henry 2008]* TXA non-statistically significantly increased the risk of stroke by 52% compared with non-active controls. There are no data in the submission on whether the small increase in stroke observed in TXA treated patients compared with non-active controls is due to thrombotic events. There were infrequent reports of pulmonary embolism and deep venous thrombosis in TXA treated patients with incidences being generally similar to non-active controls.

d. The overall incidence of death was similar in TXA treated patients (1.7% [n=64]) and non-active controls (1.8% [n=22]). The incidence of death in high risk patients was lower in TXA treated patients (3.5% [n=38]) than in non-active controls (6.8% [n=14]). Cardiac disorders were the most common causes of death in TXA treated patients and non-active controls followed by cerebrovascular disorders. In *Fergusson 2008*, aprotinin was associated with a statistically significant 2.47 fold increase in death due to "any" cardiac cause compared with TXA. In this study, death due to cardiogenic shock, myocardial infarction and right ventricular failure occurred more commonly in TXA treated patients than in non-active controls while the reverse relationship was seen for congestive heart failure. In *Fergusson 2008*, the incidence of death due to "any" non cardiac cause was similar in with TXA and aprotinin. In the *Cochrane Review [Henry 2008]*, TXA non-statistically significantly reduced the risk of death by 45% compared with non-active controls.

e. Head to head comparison of TXA and non-active controls in 7 large randomised, double-blind studies showed no significant differences between treatments in serious adverse events over a wide range of doses. The results from these individual studies provide reassurance about the safety of TXA in cardiac surgery.

f. On balance, it is considered that the submitted data have satisfactorily demonstrated the safety of TXA in low and high risk cardiac surgery procedures. The safety of the TXA is better in low risk compared with high risk cardiac surgery procedures. However, the interpretation of safety in high risk cardiac surgery procedures is complicated by the absence of a non-active control group in *Fergusson 2008*, the primary safety study in patients undergoing high risk procedures. Overall, it is considered that the risk-benefit for TXA in patients undergoing cardiac surgery is favourable. Nevertheless, there are risks associated with the use of TXA in cardiac surgery relating particularly to unexplained renal impairment in high risk procedures. Both cardiogenic shock and respiratory failure occurred more frequently in high risk TXA treated patients compared with non-active controls and the reasons for these observations are unknown. There was a small unfavourable imbalance in the risk of stroke associated with TXA compared with non-active controls in high risk cardiac surgery procedures and it is unknown whether this is due to an increase in cerebrovascular thromboembolic events. TXA was not associated with an increased risk of other thromboembolic adverse events such as myocardial infarction, pulmonary embolus and deep vein thrombosis. The overall incidence of death was similar in TXA treated patients and non-active controls, but the incidence of death in high risk patients was lower in TXA treated patients than in non-active controls.

Safety – Orthopaedic Surgery (Adults)

a. The summary safety information on 492 TXA treated patients undergoing knee arthroplasty and 261 TXA treated patients undergoing hip arthroplasty. Only 82 (16.7%) of the total number of TXA treated patients undergoing knee arthroplasty received total doses \geq 60 mg/kg (that is, the total proposed dose). No patients undergoing hip arthroplasty received total doses of \geq 60 mg/kg with the maximum total TXA dose in these patients being 30 mg/kg.

b. The overall incidence of adverse events in knee arthroplasty was 13.4% (n=66) in TXA treated patients compared with 7.6% (n=406) in non-active controls. The most common adverse event in knee arthroplasty was DVT and the majority of these adverse events came from one study [Tanaka 1991]. The incidence of DVT in the total data including that from *Tanaka 2001* was 11.8% (n=58) in TXA treated patients and 6.2% (n=25) in non-active controls. The overall incidence of adverse events in hip arthroplasty was lower than in knee arthroplasty with the incidence in TXA treated patients being 5.0% (n=13) compared with

2.9% (n=8) in non-active controls. The most common adverse event in hip arthroplasty was DVT with the incidence in TXA treated patients being 2.7% (n=7) compared with 1.5% (n=4) in non-active controls. In both the knee and hip surgery studies there were only a small number of adverse events other than DVT reported in TXA treated patients.

c. Only serious adverse events were reported in the knee and hip surgery studies and there is no further safety information on TXA in these studies. The available limited safety data suggest that TXA can be safely used in adult patients undergoing knee and hip arthroplasty. However, most of the data relate to total TXA doses lower than the 60 mg/kg dose being proposed for use in these surgical procedures.

Safety – Paediatric Surgery

The safety data on TXA in paediatric cardiac and spinal surgery are limited to brief, descriptive summaries reported in the individual studies. The nine individual paediatric surgical studies (six cardiac, three spinal) included a total of 307 TXA treated patients (247 had cardiac surgery and 60 had spinal surgery) given doses ranging from < 20 mg/kg to > 100 mg/kg. There were no significant safety issues reported with TXA in children and adolescents. The post marketing data on children < 12 years of age were limited. Despite the limitations of the safety data in children and adolescents it is considered that the safety reports in the individual show that safety is satisfactory in this patient group.

Clinical evaluator recommendations

a. It is recommended that TXA be approved "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".

b. It is recommended that the TXA dose for use in adult patients undergoing cardiac surgery be "after induction of anaesthesia but before skin incision a loading dose of 15 mg/kg, followed by an infusion of 4.5 mg/kg/hour for the duration of surgery of which 0.6 mg/kg may be added to the pump-line".

c. It is recommended that the TXA dose for use in adult patients undergoing total knee arthroplasty be

"15 mg/kg prior to release of the tourniquet followed by repeat bolus injection of 15 mg/kg at 8 hour intervals after the initial dose up to a maximum of 24 hours after surgery".

d. It is recommended that TXA for use in adult patients undergoing hip surgery be rejected on the grounds that the submitted data have failed to satisfactorily establish the efficacy of TXA for this indication.

e. It is recommended that TXA for use in paediatric patients undergoing cardiac surgery be rejected on the grounds that the submitted data have failed to satisfactorily establish the efficacy of TXA for this indication.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Data was provided to support a shelf life of 36 months when stored below 25°C, with the additional storage conditions, 'Protect from light' and 'Do not freeze'. Approval was recommended with respect to chemistry, quality control, sterility & endotoxin aspects. No bioavailability data were required since bioavailability can be considered 100% as the proposed products are to be administered intravenously. It was considered at the 131th meeting of the PSC that all quality issues had been resolved.

Nonclinical

- i) No new non-clinical data were submitted. An updated Non-clinical Overview and a literature search of published papers on tranexamic acid since 1987 were provided.
- ii) There were no non-clinical objections to the registration of an IV formulation of tranexamic acid for the once only, surgical indications in adults. Longer term use of tranexamic acid in conditions of general fibrinolysis may carry risks of ocular and/or renal toxicity and is therefore not recommended.
- iii) Given the pharmacological properties of tranexamic acid, even once only use via the IV route carries the risk of possible thromboembolic complications at therapeutic doses and possible CNS hyperexcitability or convulsions at supra-therapeutic IV doses (6-fold safety margin to the NOEL in dogs). Therefore, careful clinical monitoring of such adverse events is warranted.
- iv) The clinical data should be assessed for local tolerance issues (for example, injection/infusion site reactions) as the non-clinical local tolerance data for the IV route were limited.
- v) Approval of the paediatric indication (use during cardiac surgery in children > 2 years old) will have to rely on clinical data as no non-clinical data in juvenile animals have been submitted.

Clinical

- vi) The clinical aspects of the application consisted of a literature-based submission aimed at supporting the registration of Cyklokapron IV (TXA or tranexamic acid) for use in cardiac surgery in adults and children and orthopaedic surgery in adults (total knee arthroplasty and total hip arthroplasty). The sponsor undertook and provided individual meta-analyses of published studies supporting the use of TXA for each of the proposed indications. In addition, the sponsor undertook and provided a meta-analysis of published studies investigating the use of TXA in children and adolescents undergoing spinal surgery for scoliosis, an indication for which the sponsor is not seeking approval.
- vii) The submitted published studies included 72 adult cardiac surgery studies (5736 TXA treated patients), 25 adult orthopaedic studies (777 TXA treated patients – 495 involving knee & 282 involving hip), 6 paediatric cardiac surgery studies (247 TXA treated patients) and three paediatric spinal surgery studies (60 TXA treated patients). As well in the submission there were another 17 published studies which included clinical pharmacology studies. The clinical evaluator was of the opinion that the sponsor has satisfactorily identified all appropriate published studies and included all relevant studies in the meta-analyses and the submission. The sponsor used the same methodology in all the meta-analyses for all indications. The primary efficacy outcome in all meta-analyses was post-operative blood loss, measured as the mean difference in post-operative blood loss in mL between treatment groups with 95% CI. Variances between control groups tended to be larger than between treatment groups and so the usual procedure of standardizing the variances in effect between treatment groups in each study was not followed. The relative risk with 95% CI of patients in

the treatment group versus those in the control group of needing blood transfusion was chosen as the estimate of effect for the secondary efficacy outcome.

