

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**Exacyl, Ugurol
(Tranexamic Acid)**

FR/W/002/pdWS/001

**Marketing Authorisation Holder(s):
Sanofi-Aventis, Rottapharm**

Rapporteur:	FRANCE
Start of the procedure (day 0):	22 December 2008
Date of this report:	2 March 2009
Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):	2 March 2009
Deadline for CMS's comments (day 85):	17 March 2009
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Deadline for CMS's comments (day 115):	2 October 2009
Finalisation procedure (day 120):	7 October 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Exacyl, Ugurol
INN (or common name) of the active substance(s):	Tranexamic Acid
MAH (s):	Sanofi-Aventis, Rottapharm
Currently approved indications:	Treatment of haemorrhagic events due to generalized primitive fibrinolytic state, or occurred during treatment with a fibrinolytic agent, or sustained by local fibrinolysis
Pharmaco-therapeutic group (ATC Code):	B02AA02
Pharmaceutical form(s) and strength(s):	500mg, coated tablet 250mg, tablet 1g, oral solution 0,5g/5ml, oral and injection solution

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I. INTRODUCTION

The aim of this EU Worksharing project is the assessment of the clinically relevant information on efficacy and safety data relative to tranexamic acid in children to enable progress on medications in this population.

Sanofi-Aventis submitted a review of the clinically relevant information on efficacy and safety relative to tranexamic acid in children. The supportive documentation available for this purpose was the following:

- Literature searches on standard medical databases (i.e. Embase, Medline). Thirteen randomised studies have been published relating the use of TXA in children, the majority being in cardiac surgery and scoliosis surgery.
- Tranexamic acid Company Core Safety Information.

A short critical expert overview has also been provided.

The MAH did not carry out any paediatric study for Tranexamic Acid, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAH stated that, due to the paucity of data and the variety of dosing schedules, the benefit-risk profile of TXA in children cannot be considered as well established and did not propose any consequential regulatory action. However, the MAH also concluded that, in the few published paediatric studies, several dose schedules have been tested and TXA has shown to have a positive effect on bleeding parameters without related safety issues.

Product background

Tranexamic acid (TXA) is a synthetic derivate of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules and thus preventing fibrin degradation. It thus promotes clot stability.

TXA is indicated in the treatment of haemorrhagic events due to generalized primitive fibrinolytic state, or occurred during treatment with a fibrinolytic agent, or sustained by local fibrinolysis.

TXA has been firstly approved in France in 1969 and has been marketed in this country since 1971. This product is now approved in over 30 countries through national procedures and is currently marketed in most of them.

It is available in tablets, ampoules for drinking solution and ampoules for injection in the dose range of 250 mg to 1 g.

Rapporteur's comment:

The indication of TXA, haemorrhagic events due to local fibrinolysis, is very large. However, some specific clinical settings are mentioned in several countries, such as menorrhagia, metrorrhagia, hematurias, bleedings following amygdectomy. A posology in children of 20 mg/kg/day is recommended in France. The MAHs submitted very few or even no data regarding these clinical settings. They are discussed in the second part of section 3. Clinical efficacy of this Assessment Report.

The MAH, as well as the Rapporteur, assessed more particularly data on TXA in paediatric cardiac surgery, even if at present time there is no indication in this target population.

Indeed, there has been a real medical need for TXA as antifibrinolytic to reduce perioperative blood loss in children since aprotinin, another antifibrinolytic drug which was used in this clinical setting, has been suspended in Europe in 2008. TXA was considered by cardiovascular surgeons and anesthesists as the only antifibrinolytic therapeutic alternative that could be used in replacement of aprotinin in this specific population, and in fact was already used by some surgery teams. In this context, at the initiative of the Afssaps (French Medical Agency), an ad-hoc expert group involving French cardiovascular surgeons and anesthesists in paediatric area was constituted in the early of the year 2008 to further codify this use on the basis of the available efficacy and safety data.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical study(ies)

No quality data was submitted.

Rapporteur's comment

Several pharmaceutical forms are marketed : tablets, coated tablets, oral solutions, solutions for injection. The majority of submitted published paediatric studies being in surgery with injectable TXA, solutions for injection are the main pharmaceutical forms concerned by this paediatric Assessment Report. TXA solutions are usually dosed at 500 mg/5ml.

II.2 Non-clinical aspects

II.2.1 Introduction

No preclinical data was submitted by the MAHs. The Rapporteur made his own assessment of published non clinical studies and focused more specifically on TXA neurotoxicity. Toxicological and pharmacological studies in animals have mostly been analysed in order to better assess the risk of convulsions caused by TXA.

II.2.2 Non clinical studies

Published toxicological and pharmacological studies on TXA in animals from 1981 to 2008 have been reviewed and are summarised below.

2.1 Acute toxicity

The LD₅₀ (50% Lethal dose) are high, > 1 g/kg : TXA does not show strong toxic potential effect in animal (chicken, dog, rodent) after single administration by oral, intravenous, subcutaneous or intra-peritoneal route.

2.2 Repeated dose toxicity

In rats, there is no particular signal following repeated administration of TXA. Overall toxicity (weight loss) is only observed at very high doses (3.4 g/kg/day) after 6 months of repeated administration.

2.3 Reproductive toxic effect

No teratogenic effect has been observed in tested animal species (rat, mouse). Reproductive effects are described in rodent : female fertility alteration at very high dose and foetotoxicity at LOAEL (Lowest Observed Adverse Effect Level) of 1.8 mg/kg/day by oral route.

2.4 Pharmacological studies in animal: characterisation of the convulsive effect

Convulsive effects following TXA application to the lumbar spinal cord or cerebral areas have been studied in 6 studies conducted in rats or cats (Furtmüller 2002, Pelligrini 1982, Schlag 2000 and 2002, Yamaura 1980).

The mechanism by which TXA can evoke epileptic seizures has been elucidated in 2002 by studies co-conducted by Baxter laboratories.

It has been demonstrated that TXA:

- does not interfere with NMDA receptors (N-Methyl-D-Aspartate)
- binds to the GABA (γ -aminobutyric acid) binding sites of GABA_A
- dose dependently inhibits binding of the GABA receptor agonist, muscimol, and consequently has an antagonist effect on GABA_A receptors. GABA-induced chloride ion flux being blocked with an IC₅₀ of 7.1 ± 3.1 mM
- has a dose dependent convulsive effect.

To conclude, the convulsive effect of TXA, after application directly *in situ* in the cortex area or the lumbar spinal cord, is induced by blocking GABA-mediated inhibition in the Central Nervous System (CSN). Two factors may increase the epileptic effect of TXA : the dose administered and the size of the exposed area. Consequently, the administration of TXA in the CSN or close to CSN can evoke epileptic seizures.

In Schlag studies, neurotoxic signs occurred in rats at doses starting from 0.5 mg/mL. At 5 mg/mL, 2 out of 6 rats showed signs of major toxicity and died. Lastly, at TXA concentration of 47.5 mg/mL, all the tested rats died.

Considering the calculated ratio between concentrations leading to neurotoxic effects estimated in rats and concentrations in the cerebrospinal fluid (CSF) after IV administration of 66 mg/kg TXA in adults or 20 mg/kg in children aged of more than 1 year, it can be concluded that convulsive effects are not expected to be commonly observed after IV administration, except situations at risk mentioned in section 4.3 of the SPC.

With intrathecal administration, the CSN is exposed to a concentration equivalent to the concentration of the TXA solution, i.e for example 100 mg/mL for Exacyl 100 mg/mL, solution for injection, if no diluted. This corresponds to 89 times the IC₅₀ of 1.12 mg/mL. This supports the contraindication related to intrathecal route.

The calculated ratios between concentrations leading to estimated neurotoxic effects based on pharmacodynamic studies and concentrations in the cerebrospinal fluid (CSF) after IV administration are of 250 to 560. These ratios should be considered according to the observed convulsive effects. However, they suggest that convulsive effects are not expected to be

commonly observed after IV administration, except specific sensitivity, as described in sections 4.3 and 4.4 of the SPC, based on recorded clinical data.

To note, in human, two cases of epileptic seizures have been reported in adults. In the first case, the patient received TXA by mistake during spinal anaesthesia. Patient developed status epilepticus immediately after intrathecal injection of 50 mg of TXA. In the other case, patient received intrathecal injection of 500 mg of TXA. Convulsions were reversed by benzodiazepine.

II.2.3 Discussion on non clinical aspects

TXA demonstrated a low overall toxicity after oral, IV or SC administration in chicken, dog or rodent (mouse, rat). TXA is not teratogenic in mouse and rat. It was only observed a foetotoxic effect in rodent, with LOAEL of 1.8 mg/kg/day. No toxic effect in juvenile animal was reported in literature.

Convulsive effect caused by TXA has been described in cat and more recently in rat. This effect, after application directly *in situ* in the cortex area or the lumbar spinal cord, is increased with the dose administered and the size of the exposed area. The mechanism is induced by blocking GABA-mediated inhibition in the Central Nervous System (CSN), TXA having an antagonist effect on GABA_A receptors by binding to the GABA (γ -aminobutyric acid) binding sites.

