17th Expert Committee on the Selection and Use of Essential Medicines
Geneva, March 2009

PROPOSAL FOR THE INCLUSION OF TRANEXAMIC ACID (ANTI-FIBRINOLYTIC – LYSINE ANALOGUE) IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

DRAFT REPORT

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1. Summary statement of the proposal

Tranexamic acid (TXA) is proposed for the inclusion in the World Health Organisation (WHO) Model List of Essential Medicines (EML) for reducing peri-operative blood loss in adults undergoing cardiac surgical procedures requiring cardiopulmonary bypass (Non-FDA labelled indication). Tranexamic acid is not FDA approved for use in paediatric cardiac surgery.

2. Name of focal point in WHO submitting or supporting the application

3. Name of the organisation consulted

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4. International Nonpropriety Name (INN, generic name) of the medicine

INN: Tranexamic acid.
Chemical name: trans-4-(Aminomethyl) cyclohexanecarboxylic acid.

5. Formulation proposed for inclusion

Injection: 10-30 mg/kg IV followed by an infusion of 1-16 mg/kg/hr and 1-2 mg/kg added to the cardiopulmonary circuit (pump prime). Currently there is no consensus regarding optimal TXA dosing in cardiac surgery.

6. International availability – sources, if possible manufacturers

Tranexamic acid is marketed under various trade names world wide. A detailed list of manufacturers and distributors is presented in Appendix A.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing of TXA on the Model List of Essential Medicines will be as an individual medicine.

8. Information supporting the public health relevance (epidemiology information on disease burden, assessment of current use, target population)

It has been estimated that between 1-1.25 million adults undergo cardiac surgery each year worldwide.[1] In the United Kingdom more than 30,000 adults have heart surgery annually.[2] Data available from the American Heart Association indicates that a total of 699,000 open-heart procedures were performed in the United States in 2005.[3] Reports have estimated that in the United States alone, cardiac surgical procedures are performed at a cost of US$9 billion per year.[4] However, massive surgical blood loss is a serious problem that affects many cardiac surgery patients and has been shown to have a strong, independent association with in-hospital mortality.[5] There is also considerable evidence that blood loss that leads to the transfusion of blood products is harmful, and that the degree of harm is directly related to the amount of blood loss.[6] Excessive peri-operative bleeding is one of the major indications for allogeneic blood transfusions worldwide.[7]

Globally, around 75 million units of blood are collected each year, with about 45 million units being collected in developed countries alone.[8] In 2004 approximately 14 million units of red blood cells (RBCs) and 9.9 million units of platelets were transfused in the United States.[9,10] It has been reported that in England between 10-15% of the blood supplied by the National Blood Service (NBS) is used in cardiac surgery units, and in the United States, close to 20% of blood transfusions are associated with cardiac surgery.[11] In the United States alone approximately 2.5 million units of blood are transfused annually to patients undergoing cardiac surgery.[12]

The direct and indirect costs of blood transfusion are substantial. A study conducted by Varney and Guest (2003)[13] in the United Kingdom (UK) found that the total National Health Service (NHS) cost attributable to blood transfusion in 2000/2001 was £898 million, consisting of £284.1 million in blood

transfusion service costs and £613.9 million in hospital resource costs. Varney and Guest (2003) found that red blood cell transfusions were the most common and the second most costly blood product, at an average cost of £635 per transfusion.[13] Further, their economic analysis showed that red blood cell transfusions were the major cost driver, accounting for 69% of the total NHS cost of blood transfusions in 2000/2001.[13] The 2005 Nationwide Blood Collection and Utilization Survey (NBCUS) conducted in the United States reported that the average cost of RBC units in 2004 increased by 30.8% over 2001 estimates. In 2004, the mean average amount paid nationally for a unit of RBCs that was O positive, leukocyte-depleted, not irradiated, and not cytomegalovirus (CMV) negative, was US$201.07 compared to US$153.68 in 2001.[10] With an acquisition cost of US$200 it is estimated that to transfuse a single unit of packed RBCs has an actual cost of between US$1,600 and US$2,400.[14] A Canadian based study conducted by Amin *et al.* (2004)[8] estimated that the aggregated mean societal unit cost of RBCs transfused on an inpatient basis in 2002 was US$264.81 (95% confidence interval [CI] $256.29 to $275.65). Amin *et al.* (2004) found that the societal cost of RBC transfusion had doubled since 1994/1995 and anticipated further increases in units costs would occur over time as additional safety measures were introduced.[8]

Patients with substantial blood loss can benefit from blood transfusion, but it is not without risk.[15] The transfusion of allogeneic red blood cells (RBCs) is recognised as a risk factor for adverse outcome after cardiac surgery.[16] Transfusions are associated with the transmission of infectious diseases, immune sensitisation, post-operative infectious complications, sternal wound infections, post-operative pneumonia, transfusion related acute lung injury (TRALI), renal dysfunction, multiple organ failure, increased intensive care unit and hospital length of stay, and increased short- and long-term mortality.[17,18] Koch *et al.* (2006) found that peri-operative red blood cell transfusion is the single most reliable factor associated with an increased risk of post-operative morbid events after isolated coronary artery bypass grafting (CABG). Further, Koch and colleagues found that each unit of RBCs transfused is associated with an incrementally increased risk of adverse outcome.[18] Varney and Guest (2003) report that the total cost of blood transfusion-related complications was estimated to be £20.6 million in 2000/2001 with 98% of the cost being attributable to fluid overload due to its high incidence of 6%. Hospital ward stay accounted for 93% of the cost (£19.1 million), drugs 7% (£1.4 million), and ICU stay and diagnostics and laboratory tests accounted for less than 1% each.[13]

The Public Health Agency of Canada reports that about 0.5% to 3% of all transfusions result in some adverse event, but the majority of these are minor reactions with no significant consequences.[19] Although the risk of infectious diseases being transmitted by transfusion in Canada is minimal, many infectious agents, including viruses, bacteria, and parasites, can be transmitted via blood transfusion. The most recognised viruses transmitted through blood transfusion include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis G virus/GB-C virus (HGV/GBV-C), human immunodeficiency virus types 1 and 2 (HIV-1/2), human T-cell lymphotropic virus types I and II (HTLV-I/II), cytomegalovirus (CMV), Epstein-Barr virus (EBV), TT virus (TTV), human herpes virus type 6 (HHV-6), SEN virus (SEN-V), and human parvovirus (HPV-B19).[19] Bacteria such as Treponema pallidum (the agent of syphilis), Yersinia enterocolitica, and Staphylococcus and Streptococcus species (common agents of bacterial contamination), and parasites such as Plasmodium species (the agent of malaria), Trypanosoma cruzi (agent of Chagas' disease), and Babesia microti (agent of babesiosis) have also been reported to be transmitted via blood transfusion. In addition, emerging blood-borne pathogens such as hepatitis E virus (HEV), human herpes virus type 8 (HHV-8), Borrelia burgdorferi (agent of Lyme disease), and the unknown agent of Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) pose a threat to the safety of blood.[19]

In Australia, the risk of HIV (human immunodeficiency virus) and HCV transmission through blood transfusion is estimated to be approximately 1 in 35.2 million units and 1 in 3.2 million units respectively.[20] A summary of the risks of transfusion transmitted infection reported by the Australian Red Cross Blood Service (ARCBS) is presented in Table 8.1. In comparison, the risk of HIV and HCV transmission through blood transfusion in Canada is estimated to be 1 in 752,000 and 1 in 225,000 donations respectively.[19] According to the American Red Cross, about 1 in 205,000

transfusions transmits hepatitis B infection, and approximately 1 in 2 million transfusions transits hepatitis C. In the United States the risk of HIV transmission from a transfusion is about 1 in 2,135,000 transfusions.[21]

Table 8.1: Risks of transfusion transmitted infection calculated from ARCBS data from 1 January 2006 to 31 December 2007

Agent and testing standard	Window period (days)	Estimate of residual risk 'per unit'[†]
HIV (antibody + RNA)	9	1 in 35.2 million
HCV (antibody + RNA)	5.4	1 in 3.2 million
HBV (HBsAg)	38	1 in 1.9 million
HTLV I & II	51	1 in 14.7 million[*]
vCJD (No testing)	-	Not yet reported
Malaria (antibody)	N/A	1 in 4.9 – 10.2 million

Abbreviations: HIV = human immunodeficiency virus; HCV = hepatitis C virus; HBV = hepatitis B virus; HTLV = human T lymphotrophic virus; vCJD = variant Creutzfeldt-Jakob Disease
[*] HTLV risk estimate based on data from 1 January 2004 to 31 December 2007
[†] Approximate estimates
Source: http://www.transfusion.com.au/Consent-and-Risk.aspx#

Non-infectious adverse events remain the most common complications associated with blood transfusion and are generally characterised as being acute immune mediated or delayed immune mediated reactions.[9,19] Acute immune mediated reactions include acute haemolytic transfusion reaction (AHTR), transfusion-related acute lung injury (TRALI), febrile non-haemolytic transfusion reaction (FNHTR), urticarial reaction and anaphylaxis.[19] Delayed immune mediated reactions consist of delayed haemolytic transfusion reaction (DHTR), transfusion associated graft-versus-host disease (TA-GVHD), and post-transfusion purpura (PTP).[19] The Public Health Agency of Canada report that FNHTR and urticarial reactions are the most frequent non life-threatening acute transfusion reactions, and AHTR is the most frequent severe reaction and the leading cause of death associated with transfusion.[19] In Canada, although TRALI and TA-GVHD are rare they are the most fatal transfusion reactions. The case fatality rate is 5% to 14% for TRALI and over 90% for TA-GVHD. TRALI has been recognized as the third leading cause of death associated with transfusion.[19] However, reported estimates of the frequency of TRALI ranges from as low as 1 in 400 to as high as 1 in 50,000 units transfused (i.e. involving plasma, platelets, or RBCs).[9] The Australian Red Cross Blood Service (ARCBS) reports that the risk of TRALI ranges from 1 in 5,000 to 1 in 10,000 per unit of blood transfused.[20] A recently published review claims that TRALI has emerged as the leading transfusion-related cause of death (15.8% - 22.3% of the total) reported to the United States Food and Drug Administration (FDA) for the years 2001-2003.[9]

The Public Health Agency of Canada claims that ABO incompatibility accounts for about 80% of AHTR-related deaths and occurs as a result of error.[19] These errors include patient misidentification, sample error, wrong blood issued, transcription error, administration error, technical error and storage error. Identification and prevention of these errors have become an increasingly important issue in transfusion safety.[19] In the United States it has been estimated that the wrong unit of blood is administered 1 in every 12,000 units and 1 in 33,000 units involves ABO mismatch. ABO-mismatched transfusions can be fatal in 10% of cases and account for at least 16 deaths every year (i.e. 1.2 deaths per million units transfused) in the United States.[9]

Reactions produced by blood transfusion can range from mild allergic reactions to severe anaphylactic reactions. Mild allergic symptoms such as rash, hives, or itching occur in 1 to 3% of transfusions, whereas severe life-threatening anaphylactic reactions occur at a rate of 1 in 20,000 to 1 in 50,000 transfusions.[9] A summary of the risks associated with blood transfusion is presented in Figure 8.1.

