18th Expert Committee on the Selection and Use of Essential Medicines
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PROPOSAL FOR THE INCLUSION OF TRANEXAMIC ACID (ANTI-FIBRINOLYTIC – LYSINE ANALOGUE) IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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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 use in adult trauma patients with on-going significant haemorrhage, or at risk of significant haemorrhage within 8 hours of injury. On-going significant haemorrhage is defined as (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute).

This proposal is based on the results of the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) Trial.[1] A summary of the results of the CRASH-2 trial can be found below:

Background
Bleeding accounts for about one third of traumatic injury deaths. Tranexamic acid (TXA) can reduce bleeding in elective surgical patients. The CRASH-2 Trial assessed the effects of the early administration of a short course of TXA on death, vascular occlusive events and the receipt of blood transfusion in trauma patients.

Methods
20,211 adult trauma patients with, or at risk of, significant bleeding were randomised within eight hours of injury to either TXA (loading dose 1 gram over 10 minutes then infusion of 1 gram over 8 hours) or matching placebo, with 99·6% follow-up. The primary outcome was death in hospital within four weeks of injury, and was described using the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multi-organ failure, head injury and "other". Secondary outcomes were vascular occlusive events and need of blood transfusion or surgical intervention. All analyses were by intention to treat.

Findings
10 096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10 060 and 10 067, respectively, were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14·5%] tranexamic acid group *vs* 1613 [16·0%] placebo group; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035). The risk of death due to bleeding was significantly reduced (489 [4·9%] *vs* 574 [5·7%]; relative risk 0·85, 95% CI 0·76–0·96; p=0·0077).

Interpretation
TXA acid safely reduced the risk of death in bleeding trauma patients in this study. Based on these results, TXA should be considered for use in bleeding trauma patients.

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

The London School of Hygiene & Tropical Medicine is a designated World Health Organisation Collaborating Centre for Research and Training in Injury and Violence Prevention.

3. Name of the organisation consulted

London School of Hygiene and Tropical Medicine

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: a loading dose of 1 gram over 10 minutes and a maintenance dose of 1 gram over 8 hours.

Currently there is no consensus regarding optimal TXA dosing in trauma patients. Participants enrolled into the CRASH-2 trial were given a loading dose of 1 gram of TXA infused over ten minutes, followed by an intravenous infusion of 1 gram over eight hours. Of the 20,211 patients enrolled into the CRASH-2 trial no adverse events considered as serious, unexpected and suspected to be related to the study treatment were reported.

6. International availability – sources, if possible manufacturers

Tranexamic acid is marketed under various trade names worldwide. 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)

Unintentional and intentional injuries are major causes of death world-wide.[2-3] Each year, over a million people die as a result of road traffic injuries around the world. Road traffic injuries are the ninth leading cause of death in the world and it is predicted that by 2020 such injuries will become the third leading cause of death and disability. About 1·6 million people die as a result of intentional acts of interpersonal, collective or self directed violence each year. More than 90% of trauma deaths occur in low- and middle-income countries.[3] Haemorrhage is responsible for about one third of in-hospital trauma deaths and may also contribute to deaths from multi-organ failure.[4]

The haemostatic system helps to maintain the integrity of the circulation after severe vascular injury, whether traumatic or surgical in origin.[5] Major surgery and trauma trigger similar haemostatic responses and in both situations massive blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma, is stimulation of clot breakdown (fibrinolysis) which may become pathological (hyper-fibrinolysis) in some.[5] Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, and do so without apparently increasing the risk of post-operative complications.[6]

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen.[5] A systematic review of the randomised trials of TXA in elective surgical patients identified 53 studies including in total 3,836 participants.[6] TXA reduced the need for blood transfusion by one third (RR=0·61, 95% CI 0·54 to 0·70),[6] with a reduction in mortality that was not statistically significant (RR=0·61, 95% CI 0·32 to 1·12).[6] Because the haemostatic responses to surgery and trauma are similar,[7] TXA might reduce mortality due to

bleeding in trauma patients. However prior to the CRASH-2 Trial, there have been no randomised trials of TXA in trauma patients.[8]

Aims

The study aims, methods and protocol have been reported previously (www.CRASH-2.LSHTM.ac.uk). The trial protocol was peer reviewed and published on the Lancet website in 2005 (http://www.thelancet.com/protocol-reviews/05PRT-1). All investigators obtained the relevant ethics committee and regulatory agencies' approvals before recruitment could begin. This study is recorded on the following clinical trial registers: ISRCTN (number 86750102); Clinicaltrials.gov (identifier NCT00375258); South African Clinical Trial Register / Department of Health (identifier DOH-27-0607-1919).

Eligibility and consent

Adult trauma patients with on-going significant haemorrhage (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute), or who were considered to be at risk of significant haemorrhage, and who were within eight hours of injury, were eligible for the trial. Patients were included if the responsible doctor was substantially uncertain whether or not to treat with TXA (i.e. entry was governed by the uncertainty principle).[9] Patients for whom the responsible doctor considered there was a clear indication for TXA were not to be randomised. Likewise, patients for whom there was considered to be a clear contraindication to TXA treatment were not to be randomised. However, if the responsible doctor was substantially uncertain as to whether or not to treat with TXA, these patients were eligible for randomisation.

Methods

Patients were randomly allocated to receive a loading dose of 1 gram of TXA infused over 10 minutes, followed by an intravenous infusion of 1 gram over 8 hours, or matching placebo (0·9% saline).

Outcome measures

The primary outcome was death in hospital within four weeks of injury. Cause of death was described using the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multi-organ failure, head injury and "other". Secondary outcomes were vascular occlusive events (myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis), surgical intervention (neurosurgery, thoracic, abdominal and pelvic surgery), receipt of blood transfusion, and units of blood products transfused. Dependency was measured at hospital discharge, or on day 28 if still in hospital, using the five point Modified Oxford Handicap Scale. The scale was dichotomised into 'dead or dependent' (dead, fully dependent requiring attention day and night, or dependent but not requiring constant attention) or 'independent' (some restriction in lifestyle but independent, minor symptoms, or no symptoms).[10] Data on the use of recombinant Factor VIIa and on gastrointestinal bleeding as a complication were also collected. As the expected complications of the trial treatment were collected on the outcome form, only adverse events that were serious, unexpected and suspected to be related to the study treatment were to be reported separately. Outcomes were recorded if they occurred while the patient was still in hospital for up to 28 days after randomisation. Data were sent to the coordinating centre either electronically (using encrypted electronic data forms which could be sent by email or uploaded to a secure server) or by fax, and were entered onto a central database at the trial coordinating centre in London. We monitored the quality of the trial data using a combination of centralised statistical data checking and site visits at which patient outcome forms were compared with clinical case notes.[11]

Pre-specified subgroup analyses

We planned to report the effects of treatment on the primary outcome subdivided by four baseline characteristics: (1) estimated hours since injury (<1, 1-3, 3-8 hours) (2) systolic blood pressure (≤75, 76-89, ≥90 mmHg) (3) Glasgow Coma Score [severe 3 to 8], moderate [9 to 12], mild [13 to 15]) and (4) type of injury (penetrating only or blunt, which included blunt and penetrating).