Rapporteur's comment

The convulsive effect of TXA has been demonstrated in animals after direct application in the cortex area or the lumbar spinal cord. This finding contra-indicates the product in case of history of convulsions or direct application on the Central Nervous System, i.e. intrathecal and intraventricular injection, intracerebral application (TXA being also used as sealant). TXA should therefore not be used in neurosurgery. Regarding its use in cardiac surgery, non-clinical data are insufficient to conclude on a potential risk of TXA to induce convulsive effect when administered by IV route. It is however necessary to assess clinical safety data before any conclusion on the clinical relevance of such safety issue (see Part 4. Clinical safety).

II.3 Clinical aspects

II.3.1 Introduction

The clinical documentation submitted by the MAH comprises the following documents:

- Literature searches on standard medical databases (i.e. Embase, Medline). The selection criteria were controlled randomised clinical studies conducted with tranexamic acid in children.
- Tranexamic acid Company Core Safety Information

None of the MAHs carry out any controlled clinical trial with TXA in children.

About 20 clinical studies were found in literature. They were performed in various clinical settings such as cardiac surgery, scoliosis surgery, cranio-facial surgery, haemophilia, dental extraction, acute promyelotic leukaemia, tonsillectomy, menorrhagia.

The Rapporteur also made his own research of published data on PK/PD, efficacy and safety, more especially in cardiac surgery setting.

II.3.2 Clinical pharmacology

No PK/PD data was submitted by the MAHs. The Rapporteur made his own review of literature. The following conclusions are presented below.

II.3.2.1 Pharmacodynamics

TXA is an antifibrinolytic drug that is used in preventive or curative treatment of haemorrhagic states due to fibrinolysis.

Fibrinolysis is degradation of intravascular fibrin clots by action of plasmin that results from plasminogen hydrolysis. TXA is a synthetic derivate of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules and thus preventing fibrin degradation. It thus promotes clot stability. Tranexamic acid also preserves platelet function by reducing the effect of plasmin on glycoprotein 1b receptors.

According to *in vitro* studies, concentration of 10 µg/mL can decrease 80% of t-PA (tissue-plasminogen activator) activity (Andersson and al, 1968) and concentration of 16 µg/mL can inhibit platelet activation induced by plasmin (Soslau and al, 1991).

Concentration of TXA necessary to prevent fibrinolysis *in vivo* is unknown. A recent PK study aiming to optimise dosing schedule in adult patients in cardiac surgery had the objective of achieving a stable plasma concentration >20 µg/mL (Nutall and al, 2008).

II.3.2.2 Pharmacokinetics

II.3.2.2.1 General PK data

The following PK data result from studies conducted in adults.

Absorption

Peak plasma ATX concentration is obtained immediately after IV administration (500mg). Then concentration decreases until the 6th hour. Elimination half-life is about 3 hours.

Distribution

TXA is delivered in the cell compartment and the cerebrospinal fluid with delay. The distribution volume is about 33% of the body mass.

Elimination

TXA is excreted in urine as unchanged compound. 90% of the administered dose is excreted by the kidney in the twelve first hours after administration (glomerular excretion without tubular reabsorption). Plasma concentrations are increased in patients with renal insufficiency.

II.3.2.2.2 PK in specific population

Two studies analysed the pharmacokinetics properties of TXA in CPB cardiac surgery in adults (Fiechtner and al, 2001 and Nutall and al, 2008). Patients received an initial dose of 10 mg/kg given over 20 minutes followed by an infusion of 1 mg/kg/hour. Plasma TXA concentrations were comprised in a range of 29 and 45 µg/mL after bolus and mean concentrations during surgery were about 25 µg/mL in one study and 13 µg/mL in the other one. On the basis of these results, authors extrapolate levels obtained in the BART study. The TXA dosing schedule in this study was 30 mg/kg load, 2 mg/kg pump prime and 16 mg/kg/hour infusion. The extrapolated levels would be 60 µg/mL after the initial load, 40 µg/mL after the prime, and roughly 160µg/mL or higher late in the infusion in patients with renal insufficiency or failure.

No PK study has been published in children. Only Murphy and al (abstract Anesthesiology 2001) have modelled the serum concentration of TXA in a 10kg child undergoing CPB surgery. The

authors used the relationship between adult and paediatric PK parameters for epsilon aminocaproic acid to predict the PK parameters for TXA using adult PK parameters for TXA. Two dosing schedules have been modelled and compared:

- one with 100 mg/kg load, 10 mg/kg/hour infusion and 100 mg/kg final (Reid and al, 1997),
- the other one with only 50 mg/kg load (Zonis and al, 1996).

Modelling suggests that only the first dosing schedule maintains therapeutic serum concentrations throughout the surgery. It suggests also that a reduced loading dose may produce adequate serum concentrations of TXA with less overshoot, while a greater infusion rate would maintain a therapeutic serum concentration, particularly during longer cases.

Rapporteur's comment

PK data in children are insufficient. However, the Murphy's model comparing two different dosing schedules explains results of some clinical studies (see Part 3. Clinical efficacy), since it provides information on the dosing schedules that are more likely to maintain therapeutic concentrations.

II.3.3 Clinical efficacy

A critical review of the available clinical studies is presented thereafter in two distinct parts:

- first focusing on cardiovascular surgery, where more literature is available;
- then on all indexed other indications, e.g. orthopaedic surgery, cranio-facial surgery, medical indication (haemophilia).

Therapeutic environment: Surgery is the most common cause of major blood loss, defined as a loss of 20% of total blood volume or more. In children, cardiovascular and major orthopaedic procedures such as scoliosis surgery are associated with severe bleeding.

Bleeding is an outcome to be avoided, as it is associated with hemodynamic instability, prolonged surgical times, reoperation, and increased need for allogeneic transfusions with all the ensuing risks.

To reduce perioperative blood loss a number of pharmacological agents have been used, including the antifibrinolytic drugs aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA).

Rapporteur's comment

Aprotinin has been largely used in paediatric cardiac surgery, notably in neonatology, due to its dual properties: antifibrinolytic and anti-inflammatory, but has been suspended in all the European countries in 2008. EACA is not available in all European countries.

Therefore, the assessment of literature on TXA is particularly important for clinical practice in paediatric cardiac surgery, where there is a real medical need to reduce perioperative blood loss. Up to now, TXA is considered by numerous experts as the only effective alternative treatment of aprotinin that can be used in paediatric cardiac surgery.

II.3.3.1 Cardiovascular surgery

Cardiopulmonary bypass (CPB) and cardiovascular surgery activate coagulation, inflammation, and fibrinolysis. Pediatric patients are especially at risk for hematologic derangement related to CPB, as they have several unique characteristics that increase their risk for bleeding: small blood volume, much smaller than that of the prime in the CPB circuit, quantitative and qualitative

immaturity of the coagulation proteins, congenital heart disease associated with coagulation abnormalities.

12 studies have been published. The MAH provided 9 studies. The Rapporteur found 3 other studies: Van der Staak 1997, Levin 2000, Breuer 2008.

Among the 12 studies, 7 are prospective, randomised, placebo controlled studies, with 3 out of 7 conducted by the same Indian investigators, Chauhan and al (with one dose comparison study), and 2 out of 7, double-blinded study, conducted with the Canadian investigators, Levin, Zonis and al, at the British Columbia's Children Hospital, Vancouver. The two others studies are also double-blinded, one American (Reid and al) with reoperated children, one Turkish (Bulutcu and al).

The five studies left are:

- a retrospective German study (Breuer and al) comparing TXA with aprotin as historical control,
- a Dutch study (Van des Staak and al) with patients on ECMO (extracorporeal membrane oxygenation) and historical controls,
- a study (Vacharaksa and al) with no placebo group, a Spanish language study (Varela Crespo and al) and a Turkish language study (Akpek and al) with only English abstracts available are considered as supportive studies.

Of note, several of these studies were also comparative studies, comparing TXA to another antifibrinolytic treatment:

- One study versus Epsilon Aminocaproic Acid (EACA) (Chauhan #3);
- Three studies versus aprotinin (Bulutcu, Akpek, Breuer).

The methodology and the main results of the clinical studies are described in the tables 1 and 2.