Adverse effect	Incidence per transfused units
Infectious	
Viral infection	
Hepatitis A	1:2 000 000
Hepatitis B	1:31 000* to 1:81 000†
Hepatitis C	1:1 935 000 to 1:3 100 000
HIV	1:2 135 000 to 1:4 700 000
HTLV I/II	1:1 900 000
Bacterial contamination	1:14 000 to 1:28 000
Parasitic infection	1:4 000 000
Prion disease	Rare
Noninfectious	
Febrile nonhemolytic reaction	1:500
Urticarial reaction	1:50 to 1:100
Anaphylactic reaction	1:23 000
Hemolytic transfusion reaction	1:9 000
Transfusion-related acute lung injury (TRALI)	1:1 300 to 1:5 000
Transfusion-associated circulatory overload (TACO)	1:17 000
Post-transfusion purpura	1:143 000

Note: HTLV = human T-cell lymphotrophic virus.
*Risk attributable to window of hepatitis B infection (before development of positive hepatitis B surface antigen [HBsAg]) and chronic carriers of hepatitis B virus who have undetectable levels of HBsAg.
†Risk attributable to window of hepatitis B infection only.

Figure 8.1: Incidence of adverse effects associated with allogeneic red blood cell transfusions
Source: Tinmouth *et al.* (2008)[22]

Concerns regarding blood safety, continual blood shortages and rising blood bank and health care costs have generated considerable interest in a range of technologies designed to reduce transfusion requirements during and after surgery.[23] The most notable of these is the anti-fibrinolytic drugs aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA). Meta-analyses of randomised trials of aprotinin have shown convincing evidence that this drug reduces peri-operative blood loss, allogeneic blood transfusion, and the need for re-operation due to continued or recurrent bleeding.[15,24-26] However, a number of observational studies suggest that the risk of death, vascular events and renal failure may be greater with aprotinin than with the lysine analogues TXA and EACA.[27-29]

The results of the BART study (Blood Conservation using Antifibrinolytics in a Randomised Trial - a randomised head-to-head comparative trial of aprotinin, TXA, and EACA in high-risk cardiac surgery) published in the NEJM (May 29, 2008), did not generally support the findings of the observational studies.[30] However, the results of the BART study did show a higher rate of death in patients treated with aprotinin compared to those treated with TXA or EACA. In the case of mortality at 30 days, the rate of death from any cause was 6.0% in the aprotinin group, compared with 3.9% in the TXA group (RR 1.55, 95% CI 0.99 to 2.42) and 4.0% in the EACA group (RR 1.52, 95% CI 0.98 to 2.36). The relative risk (RR) of death in the aprotinin group, compared with that in both groups receiving the lysine analogues TXA and EACA, was 1.53 (95% CI 1.06 to 2.22). It is important to note that on the basis of interim data for 2163 patients the BART study was terminated early on the recommendation of the independent data and safety monitoring committee because of higher mortality in the aprotinin group than in the TXA and EACA groups.[30] In the case of renal failure the results of the BART study showed that aprotinin did not significantly increase the risk of renal failure

or the need for post-operative renal replacement therapy (RRT). This finding is at odds with the findings of the observational studies.

Based on the findings of the observational studies by Mangano *et al.* (2006 & 2007)[27,28] and Kakouti *et al.* (2006)[29] and the interim results of the BART study the FDA suspended the marketing of aprotinin (Trasylol®) by Bayer Pharmaceuticals on November 5, 2007. The FDA is currently working with Bayer Pharmaceuticals to phase aprotinin (Trasylol®) out of the market-place.[31] Therefore, it is important and timely, to examine the efficacy, safety, and cost-effectiveness of tranexamic acid in reducing excessive bleeding during cardiac surgery.

9. Treatment details (dosage regimen, duration, reference to existing WHO and other clinical guidelines, need for special diagnostic or treatment facilities and skills)

The Product Information for tranexamic acid (Cyklokapron®) states:

> Tranexamic acid is a competitive inhibitor of plasminogen activation, and at much higher concentrations, a non-competitive inhibitor of plasmin, i.e., actions similar to 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 receptor 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 per ml does not aggregate platelets *in vitro*. Tranexamic acid in concentrations up to 10 mg per ml blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. On the other hand, tranexamic acid in concentrations of 10 mg and 1 mg per ml blood prolongs the thrombin time.[32]
>
> The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin. After an intravenous dose of 1 g, the plasma concentration time curve shows a tri-exponential 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 the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg per kg body weight. Only a small fraction of the drug is metabolized. An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to seven or eight hours.[32]

9.1 Dosage regimen and duration

The amount of TXA needed to prevent fibrinolysis *in vivo* remains unknown.[33] The dose of TXA administered prophylactically varies considerably between institutions with dosing schedules for TXA varying a much as 10-fold in the published literature.[34] A systematic review of randomised comparative trials of aprotinin, TXA, and EACA in cardiac surgery showed the loading dose of TXA ranged from as low as 10 mg/kg to as high as 10 grams (Appendix C), whereas maintenance doses ranged from 1 mg/kg/hr to 3 mg/kg/hr.[23] A Cochrane review of anti-fibrinolytic drugs published in 2007, identified 29 trials of TXA involving cardiac surgery.[24] For these trials the TXA loading dose ranged from 2.5 mg/kg to 100 mg/kg and the maintenance dose of TXA ranged from 0.25 mg/kg/hr to 4.0 mg/kg/hr infused over 1-12 hours. The recently published BART study used a loading dose of 30 mg/kg of TXA administered over 20 minutes, a maintenance dose of 16 mg/kg/hr, and added a further 2 mg/kg of TXA to the pump prime solution.[30] The study by Fiechtner *et al.* (2001) found that an initial loading dose of 10 mg/kg of TXA followed by an infusion of 1 mg/kg/hr resulted in an adequate plasma concentration defined by *in vitro* studies to prevent fibrinolysis.[35] The pharmacokinetic study conducted by Dowd *et al.* (2002) suggested a 30 minute loading dose of 12.5 mg/kg with a maintenance infusion of 6.5 mg/kg/hr and 1 mg/kg added to the pump prime will maintain a TXA concentration greater than 334 μm, and a higher dose based on a 30 mg/kg loading dose plus 16 mg/kg/hr continuous infusion and 2 mg/kg added to the pump prime would maintain TXA concentrations greater than 800 μm.[34] The recent study by Nuttall *et al.* (2008) recommended a loading dose of 10 mg/kg, a pump prime dose of 50 mg (2.5 litre circuit) or 40 mg (2 litre circuit), and an infusion of 2 mg/kg/hr for patients with normal renal function.[33] Nuttall *et al.* (2008) proposed that patients with renal insufficiency receive an infusion of 1.5 mg/kg/hr for a serum creatinine of 1.6 to 3.3 mg/dL, an infusion of 1 mg/kg/hr for a serum creatinine of 3.3 to 6.6 mg/dL, and an infusion of

0.5 mg/kg/hr for a serum creatinine >6.6 mg/dL.[33] Prescribing information available from Thomson Healthcare (MICROMEDEX® 1974-2008) states that TXA should be administered intravenously as a bolus dose of 15 mg/kg followed by an infusion of 1 mg/kg/hr for 5-6 hours started prior to initiating coronary bypass.[36] Consensus regarding optimal TXA dosing in cardiac surgery is urgently required.

9.2 Reference to existing WHO and other clinical guidelines

The Clinical Practice Guideline (CPG) titled 'Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery' developed by the Society of Thoracic Surgeons (STC) and the Society of Cardiovascular Anesthesiologists (SCA) and published in 2007, recommends the use of epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) for blood conservation in cardiac surgery (Level A/Class I Evidence).[37] This CPG states that TXA and EACA limit total blood loss and the number of patients who require blood transfusion after cardiac procedures. Further, the lysine analogues are slightly less potent blood sparing drugs compared to aprotinin but may have a more favourable safety profile.[37] However, this guideline does not recommend a specific dose regimen for either TXA or EACA. It should be noted that this guideline also recommends the use of high-dose aprotinin in high-risk cardiac surgery patients with the benefits of its use balanced against the increased risk of renal dysfunction.[37] Given this guideline was published before the marketing suspension of aprotinin (5 November 2007), it is anticipated changes will be made to future STC/SCA recommendations regarding the use of aprotinin in cardiac surgery.

The National Clinical Guideline titled 'Perioperative Blood Transfusion for Elective Surgery' developed by the Scottish Intercollegiate Guidelines Network (SIGN) and published in 2001 and updated on 31 August 2004, recommends the use of aprotinin or tranexamic acid for patients undergoing cardiac surgery which carries a high risk of transfusion (e.g. repeat cardiac operations, multiple valve replacements, thoracic aortic operations, patients on pre-operative aspirin therapy and procedures with anticipated long bypass times).[38] The SIGN guideline claims that there was insufficient high quality evidence to recommend the use of aprotinin in primary CABG. The SIGN guideline states that in low-risk primary CABG the routine use of aprotinin is not recommended.[38] However, this guideline does not recommend a specific dose regimen for either aprotinin or TXA. The marketing suspension of aprotinin is likely to impact on future SIGN recommendations.

Clinical Practice Guidelines developed by the American Society of Anesthesiologists (ASA)[39] and published in 2006, provides the following guidance:

> Antifibrinolytic therapy should not be routinely administered. However, such therapy may be used for reducing the volume of allogeneic blood transfused for patients at high risk of excessive bleeding (e.g., repeat cardiac surgery). The risks and benefits of instituting antifibrinolytic therapy should be assessed on a case-by-case basis.[39]

The guidelines prepared by the Audit and Guidelines Committee of the European Association for Cardio-Thoracic Surgery (EACTS)[40] and published in 2008, provides the following recommendations regarding the use of aprotinin and TXA in cardiac surgery to reduce peri-operative blood loss and blood product use:

> Recommendation:
> Aprotinin reduces blood loss and the need for blood transfusion in cardiac surgery; however there is a proven association with postoperative renal dysfunction and a probable association with increased mortality after a large randomised controlled trial has been stopped early due to these concerns. Routine use of aprotinin in cardiac surgery is not recommended, but use in patients at particularly high risk of bleeding may still be justified. This is the subject of current FDA and MRHA review, and these recommendations may change in the near future. (Grade A recommendation based on level 1a and 1b studies).[40]
>
> Recommendation:
> Tranexamic acid reduces blood loss, requirement for blood transfusion, and the risk of re-operation for bleeding. (Grade A recommendation based on level 1a and 1b studies) No study has yet looked directly

at vein graft patency with tranexamic acid, but equally no randomised studies have raised concerns over its safety. (Grade B recommendation based on individual level 1b studies).[40]

9.3 Need for special diagnostic or treatment facilities and skills

Although no specialist treatment facilities and skills are required to administer intravenous TXA, patients that undergo cardiac surgery do so in suitably equipped and authorised healthcare facilities. Best clinical practice dictates that cardiac surgical patients receiving TXA will be closely monitored during their period of hospitalisation. Generally, cardiac surgical patients receive follow-up care by their cardiothoracic surgeon, cardiologist, and/or general physician.