The clinical evaluator has recommended that TXA be approved “*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*”. The clinical evaluator has recommended rejection of the indications for use in adult patients undergoing hip surgery and for use in paediatric patients undergoing cardiac surgery on the grounds that the submitted data have failed to satisfactorily establish the efficacy of TXA for these indications.

Pharmacodynamics

- viii) The sponsor identified 11 studies which reported fibrinolytic parameters at various time points before, during and after surgery (10 cardiac surgery studies and one total knee arthroplasty study).
- ix) The clinical pharmacodynamic data primarily examined the *in vivo* effect of TXA on pro-thrombotic and fibrinolytic factors. In general, the cardiac surgery studies showed similar changes in anti-thrombin and anti-plasmin complexes in both TXA-treated and placebo-treated patients. In the one study involving total knee arthroplasty, PF 1 + 2 coagulation factor levels increased to a similar extent in both TXA & placebo groups. Overall, these limited clinical PD data suggest that TXA does not promote *in vivo* thrombus formation.
- x) In the cardiac surgery studies, D-dimer and FSP results suggest that TXA inhibits fibrinolysis compared with non-active controls. In the one study involving total knee arthroplasty patients, there was no evidence of inhibition of fibrinolysis in peripheral blood in either treatment group while there was evidence of such inhibition in wound blood in the TXA-treated patients compared with those on placebo.
- xi) It is not clear whether there were any PD studies conducted in children. The sponsor is asked to comment on this and whether there would be any expected PD differences, especially with respect to the degree of those differences, in children.

Pharmacokinetics

- xii) The approved Cyklokapron PI includes previously evaluated information on the pharmacokinetics of TXA. The drug is cleared predominantly unchanged by the kidneys with about 90% excretion of a 10 mg/kg IV dose at 24 hours. The calculated renal clearance is close to creatinine clearance, suggesting that TXA is eliminated by glomerular filtration. The drug does not bind to serum albumin and protein binding is about 3%, almost all to plasminogen.
- xiii) The current submission provided new PK information on TXA IV doses required to maintain satisfactory plasma concentrations during cardiac and orthopaedic surgery and on plasma concentrations in renal impairment. There were four studies in cardiac surgery, all in adults and one in adult patients undergoing total hip replacement (THR).
- xiv) *in vitro* data have previously shown that there 80% reduction in tissue plasminogen activity at TXA concentrations of 10 µg/mL and the half maximal inhibitory concentration (IC₅₀) of TXA in relation to plasmin induced platelet activation is 16 µg/mL. However, the TXA concentration needed to inhibit fibrinolysis *in vivo* is unknown and no direct association has been identified between blood loss and *in vivo* TXA plasma concentration. The TXA treatment regimens varied among the four PK cardiac surgery studies but common features were a pre-skin incision loading dose followed by maintenance infusion for the duration of surgery.

- xv) There were four studies in cardiac surgery. In the first, two dosage regimens were proposed, one for “typical” patients (39.5 mg/kg) and one for patients at high risk of bleeding (96 mg/kg). The sponsor proposes that only one dosage regimen, 33.6 mg/kg be used in both low and high risk cardiac surgery patients based on similar clinical efficacy. This same study showed that TXA is rapidly eliminated when given as a bolus in patients undergoing cardiac surgery. The second study assessed so-called “standard” and “new” dosage regimens but neither produced TXA concentrations consistently above 20 µg/mL. The authors of this study concluded that the dose of TXA needed to prevent fibrinolysis was unknown. In the remaining two studies, the results showed that in patients with renal impairment, dosage reductions are required.
- xvi) The data from the one study in THR patients showed that a total dose of 20 mg/kg was too low to maintain TXA plasma concentrations > 10 µg/mL. There were no PK data on the proposed total dose of 60 mg/kg in orthopaedic surgery patients.
- xvii) There were no PK data in patients with hepatic or cardiac impairment, nor any PK drug-drug interaction data involving IV TXA. Neither were there any PK studies in children or adolescents undergoing cardiac or spinal surgery nor any PK data grouped by sex or race.

Efficacy

Cardiac Surgery: TXA versus Placebo or no anti-fibrinolytic treatment

- xviii) The sponsor identified 53, published, prospective, randomised, controlled (versus placebo or no anti-fibrinolytic treatment) studies that examined the effects of TXA on post-operative blood loss &/or on the incidence of allogeneic blood transfusion in patients undergoing cardiac surgery. Of these 53 identified studies, 37 were included in meta-analyses of post-operative blood loss and 35 in meta-analyses of blood transfusion. In the 53 studies, a total of 2,112 adult patients were treated with total doses of TXA ranging from 20 mg/kg to above 100 mg/kg. About 70% underwent CABG, 16% valve replacement, 5% CABG + valve replacement and 9% repeat CABG, repeat valve replacement, atrio-septal repair or repair of aortic dissection or aneurysm.

Primary efficacy outcome – post-operative blood loss

- xix) Of the 53 identified studies, 37 reported post-operative blood loss as mean ± SD or mean and 95% CIs which allowed the results to be pooled.
- xx) In the “duplicates included” meta-analysis, TXA over the total dose range 5.5-250 mg/kg reduced post-operative blood loss by 226 mL, 95% CI [181, 271], compared with placebo. In the “duplicates removed” meta-analysis, TXA over the total dose range 12-188 mg/kg reduced post-operative blood loss by 240 mL, 95% CI [188, 292], compared with placebo. These results represent a saving in post-operative blood loss due to TXA compared with placebo of about 31%. Heterogeneity among the studies, for example, differences in TXA dose or administration regimen, surgical procedures and so on, was significant.
- xxi) Based on a 2 hour procedure, the proposed total TXA dose is 24 mg/kg and so the 20-50 mg/kg total dose sub-group is considered the most relevant in the meta-analysis. In this sub-group, the reduction in post-operative blood loss was 218 mL, 95% CI [173, 264], with heterogeneity not significant. The saving in post-operative blood loss is about 33%.
- xxii) The results from the Cochrane Review meta-analysis of 17 trials showed that, on average, TXA (n = 595) reduced post-operative blood loss by 262 mL, 95% CI [206,318], compared with control (n = 535). Heterogeneity amongst the 17 trials was

significant. In a sub-group meta-analysis, the 17 trials were divided by total TXA dose into 9 trials of < 2 g and 8 trials of 2-10 g. In both groups there were statistically significant reductions in post-operative blood loss, 251 mL and 272 mL, respectively, with the difference of about 20 mL not considered clinically significant. In the < 2 g group, heterogeneity was not statistically significant while for the 2-10 groups, it was statistically significant.

- xxiii) TXA was also shown to significantly reduce blood loss compared with control for each of the control group blood loss categories (the higher the blood loss in the control group, the higher the risk of the procedure). The volume of blood saved by TXA increased with increasing control group blood loss category. These results were confirmed for the TXA 20-50 mg/kg subgroup with the added advantage that heterogeneity was not significant, either according to control blood loss group category or overall. The control blood loss category meta-analysis showed that the dose of TXA need not be increased with high risk surgical procedures.
- xxiv) The effect of dosage regimens on blood loss was also examined in the 37 studies included in the post-operative blood loss meta-analysis. Pre-surgery dose + infusion \pm pump line dose regimens were the most commonly used and the mean total dose for these regimens, 22 mg/kg, was the one closest to the proposed TXA total dose of 24 mg/kg. In this group, the mean saving in blood loss, 262 mL, was clinically meaningful.

Secondary efficacy outcome – allogeneic blood transfusion

- xxv) The submission included a meta-analysis of 35 studies with allogeneic blood transfusion data from about 1300 patients treated with TXA and about the same number of controls who received packed red blood cells or whole blood.
- xxvi) The results showed that both TXA 12-150 mg/kg total dose and TXA 20-50 mg/kg total dose statistically significantly reduced the relative risk of blood transfusion by 29% and 28%, respectively. These results were also consistent with those in Cochrane Review.