Statistical analyses

The statistical analysis plan was sent to all Ethics Committees and Regulatory Agencies before un-blinding. As the risk of death might be around 20%, and even a two percent survival difference (corresponding to a relative risk of death with TXA of 0.9) would be important, a trial involving 20,000 patients was planned, which would then have an 85% chance of achieving 2P<0·01 and a 95% chance of 2P<0·05. All analyses were conducted on an 'intention-to-treat' basis. For each binary outcome, we calculated relative risks and 95% confidence intervals and two-sided p-values for statistical significance. The relative risk gives the number of times more likely (RR > 1) or less likely (RR < 1) an event is to happen in the TXA group compared with the placebo group. For analysis of the pre-specified subgroups (primary outcome only) we calculated relative risks with 99% confidence intervals with two-sided p-values. Heterogeneity in treatment effects across subgroups was assessed using chi-squared tests. We pre-specified that unless there was strong evidence (p<0·001) against homogeneity of effects, the overall relative risk would be considered the most reliable guide to the approximate relative risks in all subgroups. Means and standard deviations were estimated for count outcomes and we calculated two-sided p-values of the difference in means of logarithms. A complete case analysis, only including cases for which the relevant outcome data were available, was conducted. There was no imputation for missing data. During the study, un-blinded interim analyses were supplied by an independent statistician to the Data Monitoring and Ethics Committee.

This study is recorded on the following clinical trial registers: ISRCTN (number 86750102); Clinicaltrials.gov (identifier NCT00375258); South African Clinical Trial Register / Department of Health (identifier DOH-27-0607-1919).

Role of the funding source

The study was designed, conducted, analysed, and interpreted by the investigators, entirely independently of all funding sources. The Writing Committee had full access to all data in the study and final responsibility to submit for publication.

Results

Patients were enrolled at 274 hospitals in 40 countries. The first patient was enrolled in May 2005. A total of 20,211 patients were randomised to TXA or placebo (figure 1), of which 20,116 were randomised through the local pack system and 95 through telephone randomisation. The data from four patients were removed from the trial because their consent was withdrawn after randomisation. Five patients enrolled in the study were later found to be younger than 16 years. Age was unknown for four patients. Twenty three patients were enrolled more than eight hours after their injury. Time of injury was not known for 11 patients. Nine patients were found to have haemorrhage from non-traumatic conditions. Three patients were given a pack different to that allocated. The planned consent procedures were not fully followed in 34 patients. The relevant ethics committees were informed and approval for use of data was obtained. All of the patients, apart from the four patients in whom consent was withdrawn, are included in the analysis.

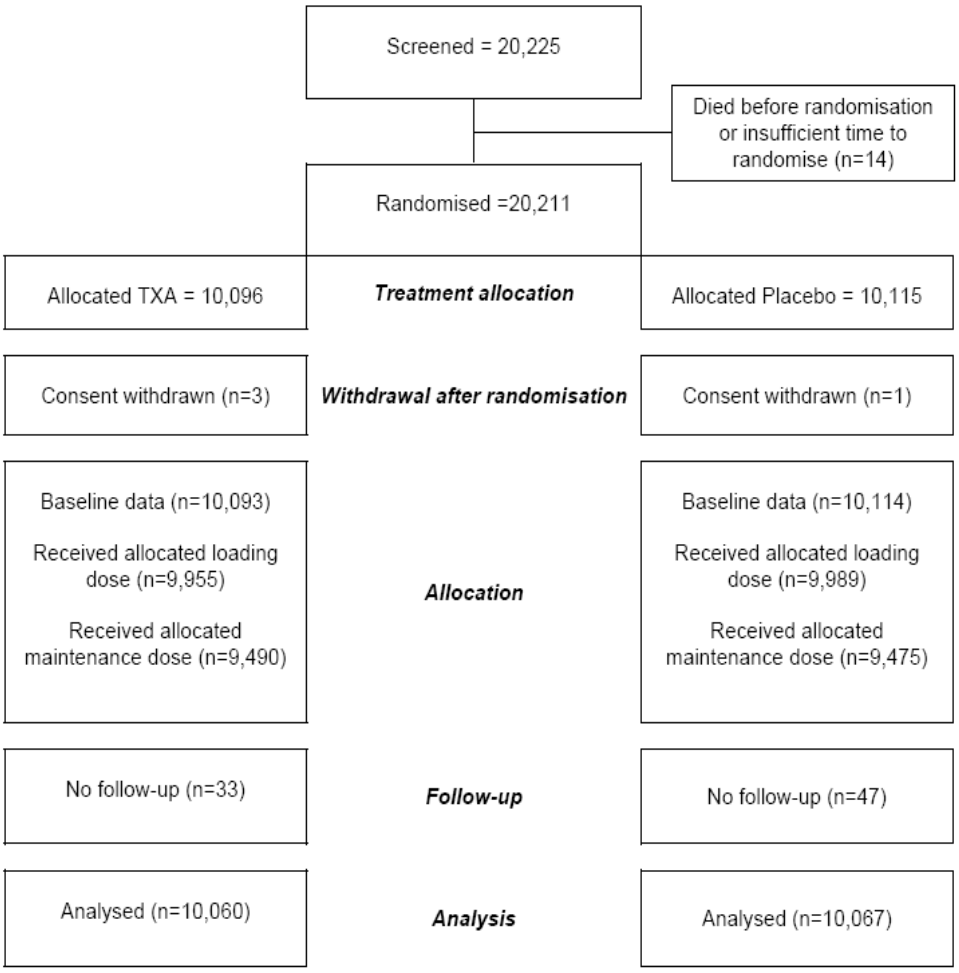

Figure 1: Trial profile. *No follow-up relates to those patients where there is no information on the primary endpoint*

Treatment groups were balanced with respect to all baseline patient characteristics (table 1). Primary outcome data were available for 20,127 (99·6%) randomised patients, 10,060 allocated to TXA and 10,067 placebo, of whom 19,944 (99·1%) patients were known to have completed the loading dose and 18,965 (94·2%) the 8-hour maintenance dose. A total of 3,076 (15·3%) patients died, of whom 1086 (35.3%) died on the day of randomisation (figure 2). There were 1,063 deaths due to bleeding, of which 637 (59.9%) were on the day of randomisation.