10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence (search strategy, systematic reviews, identified, reasons for selection/exclusion of particular data)

To identify systematic reviews and randomised clinical trials of tranexamic acid the following databases were searched: Medline (1950 to October, 2008), EMBASE (1980 to October, 2008), the Cochrane Database of Systematic Reviews (Issue 3, 2008), and the Cochrane Central Register of Controlled Trials (CENTRAL). To maximise the sensitivity for the retrieval of all potentially relevant studies, the electronic searches of these databases were searched initially using an unrestricted search strategy, employing exploded MeSH terms (exp Tranexamic Acid/) and specific text-word terms for tranexamic acid. The specific text-word terms included: 'tranexamic', 'cyklokapron', 'pharmacia', 't-amcha', 'amca', 'amcha', 'urugol', 'transamin', 'kabi', 'exacyl', and 'anvitoff'. To restrict and improve the specificity of these searches, three search filters were used. Firstly, a filter to identify randomised controlled trials,[41] secondly a filter to identify systematic reviews and meta-analyses, and thirdly a filter to identify studies with blood loss and transfusion as study outcomes (Search strategies are provided in Appendix B). The internet was widely searched using Google™ and Google™ Scholar. The reference lists of identified trials, reviews, reports and guidelines were searched for potentially relevant studies.

Studies were included for review if they were systematic reviews, randomised controlled parallel group trials, or randomised head-to-head direct comparison trials, and evaluated the effectiveness of prophylactic intravenous tranexamic acid in reducing peri-operative blood loss and allogeneic blood transfusion in the context of cardiac surgery. Studies that evaluated the use of prophylactic intravenous tranexamic acid in surgical settings other than cardiac surgery (i.e. orthopaedic, liver transplantation) were not included for review.

10.2 Summary of comparative effectiveness - adults

Four systematic reviews of tranexamic acid in cardiac surgery were identified by the literature searches.[15,23,24,42] A further systematic review awaiting publication in the Canadian Medical Association Journal (CMAJ) was known to the author of this review.[43] The systematic reviews of Henry *et al.* (2007 & 2008)[24,43] and Brown *et al.* (2007)[15] form the basis of this review.

10.2.1 Peri-operative blood loss – meta-analyses of randomised placebo-controlled trials

The Cochrane review by Henry *et al.* (2007)[24] identified 17 trials of TXA involving cardiac surgery that reported post-operative blood loss data. The results of the meta-analysis showed that the use of TXA reduced post-operative blood loss on average by around 263 millilitres (mls) per patient compared to control (Weighted mean difference [WMD] -262.6 mls, 95% confidence interval [CI] -318.62 to -206.59 mls). However, heterogeneity of treatment effect was statistically significant (P = 0.01; I^2 = 48%). In comparison, the use of aprotinin reduced post-operative blood loss on average by 380 mls per patient (67 trials; WMD -380.30, 95% CI -421.96 to -338.63 mls) and EACA reduced the amount of post-operative blood loss by around 196 mls per patient (11 trials; WMD -196.27 mls, 95% CI -271.75 to -120.79 mls).

Henry *et al.* (2007)[24] found that the use of TXA in cardiac surgery reduced intra-operative blood loss on average by around 287 mls per patient compared to control (3 trials; WMD -287.16 mls, 95% CI -481.57 to -92.75 mls). In comparison, the use of aprotinin reduced the volume of blood loss during the

intra-operative period by 140 mls per patient (5 trials; WMD -140 mls, 95% CI -244.42 to -35.59 mls) and EACA reduced intra-operative blood by around 214 mls per patient (2 trials; WMD -213.58 mls, 95% CI -310.03 to -117.13 mls).

The systematic review conducted by Henry *et al.* (2007)[24] identified three trials of TXA that reported total blood loss data (intra- and post-operative blood loss combined). Prophylaxis with TXA reduced the total amount of peri-operative blood loss by approximately 440 mls per patient compared to control (3 trials; WMD -439.82 mls, 95% CI -606.50 to -273.15 mls). In comparison, the use of aprotinin reduced the volume of blood loss during the peri-operative period by around 490 mls per patient (5 trials; WMD -489.06 mls, 95% CI -571.32 to -406.80 mls). Data for this outcome were not available from trials of EACA.

The systematic review by Brown *et al.* (2007)[15] found that on average prophylactic TXA reduced total blood loss by 285 mls per patient compared to control (11 trials; WMD -285 mls, 95% CI -394 to -175 mls; $P < 0.001$). In comparison, high-dose aprotinin reduced total blood loss by 348 mls per patient (22 trials; WMD -348 mls, 95% CI -416 to -281 mls; $P < 0.001$), low-dose aprotinin reduced total blood loss by 226 mls per patient (6 trials; WMD -226 mls, 95% CI -277 to -175 mls; $P < 0.001$), and EACA reduced total blood loss by 240 mls per patients (3 trials; WMD -240 mls, 95% CI -341 to -140 mls; $P < 0.001$).

The Cochrane review conducted by Henry *et al.* (2007)[24] stratified post-operative blood loss data by the dose of TXA administered to determine whether higher doses of TXA (2.0-10.0 grams total dose) were more effective than lower doses of TXA (<2.0 grams total dose). The results of the meta-analysis showed that lower doses of TXA were as effective as higher doses of TXA in reducing post-operative blood loss compared to control (Fig. 10.2.1). In the case of trials that used lower doses of TXA, post-operative blood loss was reduced by around 241 mls per patient (WMD -240.98, 95% CI -336.63 to -145.34 mls) compared to 273 mls per patient in trials that administered higher doses of TXA (WMD -272.85 mls, 95% CI -340.79 to -204.90 mls).

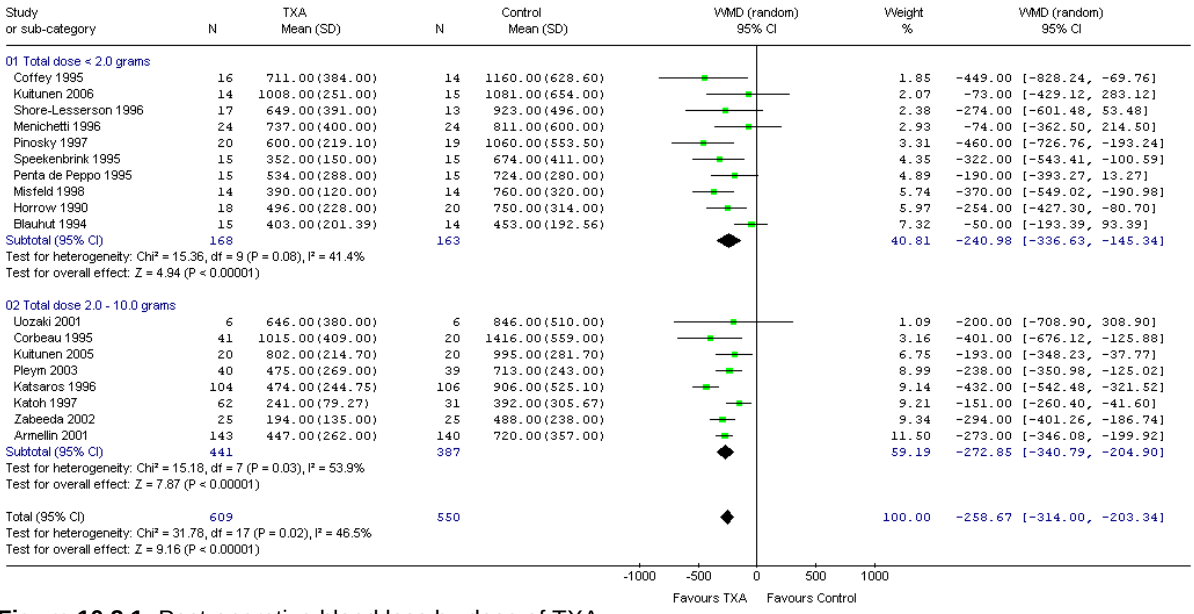

Figure 10.2.1: Post-operative blood loss by dose of TXA
Source: Henry *et al.* (2007)[24]

10.2.2 Peri-operative blood loss – meta-analyses of randomised head-to-head comparisons

The Cochrane review by Henry *et al.* (2007)[24] identified 12 trials of aprotinin versus TXA involving cardiac surgery and reported data for post-operative blood loss (Fig. 10.2.2). The meta-analysis of trial data showed that aprotinin appeared to be more effective in reducing post-operative blood loss than TXA (12 trials; WMD -131.54, 95% CI -192.15 to -70.94 mls). However, heterogeneity in treatment effect was statistically significant ($P = 0.004$; $I^2 = 60.2\%$).

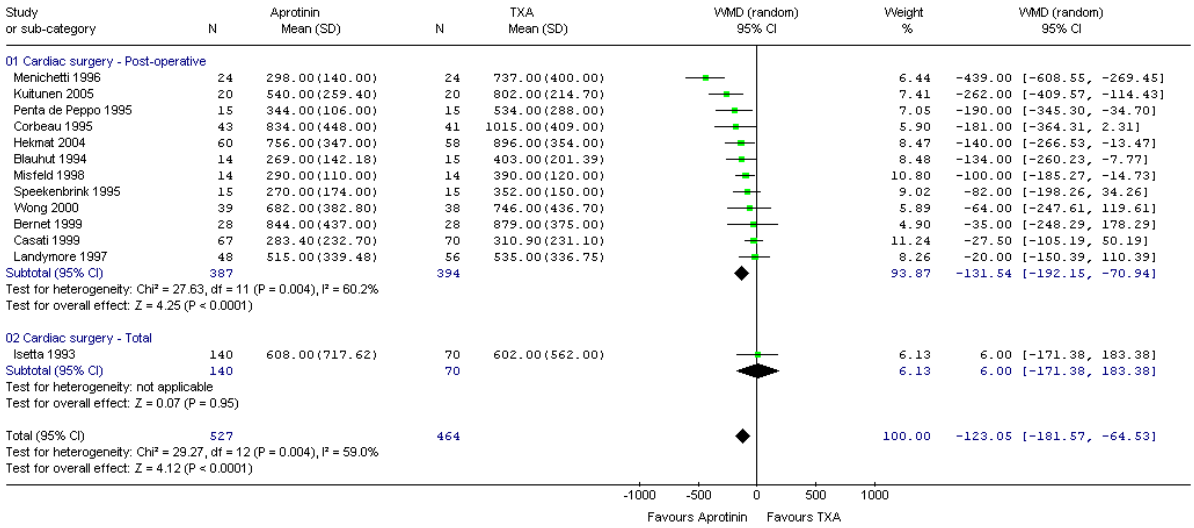

Figure 10.2.2: Post-operative blood loss – Aprotinin versus TXA
Source: Henry *et al.* (2007)[24]

Brown *et al.* (2007)[15] report that the use of high-dose aprotinin in cardiac surgery resulted in 195 mls less total blood loss compared with TXA (6 trials; 95% CI -286 to -105 mls; $P < 0.001$). Brown *et al.* found that EACA and TXA did not differ significantly in the amount of total blood loss (3 trials; WMD -64 mls, 95% CI -214 to 85 mls; $P = 0.4$). A similar non-significant difference between TXA and EACA was reported by Henry *et al.* (2007). They found that there was no statistically significant difference between TXA and EACA in the volume of blood lost during the post-operative period (6 trials; WMD -4.36 mls, 95% CI -163.35 to 154.63 mls).