Table 1 - Overview of the clinical efficacy studies with tranexamic acid in cardiovascular surgery in children -published studies provided by the MAH

Study	Patients Methodology	Treatment <i>1st bolus after induction of anaesthesia and prior to skin incision</i> <i>± continuous infusion</i> <i>± bolus administered into the pump prime</i> <i>± bolus at the end of CPB</i>	Results
Zonis (J Thorac Cardiovasc Surg) 1996 Canada	N=88 Age range : 1 day - 14 years CPB surgery prospective, randomised, doubleblind	- TXA : bolus 50 mg/kg I.V. (n=40) - Saline placebo (n=42)	Criteria : Blood loss and fluid replacement, coagulation parameters Efficacy results: <u>All children</u> : no significant difference <u>Children with cyanosis</u> : Significant reduction in post-operative blood loss and blood product requirements : - blood loss (11.2 ± 3.7 vs.27.2 ± 11.4 ml/kg/6 hours; p < 0.002and 23.7 ± 7.5 vs. 48.9 ± 27.6 ml/kg/24 hours; p < 0.02 - red cell transfusions (1/8 vs. 7/10 ; p = 0.02) - platelet transfusions (0/8 vs. 6/10 ; p = 0.01)
Reid (Anesth Analgesia) 1997 US	N=41 Age range : 6 months - 12 years Repeat sternotomy for repair of congenital heart defects CPB surgery randomised, doubleblind	- TXA (n=20) 1 st bolus 100 mg/kg + infusion 10 mg/kg/h + 2 nd bolus 100 mg/kg into the pump prime - Saline placebo (n=21)	Criteria : Total blood loss and transfusion requirements at 24h Efficacy results: Total blood loss: 26 ± 7 vs. 34 ± 17 mL/kg → 24% reduction (p=0.03) Transfusion requirements: 24 ± 5 vs. 39 ± 20 mL/kg → 38% reduction (p=0.04)
Vacharaksa (J Medic Assoc Thai) 2002 Thailand	N=62 Age range : 4 months - 14 years Congenital cyanotic heart disease CPB surgery prospective, randomised, double-blind	- TXA (n=33): 1 st bolus 15 mg/kg + 2 nd bolus 15 mg/kg at the end of CPB - TXA (n=29) 1 st bolus 15 mg/kg + 2 nd bolus placebo at the end of CPB	Criteria : Blood loss and transfusion requirements at 24h, coagulation parameters Efficacy results: No significant difference in postop blood loss between groups (12.51 +/- 13.20 ml/kg/24 h vs. 10.68 +/- 6.38 ml/kg/24 h) Transfusion: no significant difference
Chauhan #1	N=120 Age range :	- TXA (n = 96):	Criteria : Blood loss and blood product usage at 24 h

(Indian J Medical Res) 2003 India	2 months – 14.5 years Congenital cyanotic heart disease CPB surgery randomised, single-blind	1 st bolus 10 mg/kg + bolus 10 mg/kg on CPB + bolus 10 mg/kg after protamine at the end of CPB - Control (n = 24): no drug.	Efficacy results: <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">(ml/kg/24h)</th> <th style="text-align: center;">TXA</th> <th style="text-align: center;">Control</th> </tr> </thead> <tbody> <tr> <td>Blood loss</td> <td style="text-align: center;">20±9</td> <td style="text-align: center;">36±12</td> </tr> <tr> <td>Packed red cells</td> <td style="text-align: center;">12±9</td> <td style="text-align: center;">19±11</td> </tr> <tr> <td>Fresh frozen plasma</td> <td style="text-align: center;">19±13</td> <td style="text-align: center;">27±11</td> </tr> <tr> <td>Platelet concentrate</td> <td style="text-align: center;">15±8*</td> <td style="text-align: center;">20±9</td> </tr> <tr> <td>Reexploration (%)</td> <td style="text-align: center;">7/96(7.3)</td> <td style="text-align: center;">4/24 (16.6)</td> </tr> <tr> <td>Sternal closure (min)</td> <td style="text-align: center;">36±8</td> <td style="text-align: center;">42±12</td> </tr> </tbody> </table> Conclusion: TXA is highly effective	(ml/kg/24h)	TXA	Control	Blood loss	20±9	36±12	Packed red cells	12±9	19±11	Fresh frozen plasma	19±13	27±11	Platelet concentrate	15±8*	20±9	Reexploration (%)	7/96(7.3)	4/24 (16.6)	Sternal closure (min)	36±8	42±12																					
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Chauhan #2 Dose comparison study (Asian Cardiovasc Thorac Annals) 2004 India	N=150 Age range : 2 months – 15 years Congenital cyanotic heart disease CPB surgery (107 tetralogy of Fallot, 24 modified Fontan, 19 Senning) randomised, open ?	- A: no drug TXA: - B: 1 st bolus 50 mg/kg - C: 1 st bolus 10 mg/kg + infusion 1 mg/kg/h - D: 1 st bolus 10 mg/kg + 10 mg/kg on CPB + 10 mg/kg after protamine - E: 1 st bolus + 20 mg/kg after protamine	Criteria : Time taken for chest closure, blood loss and blood product usage at 24 h, coagulation parameters Efficacy results: <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">(mL/kg)</th> <th style="text-align: center;">A</th> <th style="text-align: center;">B</th> <th style="text-align: center;">C</th> <th style="text-align: center;">D</th> <th style="text-align: center;">E</th> </tr> </thead> <tbody> <tr> <td>Blood loss 24h</td> <td style="text-align: center;">36±19</td> <td style="text-align: center;">31±12</td> <td style="text-align: center;">28±12</td> <td style="text-align: center;">20±13</td> <td style="text-align: center;">22±12</td> </tr> <tr> <td>PRBC 24h</td> <td style="text-align: center;">19±12</td> <td style="text-align: center;">18±13</td> <td style="text-align: center;">14±11</td> <td style="text-align: center;">12±9</td> <td style="text-align: center;">13±9</td> </tr> <tr> <td>FFP 24h</td> <td style="text-align: center;">27±11</td> <td style="text-align: center;">25±12</td> <td style="text-align: center;">24±17</td> <td style="text-align: center;">21±13</td> <td style="text-align: center;">20±12</td> </tr> <tr> <td>PC 24h</td> <td style="text-align: center;">20±9</td> <td style="text-align: center;">18±9</td> <td style="text-align: center;">17±8</td> <td style="text-align: center;">15±8</td> <td style="text-align: center;">15±8</td> </tr> <tr> <td>Sternum closure (min)</td> <td style="text-align: center;">46±16</td> <td style="text-align: center;">38±12</td> <td style="text-align: center;">36±13</td> <td style="text-align: center;">30±9</td> <td style="text-align: center;">32±11</td> </tr> <tr> <td>Reexploration</td> <td style="text-align: center;">5/30</td> <td style="text-align: center;">4/30</td> <td style="text-align: center;">2/30</td> <td style="text-align: center;">0/30</td> <td style="text-align: center;">0/30</td> </tr> </tbody> </table> Conclusion: Groups C, D, E significantly more effective than Control A, Group D significantly more effective than Group B	(mL/kg)	A	B	C	D	E	Blood loss 24h	36±19	31±12	28±12	20±13	22±12	PRBC 24h	19±12	18±13	14±11	12±9	13±9	FFP 24h	27±11	25±12	24±17	21±13	20±12	PC 24h	20±9	18±9	17±8	15±8	15±8	Sternum closure (min)	46±16	38±12	36±13	30±9	32±11	Reexploration	5/30	4/30	2/30	0/30	0/30
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Chauhan #3 (J Cardiothorac Vasc Anesth) 2004 India	N=150 Age range : 2 months – 14.5 years Congenital cyanotic heart disease CPB surgery prospective randomised Open ?	- EACA: 1 st bolus 100 mg/kg + 100 mg/kg on CPB + 100 mg/kg after protamine, - TXA: 1 st bolus 10 mg/kg + 10 mg/kg on CPB + 10 mg/kg after protamine - Control: no drug.	Criteria : Time taken for chest closure, blood loss and blood product usage at 24 h, coagulation parameters Efficacy results: <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;"></th> <th style="text-align: center;">EACA</th> <th style="text-align: center;">TXA</th> <th style="text-align: center;">Control</th> </tr> </thead> <tbody> <tr> <td>Blood loss (ml/kg/24h)</td> <td style="text-align: center;">28 ± 13</td> <td style="text-align: center;">27 ± 14</td> <td style="text-align: center;">36 ± 18</td> </tr> <tr> <td>PRBC (ml/kg/24h)</td> <td style="text-align: center;">13 ± 11</td> <td style="text-align: center;">12 ± 9</td> <td style="text-align: center;">19 ± 12</td> </tr> <tr> <td>FFP(ml/kg/24h)</td> <td style="text-align: center;">21 ± 13</td> <td style="text-align: center;">20 ± 12</td> <td style="text-align: center;">27 ± 11</td> </tr> <tr> <td>PC(ml/kg/24h)</td> <td style="text-align: center;">15 ± 7</td> <td style="text-align: center;">15 ± 8</td> <td style="text-align: center;">20 ± 9</td> </tr> <tr> <td>Reexploration</td> <td style="text-align: center;">2/50</td> <td style="text-align: center;">1/50</td> <td style="text-align: center;">6/50</td> </tr> <tr> <td>Sternal closure (min)</td> <td style="text-align: center;">32 ± 11</td> <td style="text-align: center;">30 ± 12</td> <td style="text-align: center;">45 ± 15</td> </tr> </tbody> </table> Conclusion: Groups EACA and TXA significantly more effective than Control, No significant difference between Groups EACA and TXA		EACA	TXA	Control	Blood loss (ml/kg/24h)	28 ± 13	27 ± 14	36 ± 18	PRBC (ml/kg/24h)	13 ± 11	12 ± 9	19 ± 12	FFP(ml/kg/24h)	21 ± 13	20 ± 12	27 ± 11	PC(ml/kg/24h)	15 ± 7	15 ± 8	20 ± 9	Reexploration	2/50	1/50	6/50	Sternal closure (min)	32 ± 11	30 ± 12	45 ± 15														
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<p>Bulutcu – Fusun</p> <p>(Pediatric Anesth) 2005</p> <p>Turkey</p>	<p>N=100 Age range : 2 months – 9.7 years</p> <p>Congenital cyanotic heart disease CPB surgery</p> <p>prospective, randomised, Double-blind</p>	<p>- Control (n=25): no drug</p> <p>- Aprotinin (n=25): 1st bolus 30.000 KIU/kg + 30.000 KIU/kg in the pump prime + 30.000 KIU/kg after CPB</p> <p>- TXA (n=25): 1st bolus 100 mg/kg + 100 mg/kg in the pump prime + 100 mg/kg after CPB</p> <p>- Aprotinin + TXA (n=25)</p>	<p>Criteria : Time taken for sternal closure, blood loss and total blood transfusion volume at 24 h, coagulation parameters</p> <p>Efficacy results:</p> <table border="1" data-bbox="1129 337 1703 613"> <thead> <tr> <th>ctl</th> <th>A</th> <th>TXA</th> <th>A+TXA</th> </tr> </thead> <tbody> <tr> <td colspan="4">Blood loss (mL/kg/24h) :</td> </tr> <tr> <td>40±18</td> <td>35±16</td> <td>34±19</td> <td>35±15</td> </tr> <tr> <td colspan="4">Time taken for sternal closure (min) :</td> </tr> <tr> <td>68±11</td> <td>40±18</td> <td>42±11</td> <td>42±13</td> </tr> <tr> <td colspan="4">Transfusions :</td> </tr> <tr> <td colspan="4">A, TXA et A+TXA more effective than control</td> </tr> <tr> <td colspan="4">Coagulation parameters :</td> </tr> <tr> <td colspan="4">No significant difference</td> </tr> </tbody> </table> <p>Conclusion: Similar efficacy between aprotinin and TXA, no increased efficacy with association A+TXA</p>	ctl	A	TXA	A+TXA	Blood loss (mL/kg/24h) :				40±18	35±16	34±19	35±15	Time taken for sternal closure (min) :				68±11	40±18	42±11	42±13	Transfusions :				A, TXA et A+TXA more effective than control				Coagulation parameters :				No significant difference			
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<p>Varela Crespo</p> <p>(Revista espanola de anestesiologia y reanimacion) Abstract 2007</p> <p>Spain</p>	<p>N=53 Weight range : 4 – 10 kg</p> <p>CPB surgery Reoperated and cyanotic patients</p> <p>Prospective, Randomised ?</p>	<p>- TXA (n = 25) : 1st bolus 50 mg/kg</p> <p>- Control (n=28)</p>	<p>Criteria : biochemical parameters, bleeding, use of blood products</p> <p>Efficacy results: Bleedings: 24.8% reduction (p= 0.02). Transfusion of blood products: 20% reduction (no significant) 72% reduction in reoperated patients (p=0.05) → Greater effect in reoperated patients</p>																																				
<p>Akpek</p> <p>(Gogus-Kalp-Damar Anestezi) Abstract 2008</p> <p>Turkey</p>	<p>N=30</p> <p>Children with transposition of the great arteries undergoing arterial switch operations.</p> <p>Prospective, Randomised Open ?</p>	<p>- Aprotinin (n = 10): 1st bolus 30,000 KIU/kg + infusion 10,000 KIU/kg/h until the end of operation</p> <p>- TXA (n = 10): 1st bolus 100 mg/kg + infusion 10 mg/kg/h until the end of operation</p> <p>- Control (n = 10): no drug.</p>	<p>Criteria : Coagulation parameters, 24-hour bleeding and transfusion requirements.</p> <p>Efficacy results: Perioperative coagulation profile, postoperative blood loss and requirements for blood and blood products at 24 hours post-op similar among the groups (p > 0.05).</p>																																				