Re-operation for uncontrolled bleeding

- xxvii) In a meta-analysis of 22 studies, there was a small, statistically significant risk difference of 3% in re-operation for uncontrolled bleeding in favour of TXA compared with placebo in high risk cardiac surgery. This represents a number needed to treat (NNT) of about 33 patients (that is, on average, TXA will abolish the need for re-operation for uncontrolled bleeding in one patient out of every 33 treated).

Cardiac Surgery: TXA versus active comparator

- xxviii) The submission included meta-analyses comparing the effects of TXA, aprotinin, ϵ -aminocaproic acid (EACA), desmopressin and dipyridamole on both post-operative blood loss and the risk of allogeneic blood transfusion. In a meta-analysis of 26 studies, the reduction in post-operative blood loss was 65 mL, 95% CI [34, 95] greater with aprotinin compared with TXA and in a meta-analysis of 22 studies, the risk of allogeneic blood transfusion was 13% greater with TXA compared with aprotinin. These differences were not considered clinically significant.

Total knee arthroplasty: TXA versus placebo or no anti-fibrinolytics

- xxix) The sponsor identified 16, prospective, randomized, controlled studies from the published literature involving 502 adult patients treated with TXA undergoing single TKA. There was also a meta-analysis of 15 studies with transfusion data.

Primary efficacy outcome – post-operative blood loss

- xxx) Of the 16 relevant studies, 11 were included in a meta-analysis of post-operative blood loss as the latter was reported as mean \pm SD or mean with 95% CI. The meta-analysis included 365 patients treated with TXA at a total dose ranging from 14 to 150 mg/kg administered by 4 different regimens and 390 control patients. The included studies were small with an average sample size of 30 patients.
- xxxii) The reductions in post-operative blood loss due to TXA were similar in the 20-50 mg/kg and > 100 mg/kg subgroups, being 345 and 359 mL, respectively. These results suggest that the dose of TXA proposed by the sponsor, 60 mg/kg total dose, should be able to significantly reduce post-operative blood loss.
- xxxiii) The submission also included a meta-analysis comparing TXA and control treatments by control blood loss categories of 300-600 mL and > 900 mL. In the first, TXA significantly reduced post-operative blood loss by 214 mL, 95% CI [155, 273], compared with control while in the > 900 mL category, TXA significantly reduced post-operative blood loss by 557 mL, 95% CI [367, 748]. Thus with similar mean doses, there were greater savings in the higher control blood loss group.

Secondary efficacy outcome – allogeneic blood transfusion

- xxxiv) The sponsor submitted a meta-analysis of 15 studies with transfusion data from patients treated with TXA (n = 487) or control (n = 514) who received packed red cells or whole blood.
- xxxv) The results showed that TXA at 14-150 mg/kg total dose significantly reduced the relative risk of receiving a blood transfusion by 64%, 95% CI [50, 75], compared with control, with the risk difference being in favour of TXA by 36%. The mean dose was 55 mg/kg, close to the proposed value of 60 mg/kg.

Total hip arthroplasty: TXA versus placebo or no anti-fibrinolytics

- xxxvi) The sponsor identified 12 studies involving the use of TXA in total hip arthroplasty. Of these 12 studies, the sponsor included 11 in a meta-analysis evaluating post-operative blood loss. Total patient numbers in each of the 11 studies ranged from about 40 to 100 and overall, the studies included 262 patients treated with TXA and 274 control patients.

Primary efficacy outcome – post-operative blood loss

- xxxvii) Overall, TXA 10-30 mg/kg statistically significantly reduced post-operative blood loss by 150 mL, 95% CI [101, 216], compared to control. The TXA 10-19 mg/kg subgroup reduced post-operative blood loss by 144 mL, 95% CI [80, 208] while the TXA 20-30 mg/kg subgroup reduced post-operative blood loss by 239 mL, 95% CI [60, 417]. The percentage blood saving due to TXA was 22.9% in the 10-19 mg/kg subgroup and 39.2% in the 20-30 mg/kg subgroup. Unfortunately, the TXA 20-30 mg/kg subgroup meta-analysis included only three studies and the reduction in mean blood loss was statistically significant in only two out of the three studies. In these two studies the mean reductions in blood loss were 146 mL in one study (result not considered clinically significant) and 381 mL (considered clinically significant). This latter study consisted only of 40 patients (20 patients in each of the TXA & control groups)
- xxxviii) Reductions in post-operative blood loss with TXA were greater in the control group blood loss categories 601-900 mL and > 900 mL compared with the 300-600 mL category.
- xxxix) No studies in the meta-analysis used total TXA doses similar to that proposed by the sponsor, that is, 60 mg/kg. In fact no studies in the submitted meta-analyses used a dose greater than 30 mg/kg.

Secondary efficacy outcome – allogeneic blood transfusion

- xxxix) The sponsor included 10 studies in a meta-analysis evaluating the effects of TXA compared with placebo on allogeneic blood transfusion requirements. Overall, TXA 10-30 mg/kg significantly reduced the risk of allogeneic blood transfusion by 40% compared with control. However, this parameter was statistically significant in only two out of the 10 trials.
- xl) The Cochrane Review included a meta-analysis of 6 orthopaedic surgery studies of which 4 involved total hip arthroplasty. The review concluded that TXA treatment was only marginally effective in reducing post-operative blood loss.

Paediatric Cardiac Surgery

- xli) The sponsor identified 6 cardiac surgery studies which assessed the effect of TXA on post-operative blood loss in children aged from 2 months to 15 years. The six studies included about 247 patients treated with TXA of whom 130 (52.6%) received doses in the range of 20-50 mg/kg.
- xlii) Of the six identified studies, the sponsor included three prospective, randomized, controlled, double-blind studies in a meta-analysis of post-operative blood loss, representing about 2/3 of the paediatric cardiac surgery patients. By age group, the reductions in post-operative blood loss due to TXA compared with control were: 14.0 mL/kg, 95% CI [12.6, 40.8] in the subgroup aged < 2 years; 10.7 mL/kg, 95% CI [4.3, 17.0] in the subgroup aged 2-4 years and 10.8 mL/kg, 95% CI [1.0, 20.6] in the > 4 years subgroup. As noted by the clinical evaluator, these results should be interpreted cautiously as the lowest age subgroup had only one study with nine patients.
- xliii) Of the six identified studies in paediatric cardiac surgery, there were three not included in the meta-analysis, one of which did not have a placebo arm and therefore was not considered further. In each of the other two studies there were comparable improvements in the amount of post-operative blood loss (approx. 7 mL/kg placebo-subtracted difference). However, in one of the studies, packed cell transfusion requirements were significantly greater in the TXA group versus the placebo group. In the opinion of the authors of this study, this lack of a transfusion sparing effect meant either that the drug was ineffective in small children (< 15 kg) or a higher dose was needed. Unfortunately, the report of this study was merely a conference abstract with several important details missing.
- xliv) Only the post-operative blood loss result for one of the three studies in the meta-analysis was statistically significant and this study used a dosage regimen of 40 mg/kg (actually two regimens, one 30 mg/kg and the other 40 mg/kg). There was also a TXA duplicates combined meta-analysis of post-operative blood loss in three studies which suggested that the optimal total dose was in the range 40-220 mg/kg.
- xlv) Because of the uncertainties over dose selection, the clinical evaluator thought that the examination of results from individual studies may be more informative and therefore chose 4 studies, the three prospective, randomized, double-blind, controlled studies in the meta-analysis and fourth, the study which did not show any transfusion sparing effect. Out of these 4, there was only one study which showed a significant reduction in post-operative blood loss and that involved children aged 2 months to 5 years and tested two different total dose regimens, that is to say, 30 mg/kg [comprised of 10 mg/kg pre-surgery, 10 mg/kg on CPB and 10 mg/kg after protamine] and 40 mg/kg [comprised of 20 mg/kg pre-surgery and 20 mg/kg after protamine]. Each regimen produced reductions in post-operative blood loss of the order of 40%. However, the regimens were different from that being proposed, that is to say, 20 mg/kg total dose

and the age of the patient population, 2 months to 5 years, was broader than that proposed, > 2 years.