Two recently published randomised, head-to-head comparative trials of aprotinin versus TXA in cardiac surgery report conflicting results.[44,45] The trial conducted by Dietrich *et al.* (2008),[45] which included 220 patients who underwent primary coronary artery revascularisation or aortic valve replacement surgery, found that 24 hour post-operative blood loss was not statistically significantly different between aprotinin and TXA (median 500 mls, IQR 300-700 mls vs. median 565 mls, IQR 300-800 mls, respectively; $P = 0.136$). In contrast, the head-to-head comparative trial by Mengistu *et al.* (2008),[44] which included 50 patients who underwent elective cardiac surgery with CPB, found that aprotinin was more effective than TXA in reducing 24 hour post-operative blood loss (575 ± 228 mls vs. 1033 ± 647 mls, respectively; $P < 0.05$).

10.2.3 Peri-operative allogeneic blood transfusion – meta-analyses of randomised placebo-controlled trials

The Cochrane review by Henry *et al.* (2007)[24] identified 29 trials of TXA versus control that involved cardiac surgery. Henry *et al.* found that there was a 31% relative reduction in the risk of exposure to allogeneic blood transfusion in those patients treated with TXA compared to control (pooled RR 0.69, 95% CI 0.60 to 0.79). However, heterogeneity in treatment effect was statistically significant ($P = 0.03$; $I^2 = 37\%$). In the case of aprotinin, Henry *et al.* found that the use of aprotinin significantly reduced the risk of exposure to allogeneic blood transfusion by a relative 34% compared to control (76 trials; pooled RR 0.66, 95% CI 0.61 to 0.72). As was the case with the TXA meta-analysis, heterogeneity in treatment effect was statistically significant ($P < 0.00001$; $I^2 = 71\%$). In comparison,

treatment with EACA reduced the risk of exposure to allogeneic blood transfusion by a relative 35% (10 trials; pooled RR 0.65, 95% CI 0.47 to 0.91).

Similar results were reported by Brown *et al.* (2007).[15] The results of the meta-analyses performed by Brown *et al.* showed that TXA reduced the rate of allogeneic blood transfusion by a relative 25% compared to control (22 trials; pooled RR 0.75, 95% CI 0.60 to 0.92; $P = 0.007$). In comparison, the use of high-dose aprotinin resulted in a relative risk reduction of 40% (49 trials; pooled RR 0.60, 95% CI 0.53 to 0.67; $P < 0.001$) and low-dose aprotinin resulted in a relative risk reduction of 24% compared to control (20 trials; pooled RR 0.76, 95% CI 0.66 to 0.86; $P < 0.001$). Brown *et al.* found that EACA when used in the context of cardiac surgery, the risk of exposure to allogeneic blood transfusion was reduced by a relative 37% compared to control (10 trials; pooled RR 0.63, 95% CI 0.44 to 0.90; $P = 0.01$).

10.2.4 Peri-operative allogeneic blood transfusion – meta-analyses of randomised head-to-head comparative trials

The Cochrane review by Henry *et al.* (2007) identified 14 head-to-head comparative trials of aprotinin versus TXA in cardiac surgery. The results of the meta-analysis indicated there was no statistically significant difference between aprotinin and TXA in the rates of allogeneic blood transfusion (pooled RR 0.85, 95% CI 0.66 to 1.09). However, heterogeneity of treatment effect was statistically significant ($P = 0.01$; $I^2 = 54\%$). When TXA was compared directly with EACA, the relative risk of receiving an allogeneic blood transfusion in patients treated with TXA compared to patients treated with EACA was 1.16 (5 trials; 95% CI 0.68 to 1.98). Henry *et al.*[43] recently updated their Cochrane review to include data from the BART study and other randomised clinical trials not included in their previous systematic reviews. The results of the updated meta-analysis indicate that, although there appeared to be a trend favouring aprotinin over TXA in reducing exposure to allogeneic blood transfusion, the result did not reach statistical significance (15 trials; pooled RR 0.87, 95% CI 0.72 to 1.05)(Fig. 10.2.4). When TXA was compared directly with EACA, there was no statistically significant difference between the two agents in reducing the risk of exposure to allogeneic blood transfusion (6 trials; pooled RR 1.07, 95% CI 0.79 to 1.46). In contrast, the results of the BART study showed that aprotinin was more effective in reducing exposure to allogeneic red cell transfusion than both TXA (RR 0.82, 95% CI 0.75 to 0.89) and EACA (RR 0.81, 95% CI 0.75 to 0.88). Of the 2330 patients included in the analysis, 53.7% of aprotinin patients received at least one unit of allogeneic red blood cells compared to 65.7% in those patients treated with TXA and 65.9% of patients treated with EACA.[30]

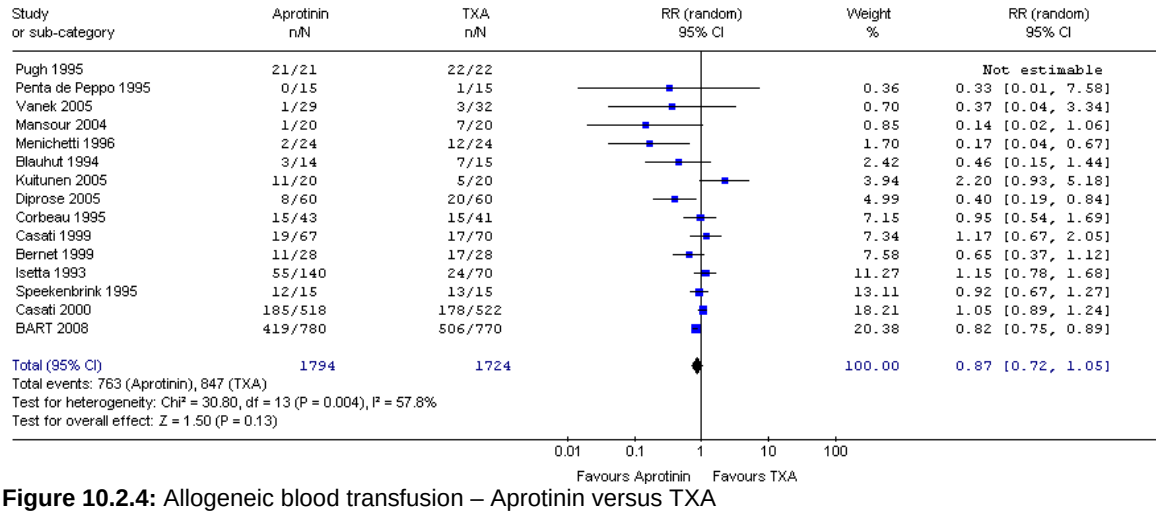

Figure 10.2.4: Allogeneic blood transfusion – Aprotinin versus TXA

The meta-analysis conducted by Brown *et al.* also found that aprotinin (high-dose) appeared to be no better than TXA in reducing the rate of allogeneic transfusion compared to TXA (11 trials; pooled RR 0.81, 95% CI 0.60 to 1.09; $P = 0.17$). The meta-analysis performed by Brown *et al.* showed that there

was no significant difference in the rates of allogeneic blood transfusion when EACA and TXA were compared directly (5 trials; pooled RR 0.81, 95% CI 0.49 to 1.34; *P* = 0.41).

The two recently published randomised, head-to-head comparative trials of aprotinin versus TXA by Dietrich *et al.* (2008)[45] and Mengistu *et al.* (2008)[44] indicated that aprotinin was more effective than TXA in reducing patient exposure to allogeneic red cell transfusion. In the case of the trial conducted by Dietrich *et al.* (2008) the number patients treated with aprotinin that required blood transfusion was significantly less than those patients treated with TXA (47% vs. 61%; *P* = 0.036). The head-to-head comparative trial by Mengistu *et al.* (2008) also found that aprotinin was more effective than TXA is reducing blood transfusion exposure (40% vs. 68%, respectively; *P* < 0.05).

10.2.5 Re-operation for bleeding – meta-analyses of randomised placebo-controlled trials

The Cochrane review conducted by Henry *et al.* (2007) identified 19 trials of TXA that involved cardiac surgery and reported data on re-operation for bleeding. The results of the meta-analysis showed that the use of TXA did not significantly reduce the risk of re-operation for bleeding compared to control (pooled RR 0.65, 95% CI 0.39 to 1.08). A similar non-significant result for TXA was reported by Brown *et al.* (2007)[15] – (21 trials; pooled RR 0.70, 95% CI 0.44 to 1.11; *P* = 0.125). In contrast, Henry *et al.* (2007) found that when aprotinin (low and high doses combined) was used in cardiac surgery, the risk of requiring re-operation due to bleeding was reduced by a relative 51% (pooled RR 0.49, 95% CI 0.34 to 0.70). Brown *et al.* found that when high-dose aprotinin was used in cardiac surgery the risk of requiring re-operation for bleeding was reduced by a relative 53% (40 trials; pooled RR 0.47, 95% CI 0.32 to 0.69; *P* < 0.001). However, low-dose aprotinin did not appear to be as effective high-dose aprotinin (20 trials; pooled RR 0.69, 95% CI 0.41 to 1.18; *P* = 0.176) and EACA appeared less effective than TXA (9 trials; pooled RR 0.51, 95% CI 0.15 to 1.82; *P* = 0.301).[15]

10.2.6 Re-operation for bleeding – meta-analyses of head-to-head comparative trials

The meta-analysis conducted by Brown *et al.* (2007)[15] found that high-dose aprotinin did not significantly reduce the rate of re-operation compared to TXA (11 trials; pooled RR 0.90, 95% CI 0.50 to 1.63; *P* = 0.73) or EACA (6 trials; pooled RR 1.04, 95% CI 0.40 to 2.72; *P* = 0.94). Brown *et al.* found that there was no statistically significant difference in the rate of re-operation when EACA was compared directly with TXA (4 trials; pooled RR 0.72, 95% CI 0.20 to 2.56; *P* = 0.62).