Table 2 - Overview of the clinical efficacy studies with tranexamic acid in cardiovascular surgery in children -published studies found by the Rapporteur, not provided by the MAH

Study	Patients Methodology	Treatment <i>1st bolus after induction of anaesthesia and prior to skin incision</i> <i>± continuous infusion</i> <i>± bolus administered into the pump prime</i> <i>± bolus at the end of CPB</i>	Results																																		
Levin (Thromb Haemost) Canada 2000 Canada	N = 56 Age range : 1 day - 16 years Congenital heart disease with or without cyanosis CPB surgery Randomised, double-blind study,	- TXA: 1 st bolus 50 mg/kg - Control: saline placebo <u>Cyanotic Patients:</u> - Control (n=12) - TXA (n=16) <u>Acyanotic Patients :</u> - Control (n=16) TXA (n=12)	Criteria: blood loss, coagulation parameters, platelet activation analysis Efficacy results: <table border="1" data-bbox="1123 487 1690 690"> <thead> <tr> <th rowspan="2">(ml/kg)</th> <th colspan="2">Cyanotic</th> <th colspan="2">Acyanotic</th> </tr> <tr> <th>TXA</th> <th>Ctl</th> <th>TXA</th> <th>Ctl</th> </tr> </thead> <tbody> <tr> <td>Blood loss</td> <td>17.9±8.5</td> <td>21.6±14.5</td> <td>10.6±9.3</td> <td>13.5±11.9</td> </tr> <tr> <td colspan="5"><u>Transfusions (0-6h)</u></td> </tr> <tr> <td>Blood</td> <td>9.0±2.9</td> <td>10.8±11.3</td> <td>6.3±2.7</td> <td>9.9±1.9</td> </tr> <tr> <td>Pl</td> <td>9.8±1.8</td> <td>11.3±8</td> <td>14.4±11.7</td> <td>12.1±11.1</td> </tr> <tr> <td>Plasma</td> <td>7.0±3.1</td> <td>11±5.0</td> <td>15.3±0</td> <td>9.9±1.9</td> </tr> </tbody> </table> Conclusion: CPB altered platelet activation state and coagulation status irrespective of the use of TXA No obvious effect of TXA on blood loss in either patient group (p>0.05)	(ml/kg)	Cyanotic		Acyanotic		TXA	Ctl	TXA	Ctl	Blood loss	17.9±8.5	21.6±14.5	10.6±9.3	13.5±11.9	<u>Transfusions (0-6h)</u>					Blood	9.0±2.9	10.8±11.3	6.3±2.7	9.9±1.9	Pl	9.8±1.8	11.3±8	14.4±11.7	12.1±11.1	Plasma	7.0±3.1	11±5.0	15.3±0	9.9±1.9
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Van der Staak (J Pediatr Surg) 1997 NL	N = 19 Age range [25%-75%] : 16-28 hours, Congenital diaphragmatic hernia ECMO, Unblinded Historical controls	- Control (n = 9) : no TXA - TXA (n = 10) Appropriate, empirically established, dosage : bolus 4 mg/kg 30 min before surgery + infusion 1 mg/kg/h during 24 h after repair surgery	Criteria: postoperative blood loss, transfusion requirements Results: Efficacy Significant reduction in blood loss : 57 vs 390 ml, p=0.005 Significant reduction in transfusion : 1,13 vs 2,95 mg/kg/h, p=0.03 Safety: 2 TXA patients : severe thrombotic complications																																		
Breuer (Eur J Cardiothorac Surg) 2009 Germany	N = 199 Age range : 1 - 19 months CPB open heart surgery Retrospective Historical Comparison	- Aprotinin (n = 85) (sept 2005 to January 2006): 1 st bolus 50 000 KIU/kg + 10 000 KIU/kg/h until chest closure + 100 000 KIU/100 mL into the prime of CPB - TXA (n = 114) (febr 2006 to june 2006) : 1 st bolus 50 mg/kg + 100 mg/100 mL into the prime of CPB + 50 mg/kg at the end of CPB	Criteria: blood loss, transfusion requirements, rethoracotomies Efficacy results: Blood loss 24 h : No significant difference Transfusions : 1) Intra-op : No significant difference : 2) 24 h post-op : - Platelets : No significant difference - Plasma : No significant difference - RBC (A vs T) : Incidence : 9 (11%) vs 25 (22%) (p=0.035) Units : 0,1±0,4 vs 0,3±0,6 (p=0,036) Rethoracotomies : 2 (2,4%) vs 11 (9,6%) Conclusion: Increased rethoracotomies and red blood cell transfusion in TXA group vs aprotinin																																		

Target population

Overall, 1073 children were included in the studies and 631 children received TXA. In most of the studies, the age range was large, including neonates, infants, children, adolescents, which makes the results analysis difficult, especially as results are not stratified by age.