Safety:

Cardiac Surgery in Adults

- xlvi) The submission included 5736 TXA treated patients of whom 2917 (51%) received TXA doses within the range 20-50 mg/kg, 697 (12.2%) within the range 5.5-19 mg/kg, 740 (12.9%) within the range 51-100 mg/kg and 1382 received doses > 100 mg/kg. The submission also included a safety summary which had pooled safety information on 3852 patients or 67% of the total.
- xlvi) The pooled safety population included 2797 low risk patients (mostly undergoing primary CABG, valve surgery or multiple procedures), 56% of who were treated with TXA at a total dose of 20-50 mg/kg and 8.6% of whom were treated with total doses > 100 mg/kg. The pooled safety summary also included 1055 high risk patients (mainly repeat or aortic surgery), 91% of whom were treated with TXA > 100 mg/kg as a single bolus at the start of surgery.
- xlvi) There were two studies (*Fergusson 2008* and *Murkin 1995*), which collected much more detailed safety data than did the other studies in the submission. The data from these two studies were considered separately from the data of the other studies in the dossier. The safety summary included only SAEs. In general, the published studies simply reported “adverse events”.
- xlix) The AE profiles of TXA, *aprotinin*, *EACA* and *non-active* control in cardiac surgery were compared in the safety summary. In low risk procedures, AEs occurred at similar rates in all four treatment groups. In high risk procedures⁷, there was a 3.1-fold increase in the risk of a patient experiencing an AE on TXA than on non-active control. The most commonly occurring AEs with TXA were, in order, *renal* (7.5 % TXA versus 0.8% non-active), *cardiac* (6.1% TXA versus 4.4% non-active), *respiratory, thoracic and mediastinal* (2.8% TXA versus 0.24% non-active), *death* (1.7% TXA versus 1.8% non-active) and *CNS* (1.4% versus 0.56% non-active). The Delegate notes that in the clinical evaluation the comparative rates for *death* are reported as TXA versus active. However, in the following text, the rate of 1.8% is quoted for the non-active arm.

Sponsor's comment:

The safety data is (sic) pooled from 43 studies representing a total of 5736 adult patients undergoing cardiac surgery and treated with TXA or an active comparator, TXA or a nonactive comparator or TXA or an active comparator or a nonactive comparator. Thus, the rates of death for tranexamic acid in the safety summary for adult cardiac surgery are compared with the rates of death of the active comparators (namely Aprotinin and Epsilon Aminocaproic Acid (EACA)) and the nonactive comparator.

- l) *Death* – The overall mortality rates were 1.7% (64/3852) TXA versus 1.8% (22/1247) non-active control. In high risk patients the rates were 3.6% (38/1055) TXA versus 6.8% (14/207) non-active, that is, almost half the risk on TXA. In low risk patients the mortality rates were similar, 0.9% (26/2797) TXA versus 0.8% (8/1040) non-active. The total, low risk and high risk mortality rates were all lower for TXA treated patients than for either aprotinin or EACA treated patients.

⁷ The marked difference in the rates of AEs in high risk patients between non-active control and the three active treatments (TXA, aprotinin & EACA) is driven mainly by the results of the two studies, *Fergusson 2008* & *Murkin 1995*. It was the observed higher risk of death in the *Fergusson* study in patients treated with aprotinin compared with either TXA or EACA that led to the worldwide marketing withdrawal of aprotinin. Unfortunately in the *Fergusson* study there was no non-active control group for comparison.

- li) *Cardiac disorders* – The incidence of cardiac AEs in low risk patients was lower on the three active treatments compared with non-active but higher than non-active in high risk patients. The most common AEs were cardiogenic shock with 2.9% (112/3852) TXA versus 0.0% (0/1247) non-active and MI with 2.1% (79/3852) TXA versus 1.5% (19/1247) non-active.
- lii) *Renal* – The majority of renal disorders in the three active treatment groups were renal dysfunction and renal failure. Renal disorders occurred much more frequently in patients undergoing high risk procedures than low risk procedures in all of the three active treatment groups. The rates of renal disorders in high risk patients were 22.7% (240/1055) TXA versus 3.4% (7/207) non-active, that is, at about 6.7 times the rate in the TXA group compared with the non-active control group. It may be of some consolation to observe that the rates were higher for aprotinin (7.7 times) and EACA (8.7 times). In the Cochrane Review, pooled data from 5 cardiac surgery studies showed that TXA did not increase the risk of renal failure or renal dysfunction compared with control.
- liii) *CNS* – The most commonly reported CNS disorder in patients in all four treatment groups was stroke. The rates of stroke were 0.18% TXA versus 0.19% non-active in low risk patients, 3.1% TXA versus 1.6% non-active control in high risk patients and 0.97% TXA versus 0.40% non-active, overall.
- liv) *Respiratory, Thoracic and Mediastinal Disorders* – For high risk patients the rate of these disorders was much higher on TXA treatment than on non-active control. The corresponding rates were 9.7% (n = 102) TXA versus 0.0% (n = 0) non-active. The most common “respiratory, thoracic and mediastinal disorder” System Organ Class (SOC) was respiratory failure which occurred only in high risk patients. There were 100 AEs of respiratory failure on TXA treatment compared with none in the non-active control group. Thus the 9.7% rate for this SOC in high risk patients was driven almost exclusively by respiratory failure. It may again be of some consolation to observe that the rates of respiratory failure were even higher on aprotinin and on EACA.
- lv) *Vascular disorders* – There were only small numbers of reports of either DVT or DVT &/or PE in all four treatment groups.
- lvi) *Summary* – The safety summary provided no information on discontinuations, clinical laboratory results nor vital sign changes. While continuous ECG monitoring would have been part of the standard intra- and post-operative care, there was no systematic reporting of ECG changes. As noted by the clinical evaluator, the major problem with the safety summary is the imbalance in the rates of SAEs between the TXA treated groups and the non-active treated groups, particularly in patients undergoing high risk cardiac surgical procedures. This was largely due to the inclusion of the data from the *Fergusson* study. Most other submitted studies were primarily designed to investigate efficacy. Also interpretation of data is complicated by the absence of a non-active control group in the *Fergusson* study. Reassuringly, comparative safety data from the larger cardiac surgery studies does not suggest any relationship between dose and rate of SAEs.

Orthopaedic Surgery in adults

- lvii) The safety summary included information on 492 TXA treated patients and 406 non-active controls who underwent knee arthroplasty and 261 TXA treated patients and 273 non-active controls who underwent hip arthroplasty.
- lviii) Of the 492 TXA treated patients who underwent knee arthroplasty, 284 (57.7%) received total doses in the range 20-50 mg, 126 (25.6%) received total doses < 20 mg/kg and 82 (16.7%) received total doses > 100 mg/kg.

- lix) Of the 261 TXA treated patients who underwent hip arthroplasty, 182 (69.7%) received total doses < 20 mg/kg and 79 (30.3%) received total doses 20-50 mg/kg. At this point it is worth observing that, although the proposed total TXA dose for adult orthopaedic surgery is 60 mg/kg, there were no patients in the submitted studies who were treated with a total dose in the range 50-100 mg/kg. In fact the highest dose tested was 30 mg/kg in *Eckback 2000*.
- lx) The submitted safety data in orthopaedic surgery in adults showed an increased risk of AEs in TXA treated patients compared with non-active controls in both knee and hip surgery. The increased risk was predominantly due to DVT AEs. All other AEs occurred infrequently.

Paediatric Cardiac Surgery

- lxi) No summary safety data from the paediatric cardiac surgery studies were submitted. The 6 studies included 247 TXA treated patients with total doses ranging from < 20 mg/kg to > 100 mg/kg. There was limited reporting of SAEs. In fact in the brief commentaries summarised by the clinical evaluator, there appear to have been no specific AEs acknowledged at all. In three of the studies, it was reported that there were no AEs attributable to TXA.