The meta-analysis conducted by Henry *et al.* (2008)[43]found that, although there appeared to be trend toward a decreased risk of requiring re-operation in patients treated with aprotinin compared to TXA when data from the BART study[30] were included in the analysis, the result failed to reach statistical significance (13 trials; pooled RR 0.74, 95% CI 0.54 to 1.02). However, this analysis was heavily weighted by the results of the BART study with the results of this trial providing over 71% of the statistical weight in the analysis (Fig.10.2.6). Interestingly, the results of the meta-analysis preceding the inclusion of the BART study data shows no clear benefit of aprotinin over TXA (12 trials; pooled RR 0.86, 95% CI 0.48 to 1.56).[24]

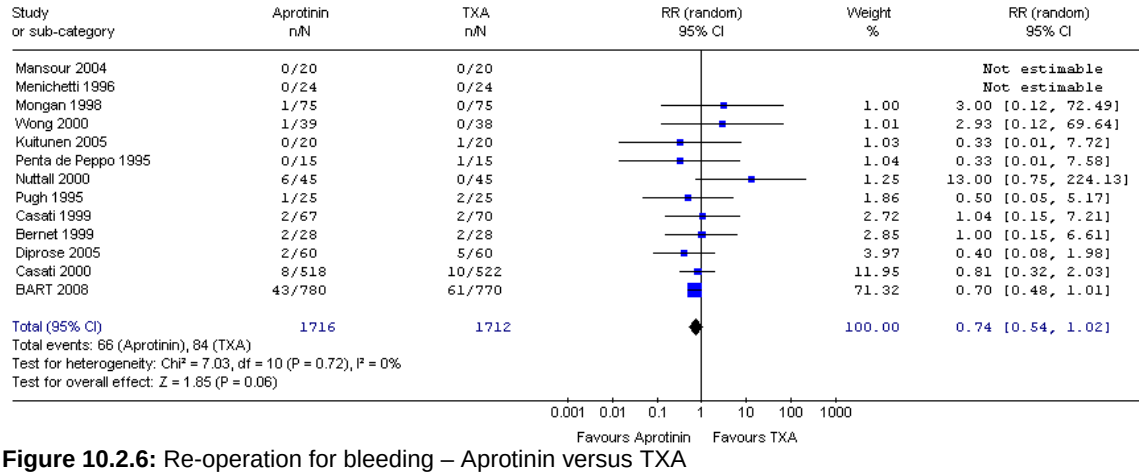

Figure 10.2.6: Re-operation for bleeding – Aprotinin versus TXA

The individual trial results of the BART study[30] and the recently published randomised head-to-head comparative trial by Dietrich *et al.* (2008)[45] showed that there was no statistically significant difference between aprotinin and TXA in the number of patients requiring re-operation for bleeding following cardiac surgery. In the case of the BART study 5.5% of patients treated with aprotinin required re-operation for bleeding compared to 8.1% of patients treated with TXA (RR 0.68, 95% CI 0.47 to 1.00). Although there appeared to be a trend toward a decreased risk of requiring re-operation in aprotinin treated patients compared to TXA treated patients the result failed to reach statistical significance. In comparison, the randomised, double-blind, comparative trial conducted by Dietrich *et al.* (2008), reported that of the 110 patients randomised to aprotinin only two (1.8%) required re-operation for bleeding compared to three (2.7%) of the 110 patients who were randomised to TXA (P > 0.999).[45]

10.2.7 Overview of results

Although systematic reviews indicate that aprotinin appears to be slightly more effective than TXA in reducing post-operative blood loss (Table 10.2.7.1) the difference between these two agents appears small and not of any real clinical significance (Table 10.2.7.2). Although both aprotinin and TXA are effective in reducing exposure to allogeneic blood transfusion compared to control (Table 10.2.7.3), meta-analyses of the head-to-head comparative trials indicate there is no statistically significant difference between aprotinin and TXA (Table 10.2.7.4). In contrast, the results of the BART study showed aprotinin was significantly more effective than TXA in reducing the risk of exposure to allogeneic blood transfusion (RR 0.82, 95% CI 0.75 to 0.89). Trends suggesting that TXA is more effective than control and aprotinin is more effective than TXA in reducing re-operation due to bleeding, failed to reach statistical significance (Table 10.2.7.5 & Table 10.2.7.6). There appeared to be very little difference between TXA and EACA across each of the efficacy outcomes assessed. Unlike aprotinin where dose regimens are well defined, there is no consensus regarding the optimal dose of TXA. The dose of TXA administered prophylactically varies considerably in the published literature with dosing schedules for TXA varying a much as 10-fold. Although the evidence suggests there is some degree of benefit in prophylactically administering TXA to cardiac surgical patients, the substantial clinical heterogeneity between trials (i.e. variability in patients studied, procedures performed, and dosing schemes used) makes it difficult to draw firm conclusions regarding the comparative effectiveness of TXA in cardiac surgery. Based on the currently available evidence, the listing of TXA on the WHO EML cannot be supported.

Table 10.2.7.1: Results for peri-operative blood loss – placebo-controlled trials

Blood loss (mls)	Aprotinin vs. control WMD (95% CI)	TXA vs. control WMD (95% CI)	EACA vs. control WMD (95% CI)
IO blood loss*	-140.00 (-244.42, -35.59)	-287.16 (-481.57, -92.75)	-213.58 (-310.03, -117.13)
PO blood loss*	-380 (-421.96, -338.63)	-262.60 (-318.62, -206.59)	-196.27 (-271.75, -120.79)
Total blood loss*	-489.06 (-571.32, -406.80)	-439.82 (-606.50, -273.15)	NR
Total blood loss†	-348 (-416, -281)	-285 (-394, -175)	-240 (-341, -140)

Abbreviations: CI = confidence interval; IO = intra-operative; PO = post-operative; mls = millilitres; WMD = weighted mean difference; TXA = tranexamic acid; EACA = epsilon aminocaproic acid; NR = not reported
* Henry *et al.* (2007)[24]
† Brown *et al.* (2007)[15]

Table 10.2.7.2: Results for post-operative blood loss – head-to-head comparative trials

Study	Aprotinin vs. TXA WMD (95% CI)	TXA vs. EACA WMD (95% CI)
Henry *et al.* (2007)[24]	-131.54 (-192, -70.94)	-4.36 (-163.35, 154.63)
Brown *et al.* (2007)[15]	-195 (-286, -105)	-64 (-214, 85)*

Abbreviations: CI = confidence interval; WMD = weighted mean difference; TXA = tranexamic acid; EACA = epsilon aminocaproic acid
* EACA vs. TXA comparison

Table 10.2.7.3: Results for allogeneic blood transfusion – placebo-controlled trials

Study	Aprotinin vs. control RR (95% CI)	TXA vs. control RR (95% CI)	EACA vs. control RR (95% CI)
Henry *et al.* (2007)[24]	0.66 (0.61, 72)	0.69 (0.60, 0.79)	0.65 (0.47, 0.91)
Brown *et al.* (2007)[15]	HD 0.60 (0.53, 0.67) LD 0.76 (0.66, 0.86)	0.75 (0.60, 0.92)	0.63 (0.44, 0.90)

Abbreviations: CI = confidence interval; HD = high dose; LD = low dose; RR = relative risk; TXA = tranexamic acid; EACA = epsilon aminocaproic acid

Table 10.2.7.4: Results for allogeneic blood transfusion – head-to-head comparative trials

Study	Aprotinin vs. TXA RR (95% CI)	TXA vs. EACA RR (95% CI)
Henry *et al.* (2007)[43]	0.87 (0.72, 1.05)	1.07 (0.79, 1.46)
Brown *et al.* (2007)[15]	0.81 (0.60, 1.09)	0.81 (0.49, 1.34)*

Abbreviations: CI = confidence interval; RR = relative risk; TXA = tranexamic acid; EACA = epsilon aminocaproic acid

* EACA vs. TXA comparison

Table 10.2.7.5: Results for re-operation for bleeding – placebo-controlled trials

Study	Aprotinin vs. control RR (95% CI)	TXA vs. control RR (95% CI)	EACA vs. control RR (95% CI)
Henry *et al.* (2007)[24]	0.49 (0.34, 0.70)	0.65 (0.39, 1.08)	0.35 (0.11, 1.17)
Brown *et al.* (2007)[15]	HD 0.47 (0.32, 0.69) LD 0.69 (0.41, 1.18)	0.70 (0.44, 1.11)	0.51 (0.15, 1.82)

Abbreviations: CI = confidence interval; HD = high dose; LD = low dose; RR = relative risk; TXA = tranexamic acid; EACA = epsilon aminocaproic acid

Table 10.2.7.6: Results for re-operation for bleeding – head-to-head comparative trials

Study	Aprotinin vs. TXA RR (95% CI)	TXA vs. EACA RR (95% CI)
Henry *et al.* (2007)[43]	0.74 (0.54, 1.02)	1.02 (0.73, 1.41)
Brown *et al.* (2007)[15]	0.90 (0.50, 1.63)	0.72 (0.20, 2.56)*

Abbreviations: CI = confidence interval; RR = relative risk; TXA = tranexamic acid; EACA = epsilon aminocaproic acid

* EACA vs. TXA comparison

10.3 Summary of comparative effectiveness – paediatrics

The systematic review conducted by Eaton (2008)[51] evaluated the efficacy and safety of aprotinin, TXA and EACA in paediatric patients undergoing cardiac surgery. This review identified 11 comparative trials of the lysine analogues EACA and TXA including more than 1000 patients, with 340 patients receiving EACA, and 404 receiving TXA. Of the 11 studies identified, seven involved TXA. These seven studies involved children and adolescents aged between 1 day and 16 years of age. The dose of TXA administered varied considerably between trials with loading doses ranging from 10-100 mg/kg, maintenance doses ranging from 0-10 mg/kg/hr, and the prime dose (TXA added to the prime solution of the cardiopulmonary bypass circuit) ranged from 0-100 mg/kg. Given the large degree of clinical and methodological heterogeneity (i.e. variability in patients studied, procedures, methods, and dosing schemes) meta-analysis of the trial data was considered impractical.[51]

Based on the results of these trials, when an adequate dose is administered both EACA and TXA appear to be effective in reducing peri-operative bleeding and blood transfusion in cyanotic patients. However, the efficacy of these drugs in other high-risk and mixed populations is not well established.[51] Eaton claimed that the available literature is inadequate to evaluate the safety of TXA in the context of paediatric cardiac surgery. Studies investigating the effects of anti-fibrinolytic drugs in congenital heart surgery have lacked sufficient power to determine safety.[51] Currently there is insufficient, high-quality evidence to support the listing of TXA on the WHO Model List of Essential Medicines for use in paediatric cardiac surgery. Further, TXA is yet to gain regulatory approval for use in paediatric cardiac surgery.

11. Summary of comparative evidence on safety

Two recently published systematic reviews of randomised controlled trials reported that the use of TXA in cardiac surgery was not associated with an increased risk of myocardial infarction, stroke, deep vein thrombosis, pulmonary embolus, renal failure/dysfunction, or death compared to placebo/control.[15,24] In particular, the Cochrane review conducted by Henry *et al.* (2007)[24] showed that TXA treatment was not associated with an increased risk of death (18 trials; pooled RR 0.55, 95% CI 0.24 to 1.25), myocardial infarction (15 trials; pooled RR 0.91, 95% CI 0.44 to 1.88), stroke (13 trials; pooled RR 1.52, 0.52 to 4.41), deep vein thrombosis (4 trials; pooled RR, 0.04 to 3.47), pulmonary embolus (6 trials; pooled RR 0.33, 95% CI 0.04 to 3.15), or renal failure / dysfunction (5 trials; pooled RR 0.73, 95% CI 0.16 to 3.32). The systematic review conducted by Brown *et al.* (2007)[15] found there was no statistically significant difference between TXA and placebo/control in the rates of mortality (pooled RR 0.67, 95% CI 0.33 to 1.37; $P = 0.28$), stroke (pooled RR 1.31, 95% CI 0.59 to 2.93; $P = 0.51$), or myocardial infarction (pooled RR 0.94, 95% CI 0.51 to 1.74; $P = 0.85$). Although there appeared to be trend toward an increased risk of renal dysfunction in patients treated with TXA the result failed to reach statistical significance (pooled RR 2.02, 95% CI 0.73 to 5.60; $P = 0.18$).[15]

The meta-analysis of direct randomised comparisons of aprotinin, TXA and EACA in cardiac surgery conducted by Henry *et al.* (2008)[43] showed that there was no statistically significant difference between aprotinin and TXA in the risk of myocardial infarction (pooled RR 1.0 (95% CI 0.71 to 1.43), death (pooled RR 1.43, 95% CI 0.98 to 2.08), stroke (pooled RR 0.87, 95% CI 0.51 to 1.47), or renal dysfunction (pooled RR 0.93, 95% CI 0.75 to 1.16). However, these results were heavily influenced by the results of the BART study which accounted for 51% of the statistical weight in the case of the myocardial infarction analysis and 71% of the statistical weight in the case of the mortality analysis.