Most of the patients were undergoing CPB (cardiopulmonary bypass) surgery for congenital heart disease. Some studies mentioned whether patients were cyanotic or no.

Endpoints

The main clinical efficacy endpoints are blood loss volume, transfusions requirements and coagulation parameters. Some other endpoints are also found in studies, such as time for chest closure, rethoracotomies, platelet activation analysis, biochemical parameters.

Of note, the endpoint blood products transfusion volume may be biased in low weight children, since blood products may also be used for hemodynamic reasons and not always consequently to perioperative blood loss.

Efficacy results

Comparison vs placebo. Efficacy results from several studies show significant decrease of blood loss and blood product requirements with TXA compared to placebo, especially in cyanotic patients.

- Chauhan and Bulutcu studies including patients of age ranging from 2 months to 15 years, exclusively cyanotic, and representing in total 316 patients treated with ATX, showed indeed a significant effect of ATX on these two endpoints.

- In Zonis study, including patients of age ranging from 1 day to 14 years, cyanotic (n=18) or no (n=64), blood loss and blood product requirements were reduced only in cyanotic patients. However, the same investigators, in Levin study, did not found any significant difference on these two endpoints, neither in the overall population (n=56), nor in the cyanotic group (n=28).

- The Reid study, performed in 41 patients undergoing repeat surgery, did not analysed cyanotic/acyanotic subgroups. In univariate analysis, total blood loss was reduced by 24% (p=0.03), total blood transfusion volume by 38% (p=0.04) and sternal closure time by 32% (p=0.01) in ATX group.

In cyanotic patients, duration of surgery, blood loss, fibrinolysis and platelet activation are increased. This may explain a better treatment response in these patients.

Overall, depending of the study :

- Postoperative blood loss volume at 24 hours decreased from 15 up to 52 %
- red blood cell (RBC) transfusion decreased from 5 up to 37 %
- when mentioned, sternal closure decreased from 14 up to 38 %
- rethoracotomies decreased from 20 up to 100 %.

Comparison vs antifibrinolytic drugs. Studies comparing TXA vs aprotinin (Bulutcu, Akpek, Breuer) did not show any significant difference between groups on blood loss. Only Breuer found increased rethoracotomies and red blood cell transfusion in TXA group vs aprotinin. Bulutcu and Akpek found similar coagulation parameters and transfusions requirements. In the EACA comparative study performed by Chauhan (#3), blood loss, transfusion requirement and time taken for chest closure were similar between groups.

Subgroup analysis by age. No subgroup analysis of the results has been conducted according to children age. And more particularly, published efficacy (and safety) data do not allow analysing effects in neonates and infants aged less than 12 months.

However, physiological characteristics, especially coagulation parameters, differ highly between neonates and adolescents. In neonates and infants aged less than 12 months, bleedings under cardiopulmonary bypass (CPB) are more related to the immaturity of the coagulation system than fibrinolysis. Furthermore, it should be noted that currently all neonates and infants aged

less than 12 months are transfused. In patients weighing less than 8 kg, the ratio blood volume/CPB pump prime volume being low, the CPB priming is performed with labile blood products, which means rapidly massive blood transfusion criteria. For example, with a neonate of 3 kg, blood volume is about 80 mL/kg i.e 240 mL, and CPB priming is 300 mL of labile blood products. Transfused volume is higher to blood volume from the start of the surgery.

Dosing schedule

No dose-effect study has been conducted with ATX. Several protocols have been studied by Chauhan and al in the dose comparative study (#2). Patients received one of the following TXA dosing schedule :

- 50 mg/kg at induction of anaesthesia,
- 10 mg/kg at induction followed by an infusion of 1 mg/kg/h,
- 10 mg/kg at induction, 10 mg/kg on bypass, and 10 mg/kg after protamine (end of surgery),
- 20 mg/kg at induction and 20 mg/kg after protamine (end of surgery).

TXA was administered by slow IV injection, except the injection into the pump prime.

Study results show the efficacy of TXA on blood loss and blood product requirements with all the dosing schedules, except the single bolus of 50 mg/kg. Therefore, the dose tested in the two Canadian studies (Levin and Zonis, British Columbia's Children Hospital, Vancouver), i.e single preoperative intravenous dose of 50 mg/kg, could explain the absence of significative effect of TXA in all children.

The dosing schedule used in several studies having shown a significant effect of TXA included administration of 3 injections of at least 10 mg/kg:

- first bolus after induction of anaesthesia and prior to skin incision,
- second bolus into the CPB pump prime or continuous infusion,
- last bolus at the end of CPB, after protamine administration.

Efficacy does not seem improved with three injections of 100 mg/kg (Bulutcu and al) compared with three injections of 10 mg/kg (Chauhan and al). Since injection into the CPB pump prime is not according to duration of the surgery, continuous infusion during surgery appears to make more sense, especially for prolonged surgeries.

Renal adjustment

In children with renal impairment, the exposure to TXA may be increased. Therefore, posology of TXA should be decreased according to creatinine clearance.

Rapporteur's comment

Efficacy study results show that TXA significantly reduced blood loss and blood product requirements in paediatric cardiac surgery at high risk of haemorrhage under cardiopulmonary bypass, especially cyanotic patients or patients undergoing repeat surgery. Dosing schedule used in studies showing the most significant results included 3 injections of at least 10 mg/kg: first bolus after induction of anaesthesia and prior to skin incision, second bolus into the CPB pump prime or continuous infusion, last bolus at the end of CPB, after protamine administration. In order to maintain adequate concentration all along surgery, continuous infusion during surgery appears to make more sense, especially for prolonged surgeries. Efficacy of single preoperative intravenous dose of 50 mg/kg is doubtful. Lastly, in renal impairment, posology of TXA should be decreased according to creatinine clearance.

In neonates and infants aged less than 12 months, the benefit of an antifibrinolytic drug is questionable.

Indeed, bleedings under cardiopulmonary bypass (CPB) in this population are more related to the immaturity of the coagulation system than fibrinolysis. Since published efficacy and safety data do not allow analysing effects in neonates and infants aged less than 12 months, no

conclusion can be drawn on TXA effect in this population. Furthermore, it should be noted that currently all neonates and infants aged less than 12 months are transfused. In patients weighing less than 8 kg, the ratio blood volume/CPB pump prime volume being low, the CPB priming is performed with labile blood products, which means rapidly massive blood transfusion criteria. For example, with a neonate of 3 kg, transfused volume is higher to blood volume at the start of the surgery. Lastly, due to the physiological characteristics of neonates and infants (immaturity of the blood-brain barrier, immaturity of renal function...), as well as the generalised inflammatory state related to CPB, there may be a potential risk of cerebral exposure to TXA concentrations evoking epileptic seizure (see parts 2. Non clinical and 4. Safety).

Consequently, TXA is not recommended in neonates and infants aged less than 12 months.

In conclusion, from the review of literature, the Rapporteur is of the opinion that sufficient data are available to codify the use of TXA in children in the setting of cardiovascular surgery, excluding neonates and infants aged less than 12 months. TXA appears to be effective in reducing blood loss and blood product requirements. A dose schedule can be also proposed from the review of clinical trials.

Following the clinical data assessment, we propose to amend the sections 4.1 and 4.2 of the SPC (see overall conclusion below for details) accordingly.

However, physiological characteristics, especially coagulation parameters, differ highly between neonates and adolescents. In neonates and infants aged less than 12 months, bleedings under cardiopulmonary bypass (CPB) are more related to the immaturity of the coagulation system than fibrinolysis. Furthermore, it should be noted that currently all neonates and infants aged less than 12 months are transfused. In patients weighing less than 8 kg, the ratio blood volume/CPB pump prime volume being low, the CPB priming is performed with labile blood products, which means rapidly massive blood transfusion criteria. For example, with a neonate of 3 kg, blood volume is about 80 mL/kg i.e 240 mL, and CPB priming is 300 mL of labile blood products. Transfused volume is higher to blood volume from the start of the surgery.

II.3.3.2 Other indications

II.3.3.2.1 Orthopaedic surgery

The search retrieved 2 studies in scoliosis surgery.

2001, Neilipovitz (*Anesth Analg*)

In this prospective, double-blind, placebo controlled study, 40 patients (9-18yr), were randomised to receive either tranexamic acid (initial dose of 10 mg/kg over 15 mn after patient final positioning followed by infusion of 1 mg/kg/h) or placebo (isotonic saline) until skin closure.

The primary outcome was the total amount of blood transfused in the perioperative period, which leads to the use of a uniform transfusion policy (transfusion threshold for all types of red blood cells was 7.0 g/dL). All the infusion volumes (fluids including all blood products) were documented. Patients were assessed daily for any clinical evidence of deep venous thrombosis. The total amount of blood transfused in the perioperative period was significantly reduced in the TXA group ($p = 0.045$). The intraoperative blood loss and the volume of packed red blood cell in the TXA group were not significantly different than in the control group. TXA was well tolerated by all subjects in the treatment group and no thrombotic complications were detected in either group.