		TXA [n=10,093]	Placebo [n=10,114]
Gender	Male	8,439 (83·6%)	8,496 (84%)
	Female	1,654 (16·4%)	1,617 (16%)
	Not known	0	1 (0·01%)
Age (years)	Mean age (SD)	34·6 (14·1)	34·5 (14·4)
	<25[#]	2,783 (27·6%)	2,855 (28·2%)
	25-34	3,012 (29·8%)	3,081 (30·5%)
	35-44	1,975 (19·6%)	1,841 (18·2%)
	>44	2,321 (23·0%)	2,335 (23·1%)
	Not known	2 (0·02%)	2 (0·02%)
Time since injury (hours)	Mean (SD)	2·8 (2·2)	2·9 (2·6)
	≤1	3,756 (37·2%)	3,722 (36·8%)
	>1 to ≤3	3,045 (30·2%)	3,006 (29·7%)
	>3*	3,287 (32·6%)	3,380 (33·4%)
	Not known	5 (0·05%)	6 (0·06%)
Type of injury	Blunt[†]	6,812 (67·5%)	6,843 (67·7%)
	Penetrating	3,281 (32·5%)	3,271 (32·3%)
Systolic BP (mmHg)	≤75	1,566 (15·5%)	1,608 (15·9%)
	76-89	1,615 (16.0%)	1,697 (16·8%)
	>89	6,901(68·4%)	6,791 (67·1%)
	Not known	11 (0·11%)	18 (0·18%)
Respiratory rate (per min)	<10	160 (1·6%)	149 (1·5%)
	10-29	8,355 (82·8%)	8,436 (83·4%)
	>29	1,491 (14·8%)	1,429 (14·1%)
	Not known	87 (0·86%)	100 (0·99%)
Central capillary refill time (secs)	2 or less	3,432 (34·0%)	3,406 (33·7%)
	3 to 4	4,665 (46·2%)	4,722 (46·7%)
	> 4	1,699 (16·8%)	1,672 (16·5%)
	Not known	297 (2·9%)	314 (3·1%)
Heart rate (per min)	<77	875 (8·7%)	871 (8·6%)
	77-91	1,727 (17·1%)	1,770 (17·5%)
	92-107	2,556 (25·3%)	2,546 (25·2%)
	>107	4,872 (48·3%)	4,853 (48·0%)
	Not known	63 (0·62%)	74 (0·73%)
Glasgow Coma Score (Total)	Severe [3-8]	1,799 (17·8%)	1,839 (18·2%)
	Moderate [9-12]	1,353 (13·4%)	1,351 (13·4%)
	Mild [13-15]	6,934 (68·7%)	6,908 (68·3%)
	Not known	7 (0·07%)	16 (0·16%)
Any protocol violation		39 (0·4%)	39 (0·4%)

Table 1: Baseline data

Note:
Percentages are of group total unless specified
[†] *includes patients with both blunt & penetrating and only blunt injuries*
**includes 23 patients randomised more than 8 hours after injury*
[#]*includes five patients aged less than 16 years*

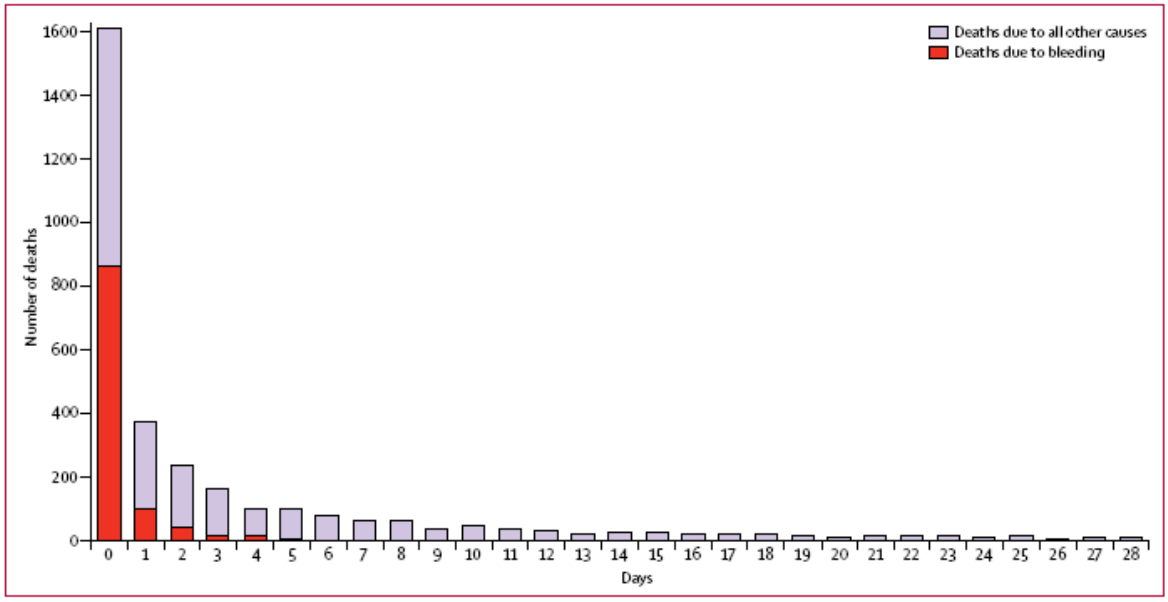

Figure 2: Mortality by days from randomisation

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: Death by cause

All-cause mortality was significantly reduced with tranexamic acid (table 2). The RR of death with tranexamic acid was 0・91 (95% CI 0・85–0・97, p=0・0035; table 2). The risk of death due to bleeding was significantly reduced (table 2). This effect was also apparent for deaths due to bleeding on the day of randomisation (282 [2・8%] tranexamic acid group *vs* 355 [3・5%] placebo group; RR 0・80, 95% CI 0・68–0・93, p=0・0036). There were 33 (0・3%) deaths in the tranexamic acid group versus 48 (0・5%) in the placebo group from vascular occlusion (table 2), including seven versus 22 deaths from myocardial infarction, eight versus five from stroke, and 18 versus 21 from pulmonary embolism, respectively. Deaths from multiorgan failure, from head injury, or due to other causes did not differ significantly in the tranexamic acid group versus the placebo group (table 2).

Vascular occlusive events (fatal or non-fatal) did not differ significantly, with 168 (1・7%) patients with one or more vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) in patients allocated to tranexamic acid versus 201 (2・0%) in those allocated to placebo.

Vascular occlusive events[#]	TXA [n = 10060]	Placebo [n = 10067]	RR (95% CI)	p-value
Any vascular occlusive event	168 (1·7%)	201 (2·0%)	0·84 (0·68 – 1·02)	0·084
Myocardial infarction	35 (0·4%)	55 (0·6%)	0·64 (0·42 – 0·97)	0·035
Stroke	57 (0·6%)	66 (0·7%)	0·86 (0·61 – 1·23)	0·42
Pulmonary embolism	72 (0·7%)	71 (0·7%)	1·00 (0·73 – 1·40)	0·93
Deep vein thrombosis	40 (0·4%)	41 (0·4%)	0·98 (0·63 – 1·51)	0·91
Management				
Any surgery	4,814 (47·9%)	4,836 (48·0%)	1·00 (0·97 –1·02)	0·79
Neurosurgery	1,040 (10·3%)	1,059 (10·5%)	0·98 (0·91 – 1·07)	0·67
Chest surgery	1,518 (15·1%)	1,525 (15·2%)	1·00 (0·93 – 1·06)	0·91
Abdominal surgery	2,487 (24·7%)	2,555 (25·4%)	0·97 (0·92 – 1·00)	0·28
Pelvic surgery	683 (6·8%)	648 (6·4%)	1·05 (0·95 – 1·17)	0·31
Blood product transfused	5,067 (50·4%)	5,160 (51·3%)	0·98 (0·96 – 1·01)	0·21
Median (IQR) units of blood product transfused*	3 (2-6)	3 (2-6)		0·59[‡]
Dependency				
No symptoms	1,483 (17·3%)	1,334 (15·8%)	1·09 (1·02 – 1·17)	0·0086
Minor symptoms	3,054 (35·5%)	3,061 (36·2%)	0·98 (0·94 – 1·02)	0·39
Some restriction	2,016 (23·5%)	2,069 (24·5%)	0·96 (0·91 – 1·01)	0·13
Dependent (not requiring constant attention)	1,294 (15·1%)	1,273 (15·1%)	1·00 (0·93 – 1·07)	0·98
Fully dependent	696 (8·1%)	676 (8·0%)	1·01 (0·92 – 1·12)	0·79
Alive (disability status not known)	54 (0·6%)	41(0·5%)		
Dead	1,463 (14·5%)	1,613 (16·0%)	0·91 (0·85 – 0·97)	0·0035