Any discussion regarding the comparative safety of the anti-fibrinolytic drugs aprotinin, TXA and EACA would not be complete without reference to the results of the BART study, the largest head-to-head comparative trial of the three anti-fibrinolytic drugs published to date.[30] This trial included 2328 subjects, of whom 779 patients were randomised to aprotinin, 769 were randomised to TXA and 780 were randomised to EACA treatment. The results of the BART study showed that at 30-days, the rate of death from any cause was 6.0% in the aprotinin group, as compared with 3.9% in the TXA group (RR 1.55, 95% CI 0.99 to 2.42) and 4.0% in the EACA group (RR 1.52, 95% CI 0.98 to 2.36). The trial was terminated early because of the higher rate of death in aprotinin treated patients compared to the TXA and EACA treated patients. There appeared to be no statistically significant difference between aprotinin and TXA in the rates of stroke (RR 0.78, 95% CI 0.45 to 1.35), myocardial infarction (RR 1.19, 95% CI 0.73 to 1.95), deep vein thrombosis/pulmonary embolism (RR 1.00, 95% CI 0.99 to 1.01), respiratory failure (RR 0.96, 95% CI 0.74 to 1.24), cardiac shock (RR 1.00, 95% CI 0.78 to 1.27), or renal failure (RR 1.05, 95% CI 0.81 to 1.36). Across all outcomes there was no statistically significant difference between TXA and EACA.

The PI for TXA (Cyklokapron®) describes tranexamic acid as being generally well tolerated with the most common adverse events being nausea, vomiting and diarrhoea (>1/100).[46] These dose-related gastrointestinal disturbances usually subside when the dose of TXA is reduced.[47] Giddiness and hypotension have been reported infrequently. Episodes of hypotension have occurred after rapid intravenous injection of TXA.[32,48] To avoid this response the PI for TXA (Cyklokapron®) suggests that the solution should not be injected more rapidly than 1 ml per minute.[32] Worldwide post-marketing surveillance data indicates thrombo-embolic events (e.g. deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) have been rarely reported in patients receiving TXA for indications other than haemorrhage prevention in patients with haemophilia (<1/1000).[32,46] There have been few reported instances of transient disturbance of colour vision associated with the use of TXA. Patients who develop this symptom should discontinue therapy.[47] Hypersensitivity skin reactions have also been reported with TXA use.[36]

12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group

12.1 Global costs of tranexamic acid

British National Formulary (2008)
Tranexamic acid (Cyklokapron®, Pfizer) – injection, tranexamic acid 100 mg/ml, net price 5-ml amp = £1.55

Costs sourced from the published literature

Spain	€3.14; 6 × 500 mg ampoules (2008 values)[49]
Sweden	€5.00; 2 × 500 mg ampoules (2001 values)[50]
United States	US$20-25; 1 g ampoule (2008 values)[51]
Canada	CAD$147; based on 100 mg/kg dose (2004 values)[4]
India	150 rupees; 30 mg/kg dose (2005 values)[52]
India	100 rupees; 20 mg/kg dose (2005 values)[52]

12.2 Comparative cost effectiveness

Using the search strategies presented in Appendix B, a number of economic studies were identified that examined the cost-effectiveness of using anti-fibrinolytic drugs in adults undergoing cardiac surgical procedures. However, all of the studies identified involved either cost-benefit or cost-effectiveness analyses of aprotinin and/or epsilon aminocaproic acid.[53-60] The literature search failed to identify a single economic analysis of TXA (i.e. cost-minimisation, cost-effectiveness, cost-benefit, or cost-utility analysis). Only one study was identified that evaluated the costs associated with tranexamic acid (TXA) compared to aprotinin and epsilon aminocaproic acid (EACA) in the context of cardiac surgery (Casati *et al.* 1999).[61] A summary of this study is presented in Table 12.2.1.

Table 12.2.1: Summary of the costs associated with tranexamic acid compared to aprotinin or epsilon aminocaproic acid - Casati *et al.* (1999)[61]

Study characteristics: Randomised, open-label study conducted at a university hospital in Italy
Population characteristics: Patients undergoing elective cardiac surgery requiring cardiopulmonary bypass (N = 210)
Interventions: *EACA* – 5 g over 20 minutes before sternotomy followed by a continuous infusion of 2 g/hr during the operation and 2.5 g added to the pump prime). EACA cost = $0.30 per gram. Cost per course of treatment = $3.80.
TXA – 1 g over 20 minutes before sternotomy, followed by a continuous infusion of 400 mg/hr during the operation and 500mg added to the pump prime). TXA cost = $1.00 per gram. Cost per course of treatment = $3.70.
AP – 280 mg over 20 minutes before sternotomy, followed by a constant infusion of 70 mg/hr during the operation and 280 mg added to the pump prime). AP cost = $31.00 per 70 mg. Cost per course of treatment = $370.00
Results: Costs associated with TXA treatment ($58.10 ± $105.10) were significantly lower than either EACA treatment ($100.70 ± $158.60) due to transfusion costs or AP treatment ($432.60 ± $118.70) due to drug costs [a]

Abbreviations: AP = aprotinin; EACA = epsilon aminocaproic acid; TXA = tranexamic acid
[a] Currency denomination and year were not provided.

Casati *et al.* (1999)[61] determined the overall costs of each treatment arm based on drug and transfusion costs only. The study by Casati *et al.* found that the costs of transfusion and pharmacological treatment were significantly less in the TXA group ($58.10 ± $105.10) compared to the EACA group ($100.70 ± $158.60) and the aprotinin group ($432.60 ± $118.70). However, the difference in overall costs between each of the treatment arms should be interpreted with caution as while there was a trend in favour of tranexamic acid in reducing the need for blood transfusions this difference did not reach statistical significance. Additionally, the Cochrane review by Henry *et al.*

(2007)[24] indicates that aprotinin may be slightly superior to tranexamic acid in reducing the need for blood transfusions. Therefore the relative difference in overall costs between tranexamic acid and aprotinin is likely to be smaller than that reported by Casati *et al.* (1999).[61] A recently published review by Eaton (2008)[51] indicated that the current acquisition costs for the anti-fibrinolytics is as follows: EACA is $1-2 for a 5-g vial, TXA is $20-25 for a 1-g vial, and aprotinin is approximately $200 for a 100 ml bottle (1 million KIU). A trial conducted by Karski *et al.* (2005)[4] reported that the cost of aprotinin was CAD$1348 per case compared to CAD$147 per case for TXA. Although the latter two studies provide more current comparative drug costs there is an urgent need for future studies to address the comparative cost-effectiveness of TXA, EACA, and aprotinin in the context of cardiac surgery.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Tranexamic acid is not FDA approved (Food and Drug Administration – United States), TGA approved (Therapeutic Goods Administration - Australia), or licensed in the United Kingdom to prevent or treat peri-operative bleeding in patients undergoing cardiac surgery. Although tranexamic acid injections are not registered in Australia, TXA injection has some use under the Special Access Scheme for individual patients.

Tranexamic acid (Cyklokapron®) is only FDA approved for use 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.[36]

TGA approved indications include (Approved by the Therapeutic Goods Administration 23 February 2001): hereditary angioneurotic oedema; short term use in the treatment of hyphema and in patients with established coagulopathies who are undergoing minor surgery; and, menorrhagia.[46]

In South Africa, the approved indications for TXA include: hereditary angioneurotic oedema; short term use in the treatment of hyphema and in patients with established coagulopathies who are undergoing minor surgery; management of dental extraction in haemophiliacs; and, menorrhagia.[48]

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

British Pharmacopoeia: Yes (British National Formulary, 56th Edition, 2008)
International Pharmacopoeia: Yes (Martindale - The Complete Drug Reference, 2008)
United States Pharmacopoeia: Yes (Martindale - The Complete Drug Reference, 2008)
Japanese Pharmacopoeia: Yes (Martindale - The Complete Drug Reference, 2008)
Chinese Pharmacopoeia: Yes (Martindale - The Complete Drug Reference, 2008)
European Pharmacopoeia: Yes (Martindale - The Complete Drug Reference, 2008)

15. Proposed (adapted) text for the WHO Model Formulary

The following was sourced and adapted from the Product Information for Cyklokapron® - Pharmacia & Upjohn Company, Kalamazoo, MI 49001, USA – Revised October 2000.[32]

TRANEXAMIC ACID – INJECTION

DESCRIPTION

Each ml of the sterile solution for intravenous injection contains 100 mg tranexamic acid and Water for Injection to 1 ml.

FORMULATION

Chemical Name: trans-4-(aminomethyl) cyclohexanecarboxylic acid.
Tranexamic acid is a white crystalline powder. Inert ingredients in the tablets are microcrystalline cellulose, talc, magnesium stearate, silicon dioxide and povidone.
The aqueous solution for injection has a pH of 6.5 to 8.0.

CLINICAL PHARMACOLOGY
Tranexamic acid is a competitive inhibitor of plasminogen activation, and at much higher concentrations, a non-competitive inhibitor of plasmin, i.e., actions similar to 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 receptor 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 per ml does not aggregate platelets *in vitro*. Tranexamic acid in concentrations up to 10 mg per ml blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood from normal subjects. On the other hand, tranexamic acid in concentrations of 10 mg and 1 mg per ml blood prolongs the thrombin time.

The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen. Tranexamic acid does not bind to serum albumin. After an intravenous dose of 1 g, the plasma concentration time curve shows a tri-exponential 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 the urine as the unchanged drug. Excretion of tranexamic acid is about 90% at 24 hours after intravenous administration of 10 mg per kg body weight.

An antifibrinolytic concentration of tranexamic acid remains in different tissues for about 17 hours, and in the serum, up to seven or eight hours. Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg per kg to pregnant women is about 30 mg per L, as high as in the maternal blood. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. In the joint fluid the same concentration is obtained as in the serum. The biological half-life of tranexamic acid in the joint fluid is about three hours. The concentration of tranexamic acid in a number of other tissues is lower than in blood. In breast milk the concentration is about one hundredth of the serum peak concentration. Tranexamic acid concentration in cerebrospinal fluid is about one tenth of that of the plasma. The drug passes into the aqueous humor, the concentration being about one tenth of the plasma concentration. Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.

CONTRAINDICATIONS
Tranexamic acid injection is contraindicated:
1. In patients with acquired defective colour vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity (see WARNINGS).
2. In patients with subarachnoid haemorrhage. Anecdotal experience indicates that cerebral oedema and cerebral infarction may be caused by tranexamic acid in such patients.
3. In patients with active intravascular clotting.

WARNINGS
Focal areas of retinal degeneration have developed in cats, dogs and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. The incidence of such lesions has varied from 25% to 100% of animals treated and was dose-related. At lower doses some lesions have appeared to be reversible. Limited data in cats and rabbits showed retinal changes in some animals with doses as low as 126 mg/kg/day (only about 3 times the recommended human dose) administered for several days to two weeks. No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials. However, visual abnormalities, often poorly characterized, represent the most frequently reported post-marketing adverse reaction 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.