The authors conclude that administration of TXA (initial dose of 10 mg/kg followed by infusion of 1 mg/kg/h) in paediatric patients with scoliosis who are undergoing posterior spinal fusion

surgery has the potential to reduce perioperative blood transfusion requirements and that no thrombotic complications or other adverse events were detected in this clinical trial.

2005, Sethna (Anesthesiology)

The authors conducted a double blind randomised study in 44 paediatric patients aged 8-18 year, scheduled to undergo surgical scoliosis correction either secondary or idiopathic. Patients were randomly assigned to receive either TXA (TXA group n = 23) or 0.9% saline (placebo group n = 21). After induction of anaesthesia and before skin incision, patients received placebo or TXA 100 mg/kg over 15 min. An infusion of placebo or TXA (10 mg/kg/h) was then initiated and continued until skin closure. Blood loss, transfusion requirements, coagulation parameters, and complications were assessed.

Intraoperative blood loss was 41% lower in patients receiving TXA ($1,230 \pm 535$ ml) compared with the placebo group ($2,085 \pm 1,188$ ml) ($p < 0.01$). The intraoperative blood loss in the secondary scoliosis was 48% lower in patients receiving TXA ($1,408 \pm 605$ ml) compared with the placebo group ($2,690 \pm 1,266$ ml) ($p < 0.01$). In the idiopathic group, there was a trend in favour of TXA but results did not reach a level of statistical significance. The amount of blood transfused did not differ significantly between the TXA and placebo groups. The mean total packed erythrocytes (PE) transfusion volume in the secondary scoliosis patients was significantly lower in the TXA patients (808 ± 531 ml) compared with the placebo patients ($1,391 \pm 723$ ml) ($p < 0.04$). However, the mean total PE transfusion volume was comparable between the treatment groups in the idiopathic patients. No safety concerns were reported.

The authors conclude that the dose of TXA (100 mg/kg over 15 min after induction of anaesthesia and before skin incision, followed by an infusion of 10 mg/kg/h until skin closure) used in this study significantly reduced surgical blood loss during posterior spinal instrumentation but had no significant effect on blood transfusion requirements.

Summary

In 2 studies in children undergoing scoliosis surgery, TXA has a beneficial effect with the following schedules:

- initial dose of 10 mg/kg followed by infusion of 1 mg/kg/h
- 100 mg/kg over 15 min after induction of anaesthesia and before skin incision, followed by an infusion of 10 mg/kg/h until skin closure.

No safety issues were reported in this setting.

Rapporteur's comment

We endorse the MAH statement that clinical data are insufficient to recommend the use of TXA in this surgical setting in children. Moreover, the dosing schedules of the two studies differ importantly. Contrary to paediatric cardiac surgery, no major clinical need has been identified by the Rapporteur.

II.3.3.2.2 Cranio-facial surgery

Duran de la Fuente (Rev Esp Anesthesiol Reanim, 2003) has conducted a randomised, single blind study in 20 patients undergoing cranial remodelling surgery. Ten patients were assigned to receive 15 mg/kg of intravenous TXA upon anaesthetic induction, every 4 hours during surgery, and every 8 hours throughout the 48 hours after surgery. Ten patients served as control. Results of blood tests, blood loss, volume transfused, time in the recovery unit, and complications related to TXA infusion were recorded and analysed.

The TXA group experienced less bleeding during surgery than did the controls (199 ± 60 vs. 290 ± 43 mL, $p < 0.05$). There was also a trend in less need of intraoperative (176 ± 104 vs. 216 ± 70 mL), in postoperative transfusion (9 ± 28 vs. 52 ± 72 mL) 24 hours after surgery, and in less time spent in the recovery unit (60 ± 14 vs. 72 ± 11 hours). Platelet count (261 ± 68.5 vs. 181.6 ± 58.1 platelets/mm³), and cephalin time (33 ± 12 vs. 49 ± 16 seconds $p < 0.05$) were significantly better in treatment group the day following surgery. No complications related to TA treatment were observed.

The authors conclude that intravenous administration of 15 mg/kg of TXA upon anaesthetic induction, every 4 hours during surgery, and every 8 hours throughout the 48 hours after surgery can reduce perioperative bleeding in the context of paediatric cranial remodelling surgery.

Rapporteur's comment

We endorse the MAH statement that clinical data are insufficient to recommend the use of TXA in this surgical setting in children. Contrary to paediatric cardiac surgery, no major clinical need has been identified by the Rapporteur.

II.3.3.2.3 Medical indication : haemophilia

In 1973 Rainsford (Thromb Diath Haemorrh) reported a double-blind cross-over study of the prophylactic value of TXA (3g/d) against spontaneous bleeding episodes in severe haemophilia. This study included 20 boys aged between 11 and 19 with severe haemophilia with coexistent joint damage. A significant reduction in spontaneous bleeding episodes and in transfusion requirements was observed. The authors reported also the good safety profile of the product and conclude that further investigation is justified.

It should be noted that this study is quite old and that management of haemophilia has been deeply improved by the availability of FVIII.

Rapporteur's comment

We endorse the MAH statement that clinical data are insufficient to recommend the use of TXA in this surgical setting in children. Contrary to paediatric cardiac surgery, no major clinical need has been identified by the Rapporteur.

II.3.3.2.4 Other indications

Literature references in other clinical settings have been found by the MAH. They assess TXA effect on haemorrhage treatment in various clinical settings in children, such as dental extractions, acute promyelotic leukaemia, tonsillectomy, menorrhagia.

Rapporteur's comment

These clinical settings have not been reviewed by the MAH in his clinical overview. After review, the Rapporteur supports the opinion that clinical data are insufficient to recommend a new indication in children. However, TXA is already indicated in some of these clinical settings in some European countries.

II.3.4 Clinical safety

II.3.4.1 MAH safety data

According to the MAH, no safety concern has been identified based on the review of safety data available in clinical trial database, post-marketing safety data and literature. TXA is well tolerated in children. The most important adverse events are reported very rarely and are listed in the SPC in the following SOCs: gastro-intestinal disorders (nausea and diarrhoea), vascular disorders (orthostatic reactions).

II.3.4.2 Rapporteur safety data analysis

The safety data analysis is based on, National pharmacovigilance database, European eudravigilance database and literature. The Rapporteur has focused the safety analysis on the risk of convulsions in paediatric population in a setting of cardiac surgery.

The risk of convulsions in paediatric cardiac surgery has previously been reported. The convulsions were due to peri-operative induced hypothermia. However, nowadays evolution of the clinical practices enables to conduct surgery with normothermic conditions which allows controlling the risk of convulsions due to hypothermia.

Published studies, National pharmacovigilance database and European eudravigilance database have been reviewed and are summarised below.

Literature

A literature review on standard medical databases (i.e. Embase, Medline) has focused on the following selection criteria: paediatric cardiac surgery, undesirable effects, TXA. Fifteen publications have been identified, and are described in the table below.

Table 3. Undesirable effects with TXA in paediatrics in cardiac surgery– literature data

Author	Objective	Conclusion - Safety
Breuer (Germany)	N = 199 Mean age [25- 75 th percentile] = 6 [1 - 19] months Historical comparison: - Aprotinine (n = 85): 50 000 KIU/kg at the beginning of CPB + 10 000 KIU/kg/h + 100 000 KIU/100 mL added to the prime of the CPB equipment - TXA (n = 114): 50 mg/kg at the beginning of CPB + 100 mg/100 ml added to the prime of the CPB equipment + 50 mg/kg at the end of CPB	Safety: Postoperative outcome. Mechanical ventilation (h) 38 (14-92) 23 (10-81) ICU stay (day) 8 (5-12) 7 (4-13) Rethoracotomy 2 (2.4%) 11 (9.6%)* Low cardiac output syndrome 11 (12.9%) 14 (12.3%) Renal injury 9 (10.6%) 11 (9.6%) Renal failure 0 2 (1.8%) Seizure 0 4 (3.5%) Other neurological events 4 (4.7%) 3 (2.6%) In-hospital mortality 3 (3.5%) 3 (2.6%) * significant
Van den Staak (Netherlands)	Effects of TXA on blood loss in congenital diaphragmatic extracorporeal membrane oxygenation (ECMO). Historical comparison: no TXA vs TXA	Safety: Four patients experienced thrombotic complications (two in each group). These complications seemed to be more severe in the patients treated with TXA.
Eaton (New York)	Review Antifibrinolytic therapy in surgery for congenital heart disease	Dosing schemes used for these drugs have been variable and not always based on sound pharmacologic principles, despite available pharmacokinetic and pharmacodynamic data. Further research should be directed toward establishing safety, evaluating the relative efficacy of the two classes of drugs, proving benefit in specific patient groups, and better defining effective dosing schemes.