Table 3: Vascular occlusive events, management and dependency

[#] *Includes both fatal and non-fatal events*
* *Transfused patients only*
[‡] *Analysis used logarithmic transformation of mean units of blood products transfused*

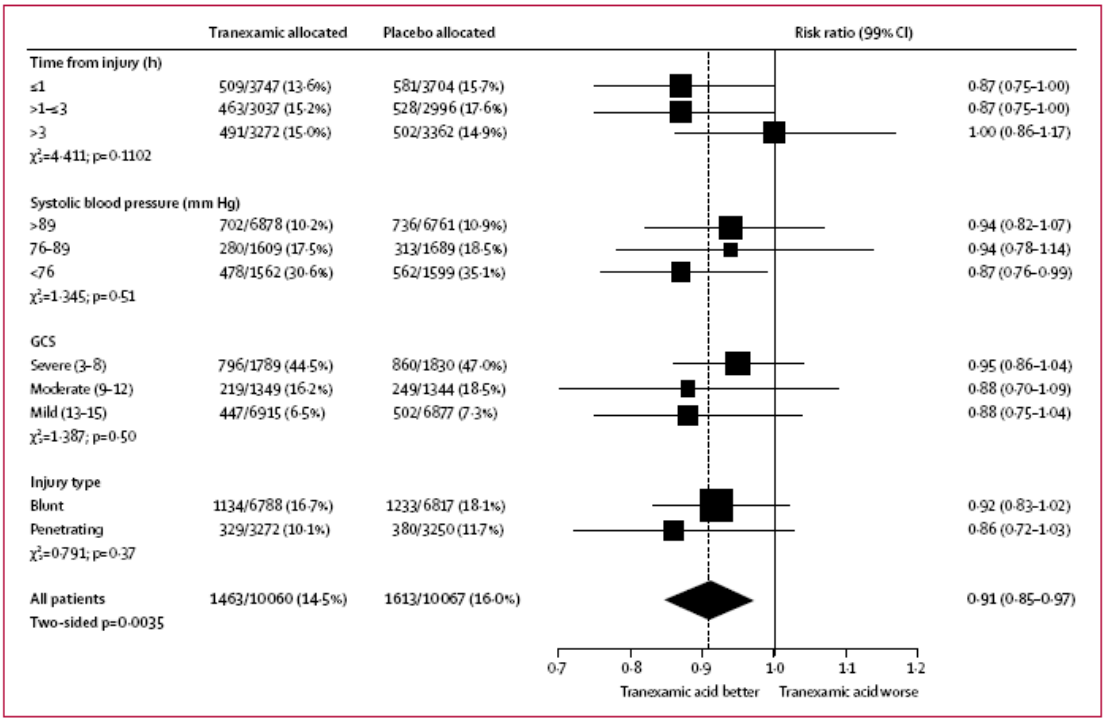

Figure 3: All-cause mortality by subgroups
GCS=Glasgow Coma Score.

Blood product transfusions were given to 5067 (50・4%) patients allocated to tranexamic acid versus 5160 (51・3%) allocated to placebo (table 3). Those allocated to tranexamic acid and transfused received a mean of 6・06 (SD 9・98) blood units, compared with a mean of 6・29 (10・31) for placebo. 4814 (47・9%) patients in the tranexamic acid group received one or more surgical intervention (neurosurgery, or chest, abdominal, or pelvic surgery) versus 4836 (48・0%) in the placebo group (table 3). Only 17 patients received treatment with recombinant Factor VIIa (13 in the tranexamic acid group *vs* four in the placebo group). 132 patients in each group had gastrointestinal bleeding (p=0・99). Of patients allocated tranexamic acid, 3453 (34・3%) were classifi ed as dead or dependent at discharge or 28 days compared with 3562 (35・4%) of those allocated to placebo (RR 0・97, 95% CI 0・93–1・00; p=0・12). 1483 (14・7%) patients in the tranexamic acid group had no symptoms at discharge or day 28 versus 1334 (13・3%) in the placebo group (table 3). 1846 (9・2%) patients were still in hospital at 28 days (958 *vs* 888).

Pre-specified subgroup analyses (primary outcome)

We had pre-specified that unless there was strong evidence against the null hypothesis of homogeneity of effects (i.e. p<0·001), the overall relative risk would be considered the most reliable guide to the approximate relative risks in all subgroups. There was no such evidence for any of the pre-specified subgroup analyses: systolic blood pressure (p=0·51); Glasgow Coma Score at randomisation (p=0·50); type of injury (p=0·37); time from injury to randomisation (p=0·11). For the last of these analyses, because of digit preference the number of patients in the early category (less than one hour) was low and the subgroup estimate was imprecise. We therefore (post hoc) defined the early category as those treated less than *or equal to* one hour from injury (figure 3).

Emergency un-blinding

There was no un-blinding of the treatment allocation for any of the 20,211 patients randomised.

Adverse events

There were no adverse events considered as serious, unexpected and suspected to be related to the study treatment reported.

Discussion

The results show that the routine administration of TXA to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in either fatal or non-fatal vascular occlusive events. All cause mortality is significantly reduced with TXA.

The trial inclusion criteria were clinical and did not depend on the results of laboratory tests. Patients were enrolled if they were judged to have on-going significant haemorrhage, as evidenced by hypotension or tachycardia, or if they were considered to be at risk of significant haemorrhage, for example patients with compensated haemorrhage and stable vital signs, or those in whom bleeding may have stopped but who might recommence bleeding following volume resuscitation. The use of clinical inclusion criteria is appropriate in the context of traumatic bleeding where it is necessary to evaluate a range of clinical signs when establishing the presence or absence of haemorrhage, whilst also taking into account remedial measures such as fluid resuscitation. The clinical inclusion criteria and the large numbers of patients studied in a wide range of different health care settings around the world, help these results to be generalised widely.