PRECAUTIONS
General
The dose of tranexamic acid injection should be reduced in patients with renal insufficiency because of the risk of accumulation.

Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with tranexamic acid.

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.

Patients with a previous history of thrombo-embolic disease may be at increased risk for venous or arterial thrombosis.

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.

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

Carcinogenesis, mutagenesis, impairment of fertility
An increased incidence of leukaemia in male mice receiving tranexamic acid in food at a concentration of 4.8% (equivalent to doses as high as 5 g/kg/day) may have been related to treatment. Female mice were not included in this experiment.

Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months.

Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic / neoplastic changes in the liver. No mutagenic activity has been demonstrated in several in vitro and in vivo test systems.

Pregnancy (Category B)
Reproduction studies performed in mice, rats, and rabbits have not revealed any evidence of impaired fertility or adverse effects on the foetus due to tranexamic acid. There are no adequate and well-controlled studies in pregnant women. However, tranexamic acid is known to pass 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, this drug should be used during pregnancy only if clearly needed.

Labour and Delivery
See above under Pregnancy.

Nursing Mothers
Tranexamic acid is present in the mother's milk at a concentration of about a hundredth of the corresponding serum levels. Caution should be exercised when tranexamic acid is administered to a nursing woman.

Paediatric Use
The drug has had limited use in paediatric patients, principally in connection with tooth extraction. The limited data suggest that dosing instructions for adults can be used for paediatric patients needing tranexamic acid therapy.

ADVERSE REACTIONS
Gastrointestinal disturbances (e.g. nausea, vomiting, and diarrhoea) may occur but disappear when the dosage is reduced. Giddiness and hypotension have been reported occasionally. Hypotension has been observed when intravenous injection is too rapid. To avoid this response, the solution should not be injected more rapidly than 1 ml per minute.

Worldwide Post-marketing Reports: Thrombo-embolic events (eg, deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) have been rarely reported in patients receiving tranexamic acid for indications other than haemorrhage prevention in patients with haemophilia. However, due to the spontaneous nature of the reporting of medical events and the lack of controls, the actual incidence and causal relationship of drug and event cannot be determined.

OVERDOSAGE
There is no known case of over-dosage of tranexamic acid injection. Symptoms of over-dosage may be nausea, vomiting, orthostatic symptoms and/or hypotension.

DOSAGE AND ADMINISTRATION
Injection: 10-30 mg/kg IV followed by an infusion of 1-16 mg/kg/hr and 1-2 mg/kg added to the cardiopulmonary circuit (pump prime). Currently there is no consensus regarding optimal TXA dosing for cardiac surgery.

For intravenous infusion, tranexamic acid injection may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and Dextran solutions. The mixture should be prepared the same day the solution is to be used. Heparin may be added to tranexamic acid injection. Tranexamic acid injection should NOT be mixed with blood. The drug is a synthetic amino acid, and should NOT be mixed with solutions containing penicillin.

SUPPLIED
Tranexamic acid injection 100 mg/ml (10 x 10 ml ampoules)

STORAGE
Store tranexamic acid injection at room temperature: 15° to 30°C (59° to 86°F).

Appendix A

DRUGDEX® Tradename List	
Tradename list for tranexamic acid	
Name, Form & Strength	**Contact**
Amcacid (FM)	Glaxo Allen, Ital.
Amchafibrin	Rottapharm, Spain
Anvitoff (FM)	Abbott, Ger.
Anvitoff (FM)	Knoll, Switz.
Caprilon (DI)	Leiras, Fin.
Caprofides Hemostatico (FM)	Fides, Spain
Ciclokapron	Pfizer, Venez.
CP-Tran	Christo, Hong Kong
Cyclotrax	Shin Poong, Philipp.
Cyklo-F (FM)	Pharmacia, Austria
Cyklo-F (FM)	Pharmacia, Neth.
Cyklo-F	Pharmacia, Swed.
Cyklokapron - 100 MG/ML - solution for injection	Pharmacia & Upjohn
Cyklokapron - 500 MG/5 ML - solution for injection	Pharmacia & Upjohn
Cyklokapron - 500 MG - coated tablet	Pharmacia & Upjohn
Cyklokapron - 500 MG - Tablet	Pharmacia & Upjohn
Cyklokapron	Meda, Fin.
Cyklokapron	Meda, Irl.
Cyklokapron	Meda, Norw.
Cyklokapron	Meda, Swed.
Cyklokapron	Pfizer, Austria
Cyklokapron	Pfizer, Canad.
Cyklokapron	Pfizer Consumer, NZ
Cyklokapron	Pfizer, Denm.
Cyklokapron	Pfizer, Hong Kong
Cyklokapron	Pfizer, Neth.
Cyklokapron	Pfizer, Philipp.
Cyklokapron	Pfizer, Singapore
Cyklokapron	Pfizer, Switz.
Cyklokapron	Pfizer, USA
Cyklokapron	Pharmacia, Austral.
Cyklokapron	Pharmacia, Cz.
Cyklokapron	Pharmacia, Ger.
Cyklokapron	Pharmacia, S.Afr.
Cyklokapron	Pharmacia, UK
Dostan	Prosel, Philipp.
Espercil	Grunenthal, Chile
Exacyl	Eumedica, Belg.

DRUGDEX® Tradename List	
Tradename list for tranexamic acid	
Name, Form & Strength	**Contact**
Exacyl	Sanofi-Aventis, Fr.
Exacyl	Sanofi-Aventis, Hung.
Exacyl	Sanofi-Aventis, Pol.
Exacyl	Sanofi Synthelabo, Cz.
Fibrinon	Jean-Marie, Philipp.
Fimoplas	Blue Sky, Philipp.
Frenolyse (FM)	Specia, Fr.
Hemoclot	Solvang, Philipp.
Hemostan	Biomedis, Philipp.
Hemotrex	Foramen, Philipp.
Hexakapron	Teva, Israel
Micranex	Vamsler, Philipp.
Proklot	Torrent, Philipp.
Qualixamin	Quality, Hong Kong
Quixil (DI)	Omrix, Ger.
Quixil	Ethicon, Fr.
Quixil	Johnson & Johnson, Ital.
Quixil	Omrix, Neth.
Sin Colgen Kowa Kaze	Kowa, Jpn
Spotof	CCD, Fr.
Tramic	TO-Chemicals, Thai.
Tranexamic Acid Injection BP 2007	
Tranexamic Acid Tablets BP 2007	
Tranex	Malesci, Ital.
Tranon	Recip, Swed.
Transamine	Fako, Turk.
Transamin	Daiichi, Hong Kong
Transamin	Daiichi, Jpn
Transamin	Daiichi, Malaysia
Transamin	Daiichi, Thai.
Transamin	Nikkho, Braz.
Transamin	Nikolakopoulos (Nikolakopoulos), Gr.
Transil (FM)	Malesci, Ital.
Trenaxin	Yung Shin, Philipp.
Tren	YSP, Malaysia
Ugurol (FM)	Bayer, Ger.
Ugurol	Rottapharm, Ital.

Martindale Products	
Tradename list for tranexamic acid	
Name, Form & Strength	**Contact**
Amcacid (Glaxo Allen, Ital.)(FM)	Glaxo Allen, Ital.
Amchafibrin (Rottapharm, Spain)	Rottapharm, Spain Rottapharm
Anvitoff (Abbott, Ger.)(FM)	Abbott, Ger. Abbott GmbH & Co. KG
Anvitoff (Knoll, Switz.)(FM)	Knoll, Switz.
CP-Tran (Christo, Hong Kong)	Christo, Hong Kong Christo Pharmaceuticals Ltd
Caprilon (Leiras, Fin.)(DI)	Leiras, Fin. Oy Leiras Finland AB
Caprofides Hemostatico (Fides, Spain)(FM)	Fides, Spain
Ciclokapron (Pfizer, Venez.)	Pfizer, Venez. Pfizer Division Consumo
Cyclotrax (Shin Poong, Philipp.)	Shin Poong, Philipp. Phil Shin Poong Pharma Inc.
Cyklo-F (Pharmacia, Austria)(FM)	Pharmacia, Austria Pharmacia Austria GmbH
Cyklo-F (Pharmacia, Neth.)(FM)	Pharmacia, Neth. Pharmacia BV
Cyklo-F (Pharmacia, Swed.)	Pharmacia, Swed. Pharmacia Sverige AB
Cyklokapron (Meda, Fin.)	Meda, Fin. Meda Oy
Cyklokapron (Meda, Irl.)	Meda, Irl.
Cyklokapron (Meda, Norw. ; Pfizer, Norw.)	Meda, Norw. Meda A/S
Cyklokapron (Meda, Swed. ; Pfizer, Swed.)	Meda, Swed. Meda AB
Cyklokapron (Pfizer Consumer, NZ)	Pfizer Consumer, NZ
Cyklokapron (Pfizer, Austria)	Pfizer, Austria Pfizer Corporation Austria GmbH
Cyklokapron (Pfizer, Canad.)	Pfizer, Canad. Pfizer Canada Inc.
Cyklokapron (Pfizer, Denm.)	Pfizer, Denm. Pfizer ApS Danmark
Cyklokapron (Pfizer, Hong Kong)	Pfizer, Hong Kong Pfizer Corporation Hong Kong Ltd
Cyklokapron (Pfizer, Neth.)	Pfizer, Neth. Pfizer BV
Cyklokapron (Pfizer, Philipp.)	Pfizer, Philipp. Pfizer Inc.
Cyklokapron (Pfizer, Singapore)	Pfizer, Singapore Pfizer Pte Ltd
Cyklokapron (Pfizer, Switz.)	Pfizer, Switz. Pfizer SA
Cyklokapron (Pfizer, USA)	Pfizer, USA Pfizer Inc.
Cyklokapron (Pharmacia, Austral.)	Pharmacia, Austral. Pharmacia Australia P/L
Cyklokapron (Pharmacia, Cz.)	Pharmacia, Cz. Pharmacia & Upjohn sro
Cyklokapron (Pharmacia, Ger.)	Pharmacia, Ger. Pharmacia GmbH
Cyklokapron (Pharmacia, S.Afr.)	Pharmacia, S.Afr.
Cyklokapron (Pharmacia, UK)	Pharmacia, UK
Dostan (Prosel, Philipp.)	Prosel, Philipp. Prosel Pharma Inc.
Espercil (Grunenthal, Chile)	Grunenthal, Chile Grunenthal Chilena Ltda
Exacyl (Eumedica, Belg.)	Eumedica, Belg.
Exacyl (Sanofi Synthelabo, Cz.)	Sanofi Synthelabo, Cz. Sanofi-Synthelabo sro
Exacyl (Sanofi-Aventis, Fr.)	Sanofi-Aventis, Fr. Sanofi-Aventis
Exacyl (Sanofi-Aventis, Hung.)	Sanofi-Aventis, Hung. Sanofi-Aventis zrt Magyarorszag
Exacyl (Sanofi-Aventis, Pol.)	Sanofi-Aventis, Pol. Sanofi-Synthelabo Sp. zo,o,, grupa Sanofi-Aventis
Fibrinon (Jean-Marie, Philipp.)	Jean-Marie, Philipp.
Fimoplas (Blue Sky, Philipp.)	Blue Sky, Philipp. Blue Sky Trading Co. Inc.