Post-marketing data

- lxii) During the period 01 Feb 2000 to 31 July 2008, there were 6 fatal cases (26 events) occurring in 790 patient-years of treatment with TXA IV, giving a rate of 0.8%. The sponsor confirmed that the most common events associated with a fatal outcome were renal & urinary disorders (2) and PE (2). There were 21 medically confirmed fatal cases.
Over the same period, TXA IV was associated with 24 serious (non-fatal) cases involving 41 serious adverse events in 790 patient-years of treatment, giving an incidence rate of 3.0%. The most common SAEs were vascular disorders (nine, which included 3 DVTs), ineffective drug (2) and chylothorax (2). There was one case of anaphylaxis and one of hypersensitivity. The Delegate also notes one case of facial oedema. The sponsor confirmed that some cases of facial oedema had features consistent with a hypersensitivity reaction including one case that also reported hypersensitivity as an event. Other features included drug eruption and eosinophilia. Most cases reported multiple suspect medications.
- lxiii) TXA IV was also associated with 9 cases involving 16 non-serious AEs in 790 patient-years of treatment, giving an incidence rate of 1.1%.
- lxiv) Overall, there appeared to be no specific signal arising from the post-marketing data.

Risk-Benefit Analysis

- lxv) *Efficacy in adult cardiac surgery* – The Delegate would agree that the efficacy for this indication has been established. The data from the TXA 20-50 mg/kg total dose subgroup is the most relevant as it includes the proposed dosage regimen likely to be used. TXA 20-50 mg/kg reduced post-operative blood loss by a mean value of 218 mL which was statistically significant and considered to be clinically significant. The same dosage regimen was also shown to reduce post-operative blood loss by increasing amounts with increasing control group blood loss amounts, the latter being a surrogate for increasing risk. There was also a significant reduction in the risk of blood transfusion with this dosage regimen. The Delegate also agrees with the clinical evaluator that, on the basis of the results of the meta-analysis grouped by control group blood group loss, there is no reason to modify the TXA treatment regimen for different types of cardiac surgery.
- lxvi) *Safety in adult cardiac surgery* – The Delegate would agree with the clinical

evaluator that the submitted data have satisfactorily demonstrated the safety of TXA both in low and high risk cardiac surgery procedures. The PI will have to adequately address the issues of unexplained renal impairment in high risk procedures and increased rates of cardiogenic shock and respiratory failure.

lxvii) Efficacy in total knee arthroplasty – In TKA, the sponsor is proposing a maximum total TXA dose of 60 mg/kg (made up of an 8 hourly repeat bolus regimen for a maximum of 24 hours). The overall results for the meta-analysis of post-operative blood loss showed that TXA (14-150 mg/kg) statistically significantly reduced blood loss by 331 mL. The TXA 20-50 mg/kg subgroup achieved a statistically significant reduction in post-operative blood loss of 345 mL with a mean saving in blood loss due to TXA of 43.9%. For the subgroup receiving TXA total dose > 100 mg, the corresponding figures were 359 mL and 42.6%. There were no patients who received total doses in the range 50-100 mg/kg. The reductions in post-operative blood loss in the 20-50 mg/kg and > 100 mg/kg subgroups are clinically meaningful and there was no significant difference between the results. That is to say, no dose response was observed between these two groups. The risk of blood transfusion was also significantly reduced by TXA compared with placebo. The Delegate agrees with the clinical evaluator that the efficacy for this indication employing the proposed dosage regimen has been established.

lxviii) Safety in total knee arthroplasty – There was almost twice the risk of DVT in TXA patients compared with non-active controls. This will have to be adequately addressed in the PI. Apart from DVT, there were only a small number of AEs reported in TXA treated patients. The Delegate would agree that safety has been adequately demonstrated.

lxix) Efficacy in total hip arthroplasty – The reasons for the clinical evaluator's rejection of the indication for total hip arthroplasty are set out clearly in the clinical evaluation. In the overall meta-analysis, TXA 10-30 mg/kg reduced post-operative blood loss by 159 mL, 95% CI [101, 206] compared with control. While statistically significant, this result was regarded as of doubtful clinical significance. The Delegate would question the latter view. The mean blood losses in the control groups ranged from about 400 mL to 1000 mL. The average of those means is a little over 600 mL. A reduction of 159 mL in comparison with the latter is not clinically insignificant. In the 20-30 mg/kg subgroup, the reduction in blood loss was 239 mL compared with control. This result was statistically significant and is clearly clinically significant. However, the Delegate, like the clinical evaluator, is concerned by the fact that in the higher dose subgroup there were only three studies and of these only one gave a statistically insignificant result. Post-operative blood loss according to control group blood loss categories suggested that TXA is likely to be more effective in patients at risk of higher blood loss. The results for the reduction in risk of allogeneic blood transfusion were also consistent with the primary results. However, again the evaluator was concerned by the fact that the results were only statistically significant for two out of 10 studies and the Delegate shares this concern.

lxx) There are 8 studies, all of good quality, which used total doses of 10-19 mg/kg. For all except the first study [*Garnetti 2004*], that is, for 7 studies, there were consistent reductions in mean blood loss in the TXA group compared with the control group. Of those 7 studies, 5 produced statistically significant results. For the 8 studies pooled, the reduction in mean blood loss was 144 mL, statistically significant and the Delegate would argue of possible clinical significance. In the view of the Delegate a

real problem occurs when one looks at the higher dose group, the so-called 20-50 mg/kg group. The latter classification is misleading. Firstly there were only three studies in this group, with two studies employing a total dose of 20 mg/kg and one study a total dose of 30 mg/kg. The first two studies using 20 mg/kg should, arguably, have been classified in the lower dose group of 8. After all, two of the latter group employed dosage regimens of 19 mg/kg and three of them 15 mg/kg. Thus there was only study which examined a total dose greater than 20 mg/kg. Unfortunately this study which used 30 mg/kg was rated as quality level 5 which stands in stark contrast to the quality assessments of all the other studies in the two tables. Unfortunately also this same study produced the largest mean reduction in blood loss of 381 mL, 95% CI [170.2, 591.8]. Thus, given the very low quality of the evidence (as assessed by the sponsor), how reliably can one make an assessment of this study? There is evidence of a dose response. The results from pooling in the following groups: 10-15 mg/kg (6 studies), 19-20 mg/kg (4 studies) and 30 mg/kg (1 study) provided in the sponsor's pre-ACPM response below (including a table on page 94).

Reductions in mean blood loss rise with the control group blood loss category. There are consistent reductions in risk of allogeneic blood transfusion, except for the *Garnetti 2004* study. However, only two out of 10 studies produced statistically significant results.

The major problem with the evidence is that there are simply no studies which have used total doses anything like 60 mg/kg total dose. The closest, 30 mg/kg, was the dose in the *Eckback 2000* study. In response to the clinical evaluation report, the sponsor argued that the mechanism of action and PD properties of tranexamic acid in the reduction of peri- and post-operative blood loss and the need for blood transfusion is common to both total knee and hip arthroplasty. The Delegate would agree with this proposition.

The sponsor's analysis also demonstrated that the efficacy of tranexamic acid in blood sparing is not dependent on the type of surgery but the maintenance of sufficient plasma levels of drug to achieve fibrinolysis during surgery and for a sufficient period post surgery. This argument has merit. For example, it was shown that on the basis of the results grouped by control group blood loss (as a surrogate for risk of bleeding), there was no reason to modify the TXA treatment regimen for different types of adult cardiac surgery.

The sponsor noted that the dosage regimens proposed are not only based upon efficacy studies conducted but also upon the PK modelling to ensure plasma levels are maintained at or above the IC_{50} for anti-fibrinolysis. The sponsor therefore contended that the dosage regimen used for knee surgery would provide sufficient anti-fibrinolytic cover in hip surgery. While this is true up to a point, PK modelling is usually done to inform appropriate dose selection in studies to be undertaken. This does not appear to have been done. There were no PK data on the proposed total dose of 60 mg/kg in orthopaedic patients.

The sponsor also took issue with the clinical evaluator's interpretation of "clinical significance" and that not enough weight was given to statistical significance. While the sponsor's argument does have some merit as has already been pointed out, it is clear that both statistical and clinical significance must be taken into account. Firstly, with post-operative blood loss, one is dealing with a parameter which displays considerable variation from individual to individual. One only has to look at the

standard deviation values in comparison with the mean values. Secondly, all of that variability is ironed out, as it were, by consideration of the mean and finally, one is pooling results across different studies. One cannot rely totally on the statistical significance of a result. Clinical significance must also be very carefully weighed up.

The sponsor is correct to point out that there were increasing reductions in blood loss with increase in the control group blood loss category. The sponsor argues, with some merit, that the clinical evaluator focused on the efficacy data categorised by TXA dosage rather than the blood loss of untreated patients. However, the clinical evaluator did acknowledge that, for patients undergoing total hip arthroplasty, the reduction in post-operative blood loss achieved by TXA when analysed according to control group blood loss category suggests that TXA is likely to be more effective in patients at higher risk of blood loss (> 600 mL) than patients at lower risk (≤ 600 mL).