Strengths and limitations

The randomisation methods ensured that participating clinicians did not have foreknowledge of treatment allocation. Baseline prognostic factors were well balanced. All analyses were on an intention-to-treat basis and because 99·6% of randomised patients were followed up, there was no need to use imputation methods for missing data.[12] The primary end point was all cause mortality and the observed reduction in mortality with TXA was both statistically significant and clinically important. The diagnosis of traumatic haemorrhage can be difficult and it is possible that some of the included patients were not actually bleeding at the time of randomisation. This would have reduced the power of the trial to demonstrate an effect of TXA on mortality from bleeding. Nevertheless, we found a highly significant reduction in death due to bleeding and so this is not a concern here. [13]

Although we found no increased risk of non-fatal vascular occlusive events with TXA, the precision of the estimates was low and we cannot exclude the possibility of some increase in risk. In the context of outcome assessment in clinical trials, it has been shown that provided that there are few false positives (high specificity), estimates of the relative risk are unbiased even when the sensitivity of diagnosis is imperfect.[13] For this reason, we sought high specificity in the diagnosis of non-fatal vascular occlusive events and stipulated that occlusive events should only be recorded if there was clear clinical evidence. As a result, we may have underreported the frequency of these events. However, our estimates of the relative risk of non-fatal occlusive events should be unbiased.[13]

Mechanism of action

One weakness of this trial is that it provides limited insight into the mechanism of action of TXA. Although the results show that TXA reduces the risk of death in bleeding trauma patients, our data do not indicate how this effect is achieved. The mechanistic rationale for the trial was the evidence that TXA reduces blood loss and the need for transfusion in surgical patients. Because one third of trauma patients die from bleeding and the haemostatic responses to trauma and surgery are similar, we hypothesised that TXA could reduce mortality after trauma. Measuring blood loss is difficult in trauma patients. Much of the bleeding occurs at the scene of the injury and the bleeding that occurs in hospital is often concealed and difficult to quantify, such as for example, bleeding into the chest, abdomen, pelvis and soft tissues. However, we did not find any substantial reduction in the receipt

of a blood transfusion or the amount of blood transfused in trauma patients. This may reflect the difficulty of accurately estimating blood loss in trauma patients when assessing the need for transfusion. Another possible explanation is that following the loading dose, TXA was infused over a period of eight hours, whereas decisions about transfusion are made soon after admission. Finally, it is important to note that there were fewer deaths among TXA allocated patients and that the patients who survived as a result of TXA administration would have had a greater opportunity to receive a blood transfusion.

Early coagulation abnormalities are frequent in severely injured trauma patients and are associated with substantially increased mortality.[14] Recent research showing that hyper-fibrinolysis is a common feature of these abnormalities raises the possibility that antifibrinolytic agents such as TXA, may operate via this mechanism.[14] Furthermore, intravenous TXA administration has been shown to have an early (within 4 hours) antifibrinolytic effect.[15] However, although this mechanism is plausible, because we did not measure fibrinolytic activity in this trial we cannot conclude that TXA acts by reducing fibrinolysis, as opposed to some other mechanism. Further studies are required into the mechanism of action of TXA in bleeding trauma patients.

Fewer haemorrhage deaths and no increase in vascular occlusion

The TXA loading dose was given within eight hours of injury, followed by a maintenance infusion over eight hours. We chose the early administration of a short course of TXA because most deaths from bleeding occur on the day of the injury and we hypothesised that TXA would act by reducing bleeding. After the first day, the risk of death from haemorrhage is reduced but the risk of vascular occlusive events remains. We therefore selected a regimen that would allow for the effect of TXA on the early risk of haemorrhage without extending into the period when the risk of vascular occlusive events might be increased by TXA. The absence of any increase in vascular occlusion with TXA, whether fatal or non-fatal, provides reassurance that this regimen is safe. Although we did not find compelling statistical evidence that the effect of TXA on all cause mortality varied substantially according to the time from injury, there was some suggestion that early treatment may be more effective. However, even if this were not the case, the fact that most deaths from haemorrhage occur in the first few hours after injury implies that every effort should be made to treat patients as soon as possible. [16-18]

The dose of TXA used in this trial was based on studies of TXA in surgical patients in which loading doses range from 2·5mg/kg to 100 mg/kg, and maintenance doses from 0·25 mg/kg/hr to 4 mg/kg/hr, delivered over time periods of one to twelve hours.[6] Studies of the impact of different doses of TXA on blood loss and blood transfusion showed no significant difference between high dose and low doses. Studies in cardiac surgery have found that a 10 mg/kg loading dose of TXA followed by an infusion of 1 mg/kg/hour produces plasma concentrations sufficient to inhibit fibrinolysis and that a larger dose does not provide any additional haemostatic benefit.[19-20] In emergency situations, the administration of a fixed dose is more practicable since determining the weight of a seriously injured patient can be difficult. We therefore selected a fixed dose within the range shown to inhibit fibrinolysis and provide haemostatic benefit that would be efficacious for larger patients (>100 kg) but also safe in smaller patients (<50 kg) to the extent that the dose/kg that smaller patients would receive has been used in surgical trials without adverse effects. The possibility that a higher dose of TXA would have a greater treatment effect remains open to question and warrants further study.

Implications for research

The knowledge that TXA reduces the risk of death from traumatic bleeding raises the possibility that it might also be effective in other situations where bleeding can be life threatening or disabling.

Traumatic brain injury (TBI) is commonly accompanied by intracranial bleeding which can develop or worsen after hospital admission. Traumatic intracranial haemorrhage is associated with an increased risk of death and disability, and regardless of location, haemorrhage size is strongly correlated with outcome.[21-23] If TXA reduced intracranial bleeding after isolated TBI then this could improve patient outcomes. Studies that assess the effect of TXA on the extent of intracranial bleeding are required.

TXA might also have a role in bleeding conditions apart from traumatic injury. Postpartum haemorrhage (PPH) is a leading cause of maternal mortality, accounting for about 100,000 maternal deaths each year.[24] Although there is evidence that TXA reduces postpartum bleeding, the quality of the existing trials is poor and none has been large enough to assess the effect of TXA on end points that are important to women.[25] A large trial is being conducted to assess the effect of TXA on the risk of death and hysterectomy in women with PPH (www.thewomantrial.Lshtm.ac.uk).[26]

Conclusions

TXA was given in a wide range of healthcare settings and safely reduced the risk of death in bleeding trauma patients in our study. The option of using TXA should be available to doctors treating trauma patients in high, middle, and low income countries and TXA should be considered for inclusion on the WHO List of Essential Medicines. Based on these results, TXA should be considered for use in bleeding trauma patients.

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.[27]

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.[27]

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.

9.1 Dosage regimen and duration

Participants enrolled into the CRASH-2 trial were given a loading dose of 1 gram (100 ml over 10 minutes) and a maintenance dose of 1 gram over 8 hours (60 ml/hr). Of the 20,000 patients enrolled into the CRASH-2 trial no adverse events considered as serious, unexpected and suspected to be related to the study treatment were reported.

In randomised trials of antifibrinolytic agents in surgery, TXA dose regimens vary widely. Loading doses range from 2.5 mg/kg to 100 mg/kg and maintenance doses from 0.25 mg/kg/hour to 4 mg/kg/hour given over periods of one to twelve hours. Studies examining the impact of different doses of tranexamic acid on bleeding and transfusion requirements showed no significant differences between a high dose and a low dose. Studies in cardiac surgery have shown that a 10 mg/kg initial dose of TXA followed by an infusion of 1 mg/kg/hour produces plasma concentrations sufficient to inhibit fibrinolysis in vitro. Horrow et al (1995) examined the dose-response relationship of TXA and concluded that 10 mg/kg followed by 1 mg/kg/hour decreases bleeding in cardiac surgery, but larger doses did not provide any additional haemostatic benefit.[20]

In the emergency situation, the administration of a fixed dose is more practicable since weighing patients with trauma would be difficult. Therefore, a fixed dose of 1 gram of TXA initially followed by a maintenance dose of 1 gram, which is within the dose range which has been shown to inhibit fibrinolysis and provide haemostatic benefit, would be recommended for patients with or at risk of significant haemorrhage. On the basis of experience in surgery, the dose selected would be efficacious for larger patients (>100 kg) but also safe in smaller patients (<50 kg), as the estimated dose/kg that the patients in the latter group would receive has been applied in other trials without significant adverse effects.