		<p>Safety:</p> <ul style="list-style-type: none"> - aminocaproic acid and TXA: thrombotic complications, including a case of fatal aortic thrombosis. - Aprotinin: thrombosis, renal effects and anaphylaxis. <p>There is not enough evidence to draw any conclusions about the safety of these drugs in children, although it appears that the risk of anaphylaxis with aprotinin in children may be less than in adults.</p>
Trudell (Pennsylvania)	Literature review of the current antifibrinolytic therapy for coronary artery revascularization 4373 patients undergoing coronary revascularization (age non specified)	<p>Safety:</p> <ul style="list-style-type: none"> - Adverse reactions expected with aminocaproic acid and TXA: seizures, renal failure, and rhabdomyolysis - Adverse reactions expected with aprotinin : increase in anaphylactic reactions. Additionally an increase of 2 folds in renal failure, 55% in myocardial infarction and heart failure and 181% in stroke or encephalopathy. <p>The study concluded that TXA was less costly than aprotinin and achieved a comparable benefit.</p>
Reid (Boston)	Comparison TXA/ saline placebo Prospective, randomized, double-blind study 41 children	<p>Safety: TXA was well tolerated by all subjects. There were no cases of hemodynamic instability, overt thrombotic complications, or other adverse effects associated with the bolus or infusion.</p>
Bulutcu (Turkey)	To investigate reducing of postoperative blood loss by using aprotinin and TXA alone or a combination of these two agents.	Safety: No adverse event reported.
Vacharaksa (Thailand)	67 children undergoing repair of cyanotic congenital heart defect. - 15 mg/kg of TXA - second bolus of TXA (15 mg/kg) or saline placebo	Safety: No adverse effects of TXA were found in this study.
Varela Crespo (Spain) (paper available in Spanish)	Effects of a single dose of TXA on bleeding and requirement for blood product transfusion in children undergoing cardiac surgery with CPB	Safety: No adverse effects attributable to the treatment were observed.
Zonis (Canada)	Effects of a single preoperative dose of TXA on blood loss after cardiopulmonary bypass. 88 children Single dose of TXA 50 mg/kg IV Or placebo	Safety: No patients died and no adverse reactions were attributed to the study drug.
Levin (Canada)	To investigate hemostatic parameters including platelet activation in 56 patients with and without cyanosis undergoing CPB.	CPB altered platelet activation state and coagulation status irrespective of the use of TXA No safety
Chauhan # 2 (India)	Dose comparison of TXA in 150 children with congenital cyanotic heart disease were randomly assigned to one of 5 groups of 30 each	Safety: No complication in the form of renal problems or cerebral events were noted in any of the children study
Chauhan # 1 (India)	Control vs TXA in children undergoing cardiac surgery. 120 children randomized into 2 groups.	Safety: No complication in the form of renal or cerebral dysfunction was noted in any of the children studied in two groups.
Chauhan # 3 (India)	Comparison of aminocaproic acid and TXA in children with cyanotic congenital heart disease	No safety
Gruber (Boston)	To determine if aminocaproic acid and tranexamic acid (TXA) are	Use of aminocaproic acid and TXA is not associated with early baffle fenestration closure

	associated with early closure of the baffle fenestration after the modified Fontan procedure	No safety
Guay (Canada)	Review Minimizing perioperative blood loss and transfusions in children	For patients with idiopathic scoliosis, predonation with or without the addition of erythropoietin is a safe and effective way to avoid the use of allogenic blood products. For open heart procedures: whole blood of less than 48 hr is helpful for children of less than two years of age undergoing complex procedures; TXA may be helpful for cyanotic heart disease and, to a lesser degree, for reoperations; while anti-kallikrein blood levels of aprotinin may both reduce the need for allogenic blood transfusions and improve postoperative oxygenation in infants. Reducing perioperative allogenic blood transfusions is possible in pediatric patients provided that prophylactic measures are adapted to age, disease and type of surgery No safety

Among the fifteen publications reviewed, four did not provide any safety data. Additionally in seven publications, the authors concluded that TXA was well tolerated during the clinical trials. In the remaining four publications (including two reviews with one not specific to paediatrics), the reported adverse events are related to reactions largely covered by the current SPC of TXA.

Regarding neurological adverse events such as convulsions:

In a retrospective study comparing TXA to aprotinin as historical controls, in open heart surgery (Breuer *et al*), among 114 infants aged from one to 19 months in the TXA group, 4 cases of epileptic seizures have been reported *versus* no case in aprotinin group. However this difference was not statistically significant. Moreover, in the absence of reported cases description, the causality of TXA cannot be assessed. It should be noted that : (i) the TXA dose administered in this study was higher than the dosing schedule recommended in this Assessment Report (see section 4.2), (ii) the median age of children was 4 months, most of them being under 1 year old, i.e the excluded population of this Report.

Similarly a retrospective study was conducted in adults, by the same investigators (Martin and al.), compared TXA to aprotinin as historical controls, in cardiac surgery, in 1188 patients. Twenty-seven cases (4.6%) of seizures out of 592 patients in the TXA group were reported. Again, in the absence of reported cases description, the causality of TXA cannot be assessed.

Furthermore, five additional studies have been analysed. The indication was scoliosis surgery (Neilipovitz *et al.* and Sethna *et al.*), haemophilia (Rainsford *et al.*), adenotonsillectomy (Verstraete *et al.*) and cranial remodelling surgery (Duran de la Diente *et al.*). No safety concern has been identified in all five studies

National Pharmacovigilance database

A review of convulsion cases related to TXA in the French National Pharmacovigilance Database has identified only 7 serious cases in adults. All cases occurred in other settings than cardiac surgery:

- Two cases related to drug misuse have described a local use during cerebral surgery. A fatal outcome was reported in both cases.
- Five cases of convulsions have been reported in patients where confounding factors were identified: history of convulsions, cerebral meningioma, cerebral surgery or other suspected drugs.

One non serious case has been reported with Frenolyse[®] (no longer marketed TXA product with the same indications as Exacyl[®]), in a 14 year old child known to be epileptic. In this poorly documented case, the causality of TXA cannot be assessed.

The review of safety data from the French National Pharmacovigilance Database does not allow any strong conclusion on the presence or absence of a signal on convulsion risk with TXA in a setting of cardiac surgery in paediatric population.

European Eudravigilance database

Review of European eudravigilance database identified 250 adverse events case reports, of which 24 occurring in children. No case of epileptic seizure/myoclonia has been reported. The clinical indications were known in 16 cases, none of them being cardiovascular surgery.

Four cases of convulsions in adults have been identified, out of the 226 reports in adults. The clinical indication was known in only 1 case (digestive bleedings). In two cases, the causality of TXA cannot be assessed due to lack of information. In the two other cases, metoclopramide is a co-suspected drug. Since metoclopramide is known to induce extrapyramidal symptoms and myoclonia, the causality of TXA is difficult to assess.

Rapporteur's comment

The safety data are based on a review of literature, National pharmacovigilance database and Eudravigilance database.

Only limited data have been available up to now in paediatric population in all indications and particularly in cardiac surgery setting. However, the data analysed have reported similar adverse reactions already identified in adult population. These reactions are largely covered by the current SPC of TXA, and are mainly represented by gastro-intestinal disorders (nausea and diarrhoea), vascular disorders (orthostatic reactions, arterial and venous thrombosis), nervous disorders (convulsions) and hypersensitivity reactions.

Additionally, no conclusions can be drawn regarding a potential epileptic risk in paediatric population particularly in cardiac surgery. The risk of convulsion has been identified during the use of TXA in intrathecal or intraventricular injection and intracerebral application. However, TXA is already contraindicated in these situations.

II.3.5 Discussion on clinical aspects

In neonates and infants aged less than 12 months, the benefit of an antifibrinolytic drug is questionable since bleedings in this population are more related to the immaturity of the coagulation system than fibrinolysis. Study results are not specifically analysed in this population. All the neonates and infants aged less than 12 months are transfused due to their very low blood volume. CPB pump prime is filled with labile blood products when blood volume is lower than pump prime volume. Lastly, there may be a potential risk of cerebral exposure to TXA concentrations evoking epileptic seizure, due to the immaturity of the blood brain barrier and the renal function. Consequently, TXA is not recommended in neonates and infants aged less than 12 months.

In children aged of more than 1 year, further to the suspension of aprotinin, in the absence of therapeutic alternatives, there is a real medical need of TXA in paediatric cardiac surgery to reduce perioperative blood loss.

Clinical studies have demonstrated that TXA significantly reduced blood loss and blood product requirements in paediatric cardiac surgery at high risk of haemorrhage under cardiopulmonary bypass, especially cyanotic patients or patients undergoing repeat surgery. Dosing schedule used in studies showing the most significant results included 3 injections of at least 10 mg/kg: first bolus after induction of anaesthesia and prior to skin incision, second bolus into the CPB pump prime or continuous infusion, last bolus at the end of CPB, after protamine administration.

In order to maintain adequate concentration all along surgery, continuous infusion during surgery appears to make more sense, especially for prolonged surgeries. Efficacy of single preoperative intravenous dose of 50 mg/kg is doubtful. Lastly, in renal impairment, posology of TXA should be decreased according to creatinine clearance.