In summary, there is evidence of a dose response in hip arthroplasty and there is evidence that TXA is likely to be more effective in patients at higher risk of blood loss. There is no fundamental reason to believe that TXA should act differently in hip arthroplasty from the way it acts in knee arthroplasty. The Delegate would be inclined to recommend approval for use in hip surgery, perhaps along the lines of a tightened indication, namely for patients at risk of large blood losses (> 600 mL) including revision of total hip arthroplasty or associated with serious cardiovascular and respiratory co-morbidities, were it not for the fact that the evidence from the one study which did use a dosage regimen approaching the one proposed, namely the study *Eckback 2000*, was judged to be of poor quality. To base a recommendation which will involve high volume of usage in terms of patient numbers on such evidence does not strike the Delegate as very good science. The sponsor was asked by the Delegate to give a clear account of why the evidence from *Eckback 2000* was rated of quality level 5 in their Pre-ACPM response (see below). Also there are no data on how many cases there were involving “revision of total hip arthroplasty or associated with serious cardiovascular and respiratory co-morbidities”.

Thus the Delegate was inclined, at this stage, to reject the proposed indication of total hip arthroplasty on the grounds that efficacy has not been satisfactorily established. However, the Delegate would seek the advice of the ACPM on this particular issue.

lxxi) Safety in total hip arthroplasty – The most common AE in hip arthroplasty was DVT with an incidence in TXA treated patients of 2.7% versus 1.5% in non-active controls. This rate was much less than the corresponding rate for the patients undergoing knee arthroplasty but, on the other hand, the doses used in hip arthroplasty were lower than those for knee arthroplasty. The Delegate would agree that the evidence for safety in hip surgery has been satisfactorily established at the doses actually used.

lxxii) Efficacy in paediatric cardiac surgery

The proposed dosage of TXA in children & adolescents undergoing cardiac surgery is 10 mg/kg before surgery + 10 mg/kg during surgery, that is, a total dose of 20 mg/kg. In the lowest age subgroup, < 2 years, there was only one study (Reid 1995) involving nine patients and a dose of 220 mg/kg. This study was assessed as providing evidence of quality level 5. It is therefore clear that there is not enough evidence in terms of patient numbers for this particular age group. As a result, the sponsor is not seeking an indication in this age group.

The clinical evaluator is correct to advise caution when interpreting the result of the meta-analysis which consisted of only three studies, one of which was a conference abstract in only 9 patients. In view of the methodological concerns associated with

the meta-analysis, the results from individual studies were evaluated separately.

The analyses for duplicates included and duplicates combined, respectively, show that there were consistent reductions in mean blood loss on TXA compared with control, admittedly not all statistically significant. The Delegate is of the opinion that the results of the *Reid 1995* study should be discounted (low quality evidence, very small patient numbers and very large dose in comparison with doses in other studies and with the dose proposed). For the remaining studies, there is also evidence of somewhat less variability in the mean blood loss on TXA compared with that on control, with smaller standard deviations.

The clinical evaluator identified a number of key studies [*Chauhan 2004*, *Zonis 1996 & Reid 1997*, *NB latter study different from Reid 1995*] and a supportive study [*Shore-Lesserson 2002*]. *Zonis 1996* did not show efficacy of TXA in acyanotic patients. Otherwise, there were consistent reductions in mean blood loss but not all statistically significant. Also the *Reid 1997* and the *Shore-Levensson 2002* clearly included children less than 2 years of age but what proportion is unknown. As noted by the clinical evaluator, the evidence which is most persuasive and most relevant is that from *Chauhan 2004*. However, the dosage regimens used, 30 mg/kg and 40 mg/kg are somewhat higher than that proposed.

This is a difficult recommendation to make. There does appear to be consistent evidence of efficacy but based on small studies and from a meta-analysis with methodological problems. Evidence in support of the paediatric indication cannot easily be carried across from the adult population, because the conditions being treated are different. There is again the problem of the precise dose which ought to be recommended. Of reassurance is that such paediatric cardiac surgery is only carried out in large tertiary referral centres, invariably teaching hospitals. Also of reassurance is that no specific safety concerns or signals arose from individual study reports (see point lxxxiv) below. On balance, the Delegate is, at this stage, just leaning in favour of the recommendation of the clinical evaluator, namely rejection. However, once again, the Delegate will be seeking specific advice on the issue from the ACPM.

lxxiii) *Safety in paediatric cardiac surgery* – The safety data are limited to brief descriptive summaries for each study. However, the comments from the studies would indicate no specific safety signals. The Delegate agrees that the safety of TXA in paediatric cardiac surgery has been satisfactorily established.

lxxiv) The Delegate proposed to **approve** the submission by Pfizer Australia to register the new dosage form, tranexamic acid 100 mg/mL solution for injection, for the following indication, as amended by the clinical evaluator and as slightly amended by the Delegate:

“for the reduction of peri- and post-operative blood loss and lessening of the need for blood transfusion in adult patients undergoing cardiac surgery or total knee arthroplasty” on the grounds that the efficacy and safety for this indication have been satisfactorily established.

The Delegate proposed to **reject** the indications proposed by the sponsor “for use in adult patients undergoing total hip arthroplasty” and “for paediatric patients undergoing cardiac surgery” on the grounds that the efficacy for neither of these indications has been established.

lxxv) The sponsor was asked to address the following issues in their Pre-ACPM response:

- The Delegate requested the results for total hip arthroplasty when the studies are pooled in the following groups by total dose: 10-15 mg/kg (6 studies), 19-20 mg (4 studies) and 30 mg/kg (1 study).

Sponsor's comment:

Results of blood loss pooled by total dose are summarised in the table below.

Total Dose	Blood Loss (All studies)	Blood Loss (corrected for heterogeneity)
10 – 15 mg/kg	125 mL	178 mL
19 -20 mg/kg	181 mL	181 mL
>20 mg/kg	381 mL	381 mL

These results are further confirmation that the submitted studies in hip surgery could be interpreted as revealing a dose response relationship. Clinically significant weighted blood loss reduction was reported when a total dose of 30 mg/kg was used but blood loss reduction was not clinically significant for the 10-15 mg/kg or the 19-20 mg/kg total dose. Studies either with a trend to reduction that did not reach clinical significance were in fact the studies using inadequate doses (a single dose of 10 mg/kg without repeat doses or infusion). At the higher doses, such as the proposed dosage regimen (> 20 mg/kg), the reduction in blood loss is clinically significant. This hypothesis is further supported in the submitted pharmacokinetic studies clearly demonstrating that a single bolus dose is unable to maintain the duration of activity required to provide efficacy.

ACPM's advice is requested on the following issues

- a) Does the ACPM agree that the evidence for the efficacy of tranexamic acid in total hip arthroplasty is inconclusive, particularly with regard to the precise effective dose which should be recommended?

Sponsor's comment:

The proposed regimen for hips is the same dosage regimen recommended for approval for knee surgery. The dosage regimens proposed are based upon meta-analyses of published efficacy studies and also on the pharmacokinetic modelling to ensure plasma levels are maintained at or above the IC₅₀ for antifibrinolysis. The Delegate's Overview agrees that this reasoning is not without merit but argues that there should be PK data for the proposed dose. While Pfizer appreciates that PK modelling provides additional information on dose selection, where the proposed regimen is the same as the dosage regimen recommended for approval and where the haemostatic responses for the different clinical settings are similar, Pfizer contends that separate PK data should not be required. As discussed in Pfizer's response to the clinical evaluation report, the proposed dosing regimen (15mg/kg followed by 15mg/kg every 8 hours to a maximum of 24 hours) for total hip arthroplasty is justified on the basis that the mechanism of action and pharmacodynamic properties of tranexamic acid in the reduction of peri- and post-operative blood loss and the need for blood transfusion is common to total knee and hip arthroplasty. The haemostatic responses to hip and knee surgery are very similar if not identical. There are no plausible scientific reasons to suggest hip surgery would not respond to anti-fibrinolytic therapy. The proposed dosage regimen results in a maximum total dose of 60 mg/kg given over 24 hours. The safety of total doses of 60 mg/kg has been demonstrated in knee surgery studies where patients received total doses as high as 135 - 150 mg/kg over 12 hours. These surgical patients are renowned for being most

susceptible to post surgical thrombosis and there was no statistically significant increased risk of thromboses in the tranexamic acid (TXA) patient group relative to controls.