Martindale Products	
Tradename list for tranexamic acid	
Name, Form & Strength	**Contact**
Frenolyse (Specia, Fr.)(FM)	Specia, Fr.
Hemoclot (Solvang, Philipp.)	Solvang, Philipp. Solvang Pharma Inc.
Hemostan (Biomedis, Philipp.)	Biomedis, Philipp. Biomedis Inc.
Hemotrex (Foramen, Philipp.)	Foramen, Philipp.
Hexakapron (Teva, Israel)	Teva, Israel Teva Pharmaceuticals Ind. Ltd
Micranex (Vamsler, Philipp.)	Vamsler, Philipp. Vamsler Phils Inc.
Proklot (Torrent, Philipp.)	Torrent, Philipp. Torrent Pharma Philippines Inc.
Qualixamin (Quality, Hong Kong)	Quality, Hong Kong Quality Pharmaceutical Laboratory Ltd
Quixil (Omrix, Ger.)(DI)	Omrix, Ger.
Quixil (Ethicon, Fr.)	Ethicon, Fr. Ethicon SAS
Quixil (Johnson & Johnson, Ital.)	Johnson & Johnson, Ital. Johnson & Johnson Divisione Farmacia S.p.A.
Quixil (Omrix, Neth.)	Omrix, Neth.
Sin Colgen Kowa Kaze (Kowa, Jpn)	Kowa, Jpn Kowa Co. Ltd
Spotof (CCD, Fr.)	CCD, Fr. Laboratoires CCD
Tramic (TO-Chemicals, Thai.)	TO-Chemicals, Thai. TO-Chemicals (1979) Ltd
Tranarest (Zydus, India)	Zydus, India Zydus Cadila Group
Tranex (Malesci, Ital.)	Malesci, Ital. Malesci Istituto Farmacobiologico S.p.A.
Tranexamic Acid Injection BP 2007	
Tranexamic Acid Tablets BP 2007	
Tranfib (Cipla, India)	Cipla, India Cipla Ltd
Tranfib MF (Cipla, India)	Cipla, India Cipla Ltd
Tranon (Recip, Swed.)	Recip, Swed. Recip AB
Transamin (Daiichi, Hong Kong)	Daiichi, Hong Kong
Transamin (Daiichi, Jpn)	Daiichi, Jpn Daiichi Pharmaceutical Co. Ltd
Transamin (Daiichi, Malaysia)	Daiichi, Malaysia
Transamin (Daiichi, Thai.)	Daiichi, Thai. Daiichi Pharmaceutical (Thailand) Ltd
Transamin (Nikkho, Braz.)	Nikkho, Braz. Quimica E Farmaceutica Nikkho do Brasil Ltda
Transamin (Nikolakopoulos (Nikolakopoulos), Gr.)	Nikolakopoulos (Nikolakopoulos), Gr.
Transamine (Fako, Turk.)	Fako, Turk. Fako Ilacari A.S.
Transil (Malesci, Ital.)(FM)	Malesci, Ital. Malesci Istituto Farmacobiologico S.p.A.
Traxamic (Systopic, India)(FM)	Systopic, India Systopic Laboratories Ltd
Tren (YSP, Malaysia)	YSP, Malaysia Y.S.P. Industries (M) Sdn Bhd
Trenaxin (Yung Shin, Philipp.)	Yung Shin, Philipp. Yung Shin (Phillipines) Inc.
Ugurol (Bayer, Ger.)(FM)	Bayer, Ger. Bayer Vital GmbH
Ugurol (Rottapharm, Ital.)	Rottapharm, Ital. Rottapharm S.r.l.

Appendix B

Unrestricted search

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update
Search Strategy:

---

1 exp Tranexamic Acid/
2 (tranexamic or cyklokapron or pharmacia).tw.
3 (t-amcha or amca or amcha).tw.
4 (urugol or transamin or kabi).tw.
5 (exacyl or anvitoff).tw.
6 or/1-5

Randomised controlled trial search filter

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update
Search Strategy:

---

1 randomized controlled trial.pt
2 controlled clinical trial.pt
3 exp Randomized Controlled Trial/
4 exp Random Allocation/
5 exp Double-Blind Method/
6 exp Single-Blind Method/
7 or/1-6
8 exp Clinical Trial/
9 clinical trial.pt
10 (clin$ adj25 trial$).ti,ab
11 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
12 exp Placebos/
13 placebo$.ti,ab
14 random$.ti,ab
15 research design.sh
16 or/8-15
17 exp Evaluation Studies/
18 follow up studies.sh
19 prospective studies.sh
20 (control$ or prospectiv$ or volunteer$).ti,ab
21 or/17-20
22 7 or 16 or 21

Systematic review search filter

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update
Search Strategy:

---

1 exp Meta-Analysis/
2 meta-analys$.mp
3 systematic review$.mp
4 critical review$.mp
5 Cochrane review$.mp
6 literature review$.mp
7 overview$.mp
8 or/1-7

Blood loss and blood transfusion search filter

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update
Search Strategy:

---

1 exp Blood Transfusion/
2 exp Hemorrhage/
3 exp Anesthesia/
4 transfusion$.tw
5 bleed$.tw
6 blood loss$.tw
7 hemorrhag$.tw
8 or/1-7

Economic search filter

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update
Search Strategy:

---

1 exp Economics/
2 exp Cost-benefit analysis/
3 exp "Costs and cost analysis"/
4 exp quality-adjusted life years/
5 cost effect$.tw
6 cost utilit$.tw
7 economic evaluation$.tw
8 QALY$.tw
9 cost benefit$.tw
10 cost minimi$.tw
11 economic analys$.tw
12 life year$.tw
13 or/1-12

Unrestricted search

Database: EMBASE <1980 to 2008 Week 39>
Search Strategy:

---

1 exp Tranexamic Acid/
2 (tranexamic or cyklokapron or pharmacia).tw.
3 (t-amcha or amca or amcha).tw.
4 (urugol or transamin or kabi).tw.
5 (exacyl or anvitoff).tw.
6 or/1-5

Randomised controlled trial search filter

Database: EMBASE <1980 to 2008 Week 39>
Search Strategy:

---

1 exp Randomized Controlled Trial/
2 exp Random Allocation/
3 exp Double-Blind Method/
4 exp Single-Blind Method/
5 exp Clinical Trial/
6 (clin$ adj25 trial$).ti,ab
7 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
8 exp Placebos/
9 placebo$.ti,ab
10 random$.ti,ab
11 exp Evaluation Studies/
12 (control$ or prospectiv$ or volunteer$).ti,ab
13 crossover trial$.mp
14 follow up studies.mp
15 comparative study.mp
16 exp Prospective Study/
17 exp Longitudinal Study/
18 or/1-17

Systematic review search filter

Database: EMBASE <1980 to 2008 Week 39>
Search Strategy:

---

1 exp Meta-Analysis/
2 exp "Systematic Review"/
3 meta-analys$.mp
4 systematic review$.mp
5 critical review$.mp
6 Cochrane review$.mp
7 literature review$.mp
8 literature overview$.mp
9 or/1-8

Blood loss and blood transfusion search filter

Database: EMBASE <1980 to 2008 Week 39>
Search Strategy:

---

1 exp Blood Transfusion/
2 exp Hemorrhage/
3 exp Anesthesia/
4 transfusion$.tw
5 bleed$.tw
6 blood loss$.tw
7 hemorrhag$.tw
8 or/1-7

Economic search filter

Database: EMBASE <1980 to 2008 Week 39>
Search Strategy:
---
1 exp ECONOMICS/
2 exp "Cost Benefit Analysis"/
3 exp "COST MINIMIZATION ANALYSIS"/
4 exp "COST EFFECTIVENESS ANALYSIS"/
5 exp "COST UTILITY ANALYSIS"/
6 exp "DRUG COST"/
7 exp "HEALTH CARE COST"/
8 exp "COST OF ILLNESS"/
9 exp "HOSPITALIZATION COST"/
10 exp Quality Adjusted Life Year/ or exp Economic Aspect/
11 quality-adjusted life years.tw
12 QALYs.tw
13 economic evaluation$.tw
14 cost effect$.tw
15 cost utilit$.tw
16 cost benefit$.tw
17 cost minimis$.tw
18 economic analys$.tw
19 life year$.tw
20 life year$.tw
21 or/1-20

Appendix C

Summary of treatment regimens reported in head-to-head comparative trials of TXA

Study	Year	Country	Type of cardiac surgery	TXA dose
Isetta et al.[62]	1993	France	NR	L = 15 mg/kg
Blauhut et al.[63]	1994	Switzerland	CABG	L = 10 mg/kg M = 1.0 mg/kg/h
Penta de Peppo et al.[64]	1995	Italy	CAGB & Valve Sx.	L = 10 mg/kg M = 1.0 mg/kg/h
Corbeau et al.[65]	1995	France	CABG & Valve Sx.	L = 15 mg/kg E = 15 mg/kg
Pugh et al.[66]	1995	UK	Primary CABG	L = 2.5 g P = 2.5 g
Speekenbrink et al.[67]	1995	The Netherlands	Primary CABG	L = 10 mg/kg M = 1.0 mg/kg/h
Menichetti et al.[68]	1996	Italy	Primary CABG	L = 10 mg/kg M = 3.0 mg/kg/h P = 10 mg/kg
Pinosky et al.[69]	1997	USA	Primary CABG	L = 15 mg/kg M = 1.0 mg/kg/h for 6 h
Mongan et al.[70]	1998	USA	Primary CABG	L = 15 mg/kg M = 2.0 mg/kg/h for 6 h
Hardy et al.[71]	1998	Canada	Primary CABG	L = 10 g
Misfeld et al.[72]	1998	Germany	Primary CABG	L = 10 mg/kg M = 1.0 mg/kg/h
Casati et al.[61]	1999	Italy	Primary CABG & Valve Sx.	L = 1.0 g M = 400 mg/h P = 500 mg
Bernet et al.[73]	1999	Switzerland	Primary CABG	L = 10 g
Nuttall et al.[74]	2000	USA	Re-do CABG & Valve Sx.	L = 10 mg/kg M = 1.0 mg/kg/h
Maineri et al.[75]	2000	Italy	Primary CABG	L = 20 mg/kg M = 2.0 mg/kg/h
Wong et al.[76]	2000	Canada	Re-do CABG & Valve Sx.	L = 10 g
Casati et al.[77]	2000	Italy	Primary CABG, Valve Sx. & ASD Repair	L = 1.0 g M = 400 mg/h P = 500 mg
Fergusson et al.[30]	2008	Canada	Re-do CABG, isolated MVR, Combined CABG & Valve Sx., Multiple valve replacement or repair & Sx. of ascending aorta	L = 30 mg/kg M = 16 mg/kg/h P = 2 mg/kg

Abbreviations: ASD = atrial septal defect; CABG = coronary artery bypass graft; MVR = mitral valve replacement; Sx = surgery; NR = not reported; L = loading dose; M = maintenance dose/continuous infusion; P = pump prime dose; E = after protamine administration; mg = milligram; g = gram; kg = kilogram; h = hour.
Source: Adapted from Table 1 & Table 3 – Carless *et al.* (2005)[23]

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