9.2 Reference to existing WHO and other clinical guidelines

The UK Summary of Product Characteristics for Cyklokapron Injection (http://www.medicines.org.uk/emc/medicine/1489) state that TXA should be used for the following indications:

Local fibrinolysis: For short term use in prophylaxis and treatment in patients at high risk of pre- and post operative haemorrhage following; postatectomy, conisation of the cervix and surgical procedures and dental extractions in haemophiliacs.

General fibrinolysis: Haemorrhagic complications in association with thrombolytic therapy and haemorrhage associated with disseminated intravascular coagulation with predominant activation of the fibrinolytic system.

The Management of bleeding following major trauma: an updated European guideline[28] states the following in relation to TXA: *We suggest that antifibrinolytic agents be considered in the bleeding trauma patient (Grade 2C). We recommend monitoring of fibrinolysis in all patients and administration of antifibrinolytic agents in patients with established hyperfibrinolysis (Grade 1B). Suggested dosages are tranexamic acid 10 to 15 mg/kg followed by an infusion of 1 to 5 mg/kg per hour or ε-aminocaproic acid 100 to 150 mg/kg followed by 15 mg/kg/h. Antifibrinolytic therapy should be guided by thrombelastometric monitoring if possible and stopped once bleeding has been adequately controlled (Grade 2C).*

TXA is also used for trauma in the treatment protocol of the Israeli Defence Force.

9.3 Need for special diagnostic or treatment facilities and skills

No specialist treatment facilities and skills are required to administer intravenous TXA, trauma patients are not generally treated in specialist trauma centres.

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

TXA – EFFICACY

Data on safety and efficacy of TXA is widely available in the literature. The following systematic reviews and meta-analyses examining the use of TXA have been produced.

- **Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, Laupacis A, Fergusson D** Antifibrinolytic use for minimising perioperative allogeneic blood transfusion (Cochrane Review). In: ***The Cochrane Library***, Issue 3, 2008. Chichester, UK: John Wiley & Sons, Ltd.[6]
- **Dunn CJ, Goa KL** TXA: a review of its use in surgery and other indications. ***Drugs***. 1999 Jun;57(6):1005-32.[29]
- **Ferrer P, Roberts I, Sydenham E, Blackhall K, Shakur H,** Anti-fibrinolytic agents in bleeding during pregnancy, delivery and puerperium: A systematic review. ***BMC Pregnancy Childbirth*** manuscript ID 4090955672420008 (submitted). [25]

TXA has been marketed for about 40 years in many countries under the trade name Cyklokapron® by Pharmacia (Pfizer Ltd). It has marketing authorisation in the UK (Product licence number PL 00032/0314).

THERAPEUTIC USE OF TXA

TXA is used routinely in a variety of clinical conditions where there is haemorrhage or the risk of haemorrhage in increased fibrinolysis and fibrinogenolysis.

Trauma:

Rates of rebleeding were reduced in patients with traumatic hyphaema with the use of TXA. A systematic review to quantify the effect of antifibrinolytic drugs in reducing blood loss, transfusion requirement and mortality after acute traumatic injury concluded that there is insufficient evidence from randomised controlled trials of antifibrinolytic agents in trauma to either support or refute a clinically important treatment effect. The CRASH-2 trial of TXA for trauma patients with significant haemorrhage recruited 20,211 patients and found that TXA safely reduced the risk of death in bleeding trauma patients. Based on these results, TXA should be considered for use in bleeding trauma patients.

Obstetric haemorrhage:
Evidence from a systematic review suggests there may be a benefit to administration of TXA to women with postpartum haemorrhage. However there is no reliable evidence available on which to make recommendations as to the suitability of TXA for this indication.

TXA has been used to treat several conditions relating to bleeding in pregnancy, and several case control studies show some evidence of benefit for antepartum bleeding. No harmful effects have been reported. However, the safety and efficacy of TXA for obstetric haemorrhage has not yet been established. TXA is secreted into human milk, but in very low quantities, and there is no evidence for a harmful effect on breastfeeding babies.

Menorrhagia:
Reductions of 34 to 57.9% versus placebo or control, in mean menstrual blood loss, occurred during TXA therapy in women with menorrhagia. Recently the MHRA approved over the counter use of oral TXA for reduction of heavy menstrual bleeding.

Surgery:
A systematic review demonstrated a 39% reduction in risk relative to control of exposure the allogeneic blood transfusion. Statistically significant reductions in both intra and post operative blood loss are also reported.

Gastrointestinal bleeding:
TXA is associated with reductions relative to placebo in mortality of 5 to 54% in patients with upper gastrointestinal bleeding. Meta-analysis indicated a reduction of 40%.

Haemophilia:
TXA significantly reduced mean blood losses after oral surgery in patients with haemophilia.[29]

Transurethral prostatic surgery, liver transplantation, hereditary angioneurotic oedema:
Reductions in blood loss were also obtained with the use of TXA in patients undergoing orthotopic liver transplantation or transurethral prostatic surgery. Clinical benefit has also been reported with TXA in patients with hereditary angioneurotic oedema.

DOSE
The dose regimens of TXA vary widely. Studies examining the impact of different doses of TXA on bleeding and transfusion requirements showed no significant difference between a high dose and a low dose. Studies in cardiac surgery have shown that a 10 mg/kg initial dose of TXA followed by an infusion of 1 mg/kg/hour produces plasma concentrations sufficient to inhibit fibrinolysis *in vitro*. Trials of the use of TXA in obstetric haemorrhage used TXA at a dose of 1 gram without major complications.

TOLERABILITY
TXA is well tolerated. Adverse events are uncommon and usually manifest as nausea or diarrhoea, or occasionally as orthostatic reactions. Results of controlled clinical studies have not confirmed concerns over the possibility of an increased thrombotic tendency in patients treated with inhibitors of fibrinolysis. The results of the CRASH-2 trial show that the routine administration of TXA to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in either fatal or non-fatal vascular occlusive events.

No increases in incidence of thrombotic events were reported with TXA in studies of patients undergoing cardiac surgery with cardio pulmonary bypass or in a retrospective case analysis of 256

women with bleeding disorders in pregnancy. No mutagenic activity or harmful foetal effects of TXA have been reported.

Retinal changes seen in dogs after very high dosages of TXA for one year have not been reported in humans receiving the drug at therapeutic dosages. However, disturbances in colour vision have been documented and patients who develop this symptom should discontinue therapy.

PRECAUTIONS FOR USE
TXA is contraindicated in patients with a history of thromboembolic disease, and dosage reductions are recommended in patients with renal insufficiency.

INCOMPATIBILITIES
TXA solution for injection should not be mixed with blood for transfusion or infusion solutions containing penicillin or Mannitol 20 or 25%.