- b) The Delegate seeks some specific comment as to the validity of the evidence from the study Ekback 2000. The latter was assessed as low quality but on the other hand demonstrated efficacy which was both statistically and clinically significant and was the only study to use a dose which approached the recommended dose.

Sponsor's comment:

*This response also addresses the following issue raised in the Delegate's Overview, **Would the sponsor give a clear account of why the evidence from Ekback 2000 was rated of quality 5?***

The Ekback 2000 study was Graded 5 because there was no specific statement of ethics oversight though it is unlikely that the study was conducted without ethics oversight given the year of publication, the location of the clinical study (Sweden) and publication in a peer review journal (Anesthesia Analog). At the time this study was published it was not routine for journals to insist on comments concerning the ethics of the studies reported. The Ekback 2000 study is a prospective, randomised double-blinded placebo-controlled study of good design quality and thus the validity of the results are not in question.

- c) Would the ACPM agree with the sponsor's clinical expert that the clinical evaluator has focused on efficacy data categorised by the dosage of tranexamic acid rather than the blood loss of untreated patients? It seems that the recommendation for approval or not could turn on the answer to this question.

Sponsor's comment:

The choice of blood loss categories was validated by the regression analysis showing blood loss category to be the best predictor of response to therapy when compared to dose or dose regimen. As this is a literature based submission it was necessary to group studies without complete knowledge of the surgical risk and across similar regimens and doses. For this reason analyses were conducted by assigned blood loss categories based on blood loss in the control groups, using this as a measure of surgical risk and repeating analyses across total dose and by regimen. There were not sufficient studies to break down the analyses by total dose and regime. Pfizer recognise that the choice of blood loss in the control group as a means of categorizing studies is unusual however, as this is a literature based submission where Pfizer do not have control over the design and conduct of the studies, some manner of categorizing the risks to patients due to different hospital procedures, surgical procedures and post operative patient management was required to address the heterogeneity identified by the overall analysis. As iterated above, blood loss categorization was the best predictor of response to therapy compared to dose or dose regimen.

- d) Are there grounds for a tightened indication in total hip arthroplasty, along the lines suggested by the clinical expert, namely for patients at risk of large blood loss (> 600 mL) including revision of total hip arthroplasty or associated with serious cardiovascular and respiratory co-morbidities? What is the sponsor's view of a tightened indication in total hip arthroplasty (along the lines suggested by the clinical expert, namely for patients at risk of large blood loss (> 600 mL) including revision of total hip arthroplasty or associated with serious cardiovascular and respiratory co-morbidities (especially taking into account the exclusion criteria for the relevant trials).

Sponsor's comments:

Pfizer believes that important clinical application of tranexamic acid for all patients undergoing hip surgery has been demonstrated in the submitted data. Tranexamic acid is

contraindicated in patients with a risk or history of coagulopathy complications. This is aligned with the exclusion criteria for the relevant trials. It is important to note that it is only two of the eleven studies in hips surgery that excluded patients with serious cardiovascular co-morbidities and one study in knee surgery that excluded patients with respiratory co-morbidity. Safety data from published literature did not indicate increased cardiovascular or respiratory risks in orthopaedic patients. Cyklokapron via the SAS scheme has been used in orthopaedic surgery. For the doses proposed, tranexamic acid is only given over a short period of time and in the environment of the operating theatre. Monitoring of cardiovascular and other systems during the surgical procedure and immediately after is intense. Even with this degree of monitoring, both Pfizer and the TGA have not noted any increase in the rates of spontaneously reported adverse events or reactions to tranexamic acid in that period.

- e) Does the ACPM agree that the evidence for the efficacy of tranexamic acid in paediatric cardiac surgery is inconclusive, again particularly with regard to the precise effective dose which should be recommended?
- f) Is the indication for tranexamic acid approvable in acyanotic paediatric cardiac surgery patients? What is the sponsor's view of an indication in paediatric surgery limited to cyanotic patient?

Sponsor's comment:

Pfizer does not believe that the indication should be restricted to cyanotic patient. Data presented in this application indicate that tranexamic acid is of clinical benefit for all paediatric cardiac surgery.

The coagulation system of a full term healthy infant reaches adult level at 6 months. Infants with congenital heart disease (CHD) are known to be associated with coagulation abnormalities, including platelet abnormalities and fibrinolysis. Platelet dysfunction and fibrinolysis are causes of increased postoperative blood loss because of pre-existing altered platelet function and enhanced fibrinolysis is worsened by cardiopulmonary bypass (CPB). (Jaggers et al, 2010). An infant's blood volume is much smaller than that of the prime in the CPB circuit, haemodilution alone produces impaired haemostasis related to dilutional effects and compounded by the immaturity of the neonatal immune system. New born plasma has 30% –70% lower levels of both procoagulant and anticoagulant proteins than adults. In addition, several neonatal coagulation proteins, such as plasminogen and fibrinogen, are structurally different to the adult forms. (Eaton et al 2008). While Levin et al indicate that there are measurable differences in fibrinolysis between cyanotic and acyanotic paediatric cardiac patients, Williams et al 1998 demonstrated that post operative blood loss increases inversely to the age and weight of the child with infants of 1 month of less and children weighing 10 kg or less at greatest risk. Comparative studies of tranexamic acid versus active comparators or placebos in paediatric heart surgery submitted with this application comprise mostly prospective, randomised, controlled trials. The results of the studies submitted with this application are summarised in the table below (Eaton et al 2008).

Study	N	Age	Bleed	Trans	Other	Load (mg/kg)	Infusion (mg/kg)	Prime (mg/kg)
Zonis (1996)	82	1 d–14 yr	+/- ^b	+/- ^b		50	0	0
Reid (1997)	41	6 m–12 yr	+	-	CT(+), PV (-)	100	10	100
Levin (2000)	56	1 d–16 y	-	-		50	0	0
Chauhan (2003)	120	2 m–14 yr	+	+	CT;PV (+)	10 ^c	0	10
Chauhan (2004)	150	2 m–15 yr	-	-	RE(-)	50	0	0
			+	+	RE(+)	10	1	0
			+	+	RE(+)	10 ^c	0	0
			+	+	RE(+)	20 ^c	0	0
Chauhan (2004 ^a)	100	2 m–14yr	+	+	CT;RE(+)	10 ^c	0	10
Bulutcu (2005)	50	2 m–9 yr	+	+	CT (+)	100 ^c	0	100

D:day(s); m: month(s); yr: year(s); Bleed: blood loss at 24 h; Trans: transfusion of red blood cells and/or products; +: significant benefit vs control; -: No benefit. Other: Time required for chest closure (CT), Reexploration for bleeding (RE), Postoperative ventilation time (PV), ^a: This was a three-group study: EACA, TXA, placebo; results shown as each drug vs placebo. ^b: Significant only in *post hoc* cyanotic sub-group. ^c: dose was repeated after weaning from CPB

All studies other than the Zonis (1996) and Levin studies enrolled cyanotic patients exclusively. Six studies showed efficacy of antifibrinolytic treatment in decreasing bleeding and transfusion. Twenty-four hour blood loss was decreased 11%–44% and treated patients received 20%–50% less blood than controls. In addition, sternal closure times were reduced 6–25 min and re-exploration rates were improved by 50%–100% with antifibrinolytic therapy. The benefit of antifibrinolytic treatment is less clear in reoperations.

Pfizer believes that as with adult patients, the best results were achieved by a dosage regimen comprising a pre-surgery dose followed by a repeat dose so that plasma levels in the antifibrinolytic range were maintained during surgery. Thus, the lack of benefit in the acyanotic patient in the Zonis et al 1996 and the Levin et al studies is not evidence of the lack of benefit in the acyanotic patients rather it is because a suboptimal dose was used. The Chauhan et al. 2004 study is confirmation of this opinion.

- g) If the product were to be recommended for use in either of the indications of total hip arthroplasty or paediatric cardiac surgery, would the ACPM agree with the Delegate that the problems in determining the precise effective dose in each case would have to be openly and adequately discussed in the PI? That is to say, there would at least have to be some discussion of the range of evidence in the dossier.

The ACPM (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents recommended approval of the submission from Pfizer Australia Pty Ltd to register a new formulation and new indication, Tranexamic acid (Cyklokapron) solutions for injection 100mg/ml, for the indication:

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cyklokapron solution for injection ampoules containing tranexamic acid 500 mg/5mL and 1000 mg/10 mL, indicated for:

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

With the following special condition:

1. During the sponsor's routine biannual aggregate safety review of Cyklokapron, cases from the paediatric population (defined by the reporter as a patient with an age <18 years or described by the reporter as newborn, neonate, infant, child, adolescent or teenager) will be extracted for a separate review and analysis to ensure all potential or actual safety issues or risks associated with this sub-population will be identified.

Nonclinical and Clinical References

Nonclinical references

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Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

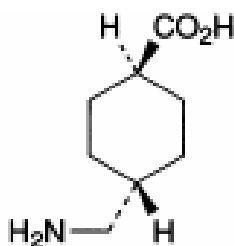
CYKLOKAPRON

NAME OF THE MEDICINE

Tranexamic acid (CAS 1197-18-8)

Chemical name: trans-4-aminomethylcyclohexane-carboxylic acid. The empirical formula of tranexamic acid is $C_8H_{15}NO_2$ and its molecular weight is 157.2.

The chemical structure of tranexamic acid is:



DESCRIPTION

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.

Each CYKLOKAPRON tablet contains 500 mg of tranexamic acid as well as the following inactive ingredients: cellulose-microcrystalline, talc-purified, magnesium stearate, colloidal anhydrous silica, povidone, hydroxypropylcellulose, titanium dioxide, macrogol 8000, vanillin and the proprietary ingredient, Eudragit E100 (ID Number 1753).

Each 5 mL ampoule of CYKLOKAPRON solution for injection contains 500 mg tranexamic acid and 5 mL Water for Injections as the inactive ingredient.

Each 10 mL ampoule of CYKLOKAPRON solution for injection contains 1000 mg tranexamic acid and 10 mL Water for Injections as the inactive ingredient.

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

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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.

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.

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.

Use in Special Populations

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.

Patients with 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 **DOSAGE AND 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 **DOSAGE AND ADMINISTRATION**).

Paediatric population

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, who have normal renal function. Dose reduction is recommended in children ≥ 2 years old who are mildly or moderately renally impaired. Tranexamic acid is not recommended in children ≥ 2 years old who are severely impaired (see **CLINICAL TRIALS, PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

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 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. This gives fibrinolytic cover for a maximum of 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 fibrinolytic cover for a maximum for 24 hours when the main blood loss occurs. There are no data to support the use of tranexamic acid beyond 24 hours.

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 IC_{50} 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 μ 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 **Pharmacokinetics** section). There were no studies in the meta-analysis that used tranexamic acid at the recommended total dose of 60 mg/kg. 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 1). 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.

Table 1: Summary of results for the relevant clinical studies, in paediatric cardiac surgery									
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 1).

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 **PRECAUTIONS, DOSAGE AND ADMINISTRATION, Paediatrics**).

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.

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.

PRECAUTIONS

The dose of tranexamic acid should be reduced in patients with renal impairment because of the risk of accumulation (see **DOSAGE AND ADMINISTRATION** section). 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 infusion for a bolus or loading dose is 50 mg/min. To administer 50 mg/min to the patient via an infusion, 0.5 mL/min of undiluted Cyklokapron solution for injection (100 mg/mL) should be administered by slow intravenous injection. To administer 50 mg/min to the patient, 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.

For adult cardiac surgery, a bolus 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 **DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS, Postmarketing Report**).

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]).

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

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

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

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

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

Patients with disseminated intravascular coagulation (DIC) who require treatment with 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.

Effects on ability to drive and use machines

Tranexamic acid may cause dizziness and therefore may influence the ability to drive or use machines.

Use in pregnancy

Australian Pregnancy Categorisation 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.

Carcinogenicity, Genotoxicity and Effects on fertility

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.

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.

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 Paediatric Population

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

Clinical experience in the paediatric population < 2 years old is limited and tranexamic acid should only be used if the benefit outweighs the risk. The benefit of an antifibrinolytic drug in neonates and infants aged < 2 year old is questionable, as bleeding under 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.

Dose reduction is recommended in children ≥ 2 years old who are mildly or moderately renally impaired. Tranexamic acid is not recommended in children ≥ 2 years old who are severely impaired (see **CLINICAL TRIALS, DOSAGE AND ADMINISTRATION**).

Interactions with other medicines

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.

ADVERSE 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 2. 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 3.

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 2: 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 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
Central nervous system disorders					
stroke	0.2	1.5	0.2	1.8	3.1
Renal 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	-	-
Respiratory, thoracic & mediastinal disorders					
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 3.

Table 3: 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 <i>cardiogenic shock</i> <i>myocardial infarction</i>	12.4 4.6	15.3 2.6	10.6 3.7
Central Nervous System disorders <i>stroke</i>	2.5	2.8	3.1
Renal disorders <i>renal dysfunction</i> <i>renal failure</i>	12.0 14.2	12.8 16.9	9.2 13.6
Respiratory, thoracic & mediastinal disorders <i>respiratory failure</i>	10.6	12.6	9.5
Vascular <i>DVT or pulmonary embolism</i>	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: anaphylactic shock

Respiratory, thoracic & mediastinal disorders: 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 4.

Table 4: Adverse events $\geq 1\%$ 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

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.

Postmarketing Reports:

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. To avoid this response, the recommended rate of infusion of a bolus or a loading dose is 50 mg/min. To administer 50 mg/min to the patient via an infusion, 0.5 mL/min of undiluted Cyklokapron solution for injection (100 mg/mL) should be administered by slow intravenous injection. To administer 50 mg/min to the patient, 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.

For adult cardiac surgery, a bolus 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 **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

DOSAGE AND 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.

Renal Impairment

Dosage Adjustments for Renally Impaired Patients for orally administered Cyklokapron.		
eGFR (mL/min/1.73m²)	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 **CLINICAL TRIALS**).

Use in Special Populations:

Elderly patients

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

Renal Impairment

Adult Cardiac Surgery

eGFR (mL/min/1.73m²)	Dosage adjustment for Cyklokapron solution for injection for renally impaired adult cardiac surgical patients		
	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/1.73m²)	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.

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 if the patient's eGFR value is in the normal range for this age group. Dose reduction is recommended for children ≥ 2 years old who have mild to moderate renal impairment. It should not be used in the severely renal impaired paediatric population (also see **CLINICAL TRIALS, Use in Paediatrics with Renal Impairment**).

Paediatric population ≥ 2 years with renal impairment

eGFR (mL/min/1.73m²)	Dosage adjustment for Cyklokapron solution for injection for renally impaired paediatric cardiac surgical patients ≥ 2 years old
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.

Mode of administration

Cyklokapron solution for injection is intended for intravenous administration (intravenous injection and infusion). The recommended rate of infusion for a bolus or loading dose is 50 mg/min. To administer 50 mg/min to the patient via an infusion, 0.5 mL/min of undiluted Cyklokapron solution for injection (100 mg/mL) should be administered by slow intravenous injection. To administer 50 mg/min to the patient, 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.

For adult cardiac surgery, a bolus 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 **PRECAUTIONS, ADVERSE EFFECTS, Post marketing Report**).

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 mLs (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.

OVERDOSAGE

Overdose data are limited. There is one report of overdose 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 and hypotension.

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.

Contact the Poisons Information Centre for advice on the management of an overdose (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

CYKLOKAPRON 500 mg tablets are white capsule-shaped tablets with a scoreline on one side and marked with “CY” on the other.

CYKLOKAPRON tablets are available in a bottle presentation of 100 tablets, whilst a 20 tablet bottle is registered but not marketed in Australia.

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

CYKLOKAPRON solution for injection is supplied as packs of 5 x 5 mL and 10 x 5 mL ampoules each containing 500 mg tranexamic acid and 5 mL Water for Injections.

CYKLOKAPRON solution for injection is also supplied as packs of 1 x 10 mL and 10 x 10 mL ampoules each containing 1000 mg tranexamic acid and 10 mL Water for Injections.

Not all pack sizes and presentations are distributed in Australia

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.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
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38–42 Wharf Road
WEST RYDE NSW 2114

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4)

DATE OF APPROVAL

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