CONCLUSIONS
TXA is useful in a wide range of haemorrhagic conditions with a known safety profile. The results of the CRASH-2 trial show that the routine administration of TXA to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in either fatal or non-fatal vascular occlusive events. All cause mortality is significantly reduced with TXA

TXA reduces postoperative blood losses and transfusion requirements in a number of types of surgery, and appears to reduce rates of mortality and urgent surgery in patients with upper gastrointestinal haemorrhage. TXA reduces menstrual blood loss and has been used successfully to control bleeding in pregnancy.

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

Data on safety and efficacy of TXA is widely available in the literature. The following systematic reviews and meta-analyses examining the use of TXA have been produced.

- **Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, Laupacis A, Fergusson D** Antifibrinolytic use for minimising perioperative allogeneic blood transfusion (Cochrane Review). In: ***The Cochrane Library***, Issue 3, 2008. Chichester, UK: John Wiley & Sons, Ltd.[6]
- **Dunn CJ, Goa KL** TXA: a review of its use in surgery and other indications. ***Drugs***. 1999 Jun;57(6):1005-32.[29]
- **Ferrer P, Roberts I, Sydenham E, Blackhall K, Shakur H,** Anti-fibrinolytic agents in bleeding during pregnancy, delivery and puerperium: A systematic review. ***BMC Pregnancy Childbirth*** manuscript ID 4090955672420008 (submitted). [25]

10.2 Summary of comparative effectiveness – adults

There are no summaries of the comparative effectiveness of TXA in adults. The CRASH-2 trial assessed TXA against a placebo (0.9 % NaCl).

10.3 Summary of comparative effectiveness – paediatrics

There are no summaries of the comparative effectiveness of TXA in children. Limited data suggest that dosing instructions for adults can be used for paediatric patients needing tranexamic acid therapy.

11. Summary of comparative evidence on safety

Adverse events with TXA therapy are relatively uncommon; nausea or diarrhoea and occasionally orthostatic reactions are most often reported.[30] There is a theoretical risk of increased thrombotic tendency during treatment with inhibitors of fibrinolysis, and there have been isolated case reports of cerebral thrombosis,[31-32] arterial thrombosis,[33] acute renal failure[34-35] and coronary graft occlusion[36] in patients receiving TXA. However, these observations have not been confirmed by the results of controlled clinical studies; indeed in the CRASH-2 trial which recruited 20,211 patients no adverse events considered as serious, unexpected and suspected to be related to the study treatment were reported and the results show that the routine administration of TXA to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in either fatal or non-fatal vascular occlusive events (see table 3 above).

Additionally several randomised studies in patients undergoing cardiac surgery with CPB have shown no excess incidence of thrombotic events in patients receiving the drug.[20, 37-39] Similar rates of thromboembolic complications were reported for placebo and TXA in both trials conducted in patients undergoing total knee arthroplasty.[40-41] However, the incidence of cerebral ischaemia was higher in patients with subarachnoid haemorrhage given TXA than in placebo recipients.

A systematic review of TXA use in surgery showed no significant increases in the risks of any of the thromboembolic events assessed.[6]

Table 4. Summary of evidence of adverse events for trials if TXA in surgery

EVENTS	EFFECT OF TXA	
	RR	95% CI
Myocardial Infarction	0.96	0.48-1.90
Stroke	1.25	0.47-3.31
Deep venous thrombosis	0.77	0.37-1.61
Renal failure	0.73	0.16-3.32

Although atrophy of the retinal rod and cone layers has been reported after 1 year's oral administration of TXA in dogs, the dosages used were of the order of 7 times those recommended in humans.[42] Moreover, no retinal changes were found in patients who received the drug at therapeutic dosages for periods ranging from 15 months to 8 years.[43] As instances of disturbance in colour vision have been reported, it is nevertheless recommended that treatment with TXA should be withdrawn from any patients who develop this symptom.[44]

No mutagenic activity of TXA has been detected in *in vitro* and *in vivo* test systems,[42, 45] and no foetal abnormalities were identified in early dysmorphology and reproductive studies in animals.[46-47]

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 (2008/9)
Tranexamic acid (Cyklokapron®, Pfizer) – injection, tranexamic acid 100 mg/ml, net price 5-ml amp =$ 2.85

Costs sourced from the published literature

Italy	$2.57; 1g (2008 values) [48]
India	$6.60; 1g (2008 values)[49]
US	$22.83; 1g (2008 values)[50]
Spain	$2.77; 1g (2008 values)[51]

12.2 Comparative cost effectiveness

In elective surgery, where clinical data is already available, several economic evaluations suggest that TXA is a cost saving intervention. [52-53] A recent study also shows that in Sub-Saharan African countries where there is either shortage of blood, or where blood is not properly screened, TXA can save lives and prevent blood borne infections. [54] The CRASH-2 trial, the largest randomized control study conducted in trauma, recently revealed that the intravenous administration of 2 g TXA can save lives if administered to trauma patients with severe ongoing bleeding. Due to the improvements in survival, TXA is also associated with a small but statistically significant increase in the number of days spent by the patient in non-intensive care (non-ICU) hospital facilities.

Although TXA is relatively inexpensive, evidence on the cost effectiveness of TXA in trauma has still to be provided. TXA prices as well as effectiveness vary between countries. In high income countries (HICs) TXA is likely to cost more compared with low income countries (LICs) because both administration cost and cost of hospital stay are higher. However, in both middle income countries (MICs) and LICs life expectancies are shorter and there will be a lower number of life years per patient. Using World Bank country classification criteria we evaluate TXA cost effectiveness in three types of countries; a High Income country United Kingdom (GNI per capita $27,700) a Low Income country Tanzania (GNI per capita $440) and a middle income country India (GNI per capita $2,930).[55] India was used as the MIC because it is one of the countries where TXA can avert the highest number of trauma deaths. Tanzania was chosen as the LIC in order to assess the cost-effectiveness of TXA when income per capita and life expectancy are low. Using results from the CRASH 2 trial cost-effectiveness was measured by the incremental cost per life-year gained.

The results of the analysis are reported in the Table below:

Item	HICs	MICs	LICs
Overall incremental cost ($)	$31,555(£27,903)	$ 20,262	$17,831
Incremental life year saved	156.42	111.06	101.54
Incremental cost per life year saved ($)	$269 (£178)	182	176

All results are per 1,000 patients

As observed administering TXA is cost increasing in all the three types of countries considered because both TXA administration cost and because of the longer non-ICU hospital stay. The incremental cost of TXA is $31,500, $20,000 and $17,800 in HICs, MICs and LICs respectively. In MICs and LICs incremental cost of TXA is lower because the unit cost of one non-ICU day and the personnel cost for administering the drug are considerably lower if compared with HICs. The life years saved reported for each of the three countries have been estimated taking into account the age distribution of trauma victims. As expected in HICs where life expectancy is high (79.9 years) TXA would allow to save the highest number of life years 156 years per 1,000 trauma patients. [56] While in LICs (Tanzania) where the average life expectancy at birth is 55.6 years TXA would save an additional 101 life years per 1,000 patients. [56]

This study suggests that TXA is not only life saving, as shown by the CRASH-2 trial, but also that it could be a highly cost effective intervention if administered routinely to bleeding trauma patients. In all the three countries considered TXA appears to be a very cheap and effective intervention the incremental cost per life years saved is $269, $182 and $176 dollar for HICs, MICs and LICs respectively. The WHO Commission on Macroeconomics suggests that healthcare interventions costing less than the gross domestic product (GDP) per capita per DALY averted should be considered "very cost effective".[57] According to the World Bank classification GDP per capita in low income countries ranges from $380 to $975, and in middle income countries GDP per capita varies between $976 and $1105 and in high Income countries GDP is higher than $1105, (UK average GDP per capita is $43,541[58]). Thus, assuming that the life years saved by TXA are spent in perfect health (one LY is equal to one DALY) TXA is a very cost effective intervention in all the types of countries considered.

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 bleeding in patients with or at risk of significant haemorrhage.

TXA is manufactured by Pfizer (previously Pharmacia Ltd), Kent, UK. It has marketing authorisation in the UK (Product licence number PL 00032/0314). In the UK TXA is licensed for use in the following indications:

Local fibrinolysis- For short term use in prophylaxis and treatment in patients at high risk of pre- and post operative haemorrhage following; postateectomy, conisation of the cervix and surgical procedures and dental extractions in haemophiliacs.

General fibrinolysis: Haemorrhagic complications in association with thrombolytic therapy and haemorrhage associated with disseminated intravascular coagulation with predominant activation of the fibrinolytic system.

Recently the Medicines and Healthcare Regulatory Authority (MHRA) approved over the counter use of oral TXA for reduction of heavy menstrual bleeding (http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con082059.pdf).

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. [27]

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 (MIMS Online. Cyklokapron® - Prescribing Information. *MIMS Australia Pty Ltd*. 2003. Available at: http://www.mims.com.au).

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 (Pharmacia South Africa Pty Ltd. Cyklokapron® - Product Information).

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 Limited, Ramsgate, Kent.

TRANEXAMIC ACID – INJECTION

QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: Tranexamic Acid Ph. Eur 500 mg

FORMULATION
Chemical Name: trans-4-(aminomethyl) cyclohexanecarboxylic acid. Tranexamic acid is a white crystalline powder. 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.

THERAPEUTIC INDICATIONS

Local fibrinolysis- For short term use in prophylaxis and treatment in patients at high risk of pre- and post operative haemorrhage following; prostatectomy, conisation of the cervix and surgical procedures and dental extractions in haemophiliacs.

General fibrinolysis: Haemorrhagic complications in association with thrombolytic therapy and haemorrhage associated with disseminated intravascular coagulation with predominant activation of the fibrinolytic system.

Patients with or at risk of significant haemorrhage: Patients judged to have on-going significant haemorrhage, as evidenced by hypotension or tachycardia, or if they are considered to be at risk of significant haemorrhage, for example patients with compensated haemorrhage and stable vital signs, or those in whom bleeding may have stopped but who might recommence bleeding following volume resuscitation.

Children: 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.

POSOLOGY AND METHOD OF ADMINISTRATION

Route of administration: by slow intravenous injection.

Local fibrinolysis: the recommended standard dose is 5-10 ml (500-1000 mg) by slow intravenous injection (1 ml/min), three times daily. If treatment continues for more than three days, consideration should be given to the use of Cyklokapron tablets or syrup. Alternatively, following an initial intravenous injection, subsequent treatment may proceed by intravenous infusion. Following addition to a suitable diluent (see interaction with other medicinal products and other forms of interaction below), Cyklokapron may be administered at a rate of 25-50 mg/kg body wt/day.

Children: According to body weight (10mg/kg body wt/ 2-3 times daily)

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

General fibrinolysis: In disseminated intravascular coagulation with predominant activation of the fibrinolytic system, usually a single dose of 10 ml (1 g) is sufficient to control bleeding. Neutralisation of thrombolytic therapy; 10 mg/kg body wt by slow intravenous injection.

Patients with or at risk of significant haemorrhage: A loading dose of 1 gram over 10 minutes and a maintenance dose of 1 gram over 8 hours.

CONTRAINDICATIONS
Cyklokapron is contra-indicated in patients with a history of thromboembolic disease.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
In patients with renal insufficiency, because of the risk of accumulation. The dose should be reduced according to the following table:

Serum Creatinine	**Dose iv**	**Dose Frequency**
120-250 mcmol/l	10 mg/kg	Twice daily
250-500 mcmol/l	10 mg/kg	Every 24th hour
> 500 mcmol/l	5 mg/kg	Every 24th hour

In massive haematuria from the upper urinary tract (especially in haemophilia) since, in a few cases, ureteric obstruction has been reported.

In patients with disseminated intravascular coagulation (DIC) treatment must be restricted to those in whom there is predominant activation of the fibrinolytic system with acute severe bleeding. Characteristically, the haematological profile approximates to the following: reduced euglobulin clot lysis time; prolonged prothrombin time; reduced plasma levels of fibrinogen, factors V and VIII, plasminogen and alpha-2 macroglobulin; normal plasma levels of P and P complex; i.e. factors II (prothrombin), VIII and X; increased plasma levels of fibrinogen degradation products; a normal platelet count. The foregoing presumes that the underlying disease state does not of itself modify the various elements in this profile. In such acute cases a single dose of 1g tranexamic acid is frequently sufficient to control bleeding. The fibrinolytic activity in the blood will be reduced for about 4 hours if renal function is normal. Anticoagulation with heparin should be instigated in order to prevent further fibrin deposition. Administration of Cyklokapron in DIC should be considered only when appropriate haematological laboratory facilities and expertise are available. Cyklokapron must not be administered in DIC with predominant activation of the coagulation system.

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
The solution for injection may be mixed with the following solutions: isotonic sodium chloride; isotonic glucose; 20% fructose; 10% invertose; dextran 40; dextran 70; ringer's solution.

Cyklokapron solution for injection may be mixed with Heparin.

PREGNANCY AND LACTATION
Although there is no evidence from animal studies of a teratogenic effect, the usual caution with the use of drugs in pregnancy should be observed. Tranexamic acid passes into breast milk to a concentration of approximately one hundredth of the concentration in the maternal blood. An anti-fibrinolytic effect in the infant is unlikely.

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.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES
None known.

UNDESIREABLE EFFECTS
Gastro-intestinal disorders (nausea, vomiting, diarrhoea) may occur but disappear when the dosage is reduced. Rapid intravenous injection may cause dizziness and/or hypotension. To avoid this response, the solution should not be injected more rapidly than 1 ml per minute. Rare cases of thromboembolic events have been reported.

OVERDOSE
No cases of overdosage have been reported. Symptoms may be nausea, vomiting, orthostatic symptoms and/or hypotension. Maintain a high fluid intake to promote renal excretion.

PRECLINICAL SAFETY DATA
There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

LIST OF EXCIPIENTS
Water for injections

INCOMPATIBILITIES
TXA solution for injection should not be mixed with blood for transfusion or infusion solutions containing penicillin or Mannitol 20 or 25%.

SHELF LIFE
3 years

SPECIAL PRECAUTIONS FOR STORAGE
None

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	Mead, 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

1. CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet Published Online June 15, 2010 DOI:101016/S0140-6736(10)60835-5. 2010.
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