The safety data are based on a review of literature, National pharmacovigilance database and Eudravigilance database. Only limited data have been available up to now in paediatric population in all indications and particularly in cardiac surgery setting. However, the data analysed have reported similar adverse reactions already identified in adult population. These reactions are largely covered by the current SPC of TXA, and are mainly represented by gastrointestinal disorders (nausea and diarrhoea), vascular disorders (orthostatic reactions, arterial and venous thrombosis), nervous disorders (convulsions) and hypersensitivity reactions. Additionally, no conclusions can be drawn regarding a potential epileptic risk in paediatric population particularly in cardiac surgery. The risk of convulsion has been identified during the use of TXA in intrathecal or intraventricular injection and intracerebral application. However, TXA is already contraindicated in these situations.

In other clinical settings (orthopaedic surgery, cranio-facial surgery, haemophilia, dental extractions, acute promyelotic leukaemia, tonsillectomy, menorrhagia), clinical data are insufficient to conclude on efficacy and safety of TXA in children. However, TXA is already indicated in some of these clinical settings in some European countries.

Request for supplementary information

On 2nd March, 2009 the Rapporteur circulated the day 70 assessment reports for the EU Worksharing Procedure for paediatric data for Tranexamic acid. Comments were received from Member States.

Member States globally agreed with the Rapporteur's Assessment Report. One Member State also agreed with the Rapporteur that the benefit/risk ratio of TXA in children for high risk cardiovascular surgeries may be positive. However, the MS requested supplementary information before final assessment of the proposed wordings for sections 4.1, 4.2, 4.4 and 5.1 of the SmPC and a list of Questions was subsequently sent to the MAHs.

The List of Questions was as follows:

- PK data for children have not been established. The applicant should put effort in better defining PK data in different age groups to better quantify the optimum treatment schedule for children.
- Efficacy has not been established for different age groups. The applicant should try to elucidate more on age-related efficacy.
- Safety with regard to the risk for myocardial infarction and mortality in children should be discussed more in detail.
- Further details regarding the use of tranexamic acid tablets for menorrhagia in children aged 12-15 yrs of age are requested.
- The applicant should be encouraged to undertake PK studies in children and adolescents for both tablet and intravenous route.

On 9th July, 2009 the MAH submitted the Applicant's Responses to the Request for Supplementary Information.

The MAH recognizes the medical/patient need in cardiac surgery in children since aprotinin Marketing Authorisation has been suspended in Europe.

The MAH agreed with the Rapporteur that available studies in cardiac paediatric surgery can be described in section 5.1 but considered that data available in cardiac paediatric surgery are too limited to support a recommended dosage in the SPC.

For menorrhagia in children 12-15 years, the MAH recognizes that the available data regarding the use of tranexamic acid are too limited to recommend a new indication in children but it appears that the medical need for treatment of menorrhagia in children is not as essential as for cardiac surgery.

Following assessment of the MAH responses, the points were all resolved. However, the Rapporteur made the main following comments:

- Cardiac surgery:

The Rapporteur agrees that at that step of knowledge of efficacy and safety data in paediatrics, a formal indication in section 4.1 of the SPC could be considered premature.

We consider that the 12 efficacy studies from the literature review (overall concerning a non negligible sample size of 631 children having received TXA) is a high value basis to mention the use of TXA in the SPC, in the context of an important medical need following the aprotinin suspension. As a reminder, we concluded in our PAR that the benefit-risk profile was positive in the setting of paediatric cardiac surgery in children over one year old following review of literature. Thus, a detailed paragraph mentioning the main efficacy results in section 5.1 of the SmPC is fully justified (see item 8 below for details on the SPC).

Regarding the proposed posology, and to clarify some MS questions on that topic, we selected from published studies the dosing schedule tested by Chauhan (first bolus of 10 mg/kg + injection into the CPB pump prime at a dose of 10 mg/kg + last injection of 10 mg/kg at the end of CPB), which appeared to show a good efficacy profile. However, based on other studies, we proposed to adapt the second dose according to clinical situations: possibility of continuous infusion of 10 mg/kg/h or injection into the CPB pump prime at a dose adapted on the CPB procedure, either according to patient weight with a 10 mg/kg dose, either according to CPB pump prime volume. To our point of view, information on this posology should also be added in section 5.1. of the SmPC (see item 8 below for details). Our proposed wording is based on a rigorous analysis of data from literature. We however recognise that in the absence of a specific PK study in this target population, this posology should only be suggested in section 5.1 of the SPC.

As a reminder, for safety reasons, children under one year old present a risk of convulsions and should not receive tranexamic acid.

- Other clinical settings:

A paediatric posology (of about 20 mg/kg/day) for indications including menorrhagia has been approved for decades in some countries, at a time where evaluation standards were different from the current ones. After review of literature, it seems that TXA is recommended for the management of menometrorrhagia in women. Some studies included young patients of 15 years old. Therefore, we propose to maintain other indications than cardiac surgery as they are currently approved in the national SPCs and we endorse the wording proposed by the MAH for section 4.2.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Cardiopulmonary bypass (CPB) and cardiovascular surgery activate coagulation, inflammation, and fibrinolysis. Paediatric patients are especially at risk for hematologic derangement related to CPB. Antifibrinolytic drugs are used to prevent haemorrhages in this clinical setting.

Literature review identified 12 efficacy studies which have included 1073 children, 631 having received TXA. Most of them were controlled versus placebo. Studied population was heterogenic in terms of age, surgery types, dosing schedules. Efficacy results have demonstrated that TXA significantly reduced blood loss and blood product requirements in paediatric cardiac surgery under cardiopulmonary bypass when there is a high risk of haemorrhage, especially cyanotic patients or patients undergoing repeat surgery, and when dosing schedule maintains therapeutic plasma concentration all along surgery.

No specific dose-effect study or PK study has been conducted in children. However, based on literature data, the optimal dosing schedule should include:

- first bolus of 10 mg/kg after induction of anaesthesia and prior to skin incision,
- continuous infusion of 10 mg/kg/h or injection into the CPB pump prime at a dose adapted on the CPB procedure, either according to patient weight with a 10 mg/kg dose, either according to CPB pump prime volume,
- last injection of 10 mg/kg at the end of CPB.

While studied in very few patients, continuous infusion appears to make more sense, since it would maintain therapeutic plasma concentration all along surgery.

Only limited data have been available up to now in paediatric population in all indications and particularly in cardiac surgery setting. However, the data analysed have reported similar adverse reactions already identified in adult population. These reactions are largely covered by the current SPC of TXA, and are mainly represented by gastro-intestinal disorders (nausea and diarrhoea), vascular disorders (orthostatic reactions, arterial and venous thrombosis), nervous disorders (convulsions) and hypersensitivity reactions. Additionally, no conclusions can be drawn regarding a potential epileptic risk in paediatric population particularly in cardiac surgery. The risk of convulsion has been identified during the use of TXA in intrathecal or intraventricular injection and intracerebral application. However, TXA is already contraindicated in these situations.

The following precautions for use should be observed before using TXA: 1) ask for history of convulsions, and not use TXA in patients with history of convulsions; 2) not perform intrathecal and intraventricular injection and intracerebral application; 3) investigate for renal function disorders and reduce TXA consequently; 4) investigate for risk factors of thromboembolic disease and not use TXA in patients with history of thromboembolism.

Lastly, TXA should not be recommended in neonates and infants aged less than 12 months.

To conclude, prevention of haemorrhages in paediatric cardiac surgery at high risk of haemorrhage under cardiopulmonary bypass should involve global medical care, in which antifibrinolytic drug use may be considered, TXA being the only antifibrinolytic drug available in all Europe. Global medical care should be specifically adapted according to the type and the duration of surgery, and characteristics of the patient.

In other clinical settings (orthopaedic surgery, cranio-facial surgery, haemophilia, dental extractions, acute promyelotic leukaemia, tonsillectomy, menorrhagia), clinical data are insufficient to conclude on efficacy and safety of TXA in children. However, TXA is already indicated in some of these clinical settings in some European countries.

The MAH answered the questions raised by the MS and proposed revisions of the SPC. It is recognised by the MAH that there is a medical need in cardiac surgery in children since aprotinin Marketing Authorisation has been suspended in Europe. In this context, the MAH agrees with the Rapporteur that available studies in paediatric cardiac surgery can be described in this section 5.1 (Pharmacodynamic properties).

Based on the provided clinical data, the SPC should be amended as follows:

A review from literature identified 12 efficacy studies in paediatric cardiac surgery (631 children having received TXA) that showed a positive benefit-risk profile in children over one year old. This is a high value basis to mention the use of TXA in paediatric cardiac surgery in section 5.1 of the SPC. Furthermore, to better inform prescribers, we propose a posology based on a rigorous analysis of data from literature.

Regarding other indications than cardiac surgery, some MS have approved a paediatric posology of 20mg/kg/day for decades. We propose to maintain these other indications as they are currently approved in National SPCs and we endorse the wording proposed by the Company for section 4.2. Member States that would be interested in recognising a new indication in menorrhagia in young patients can ask the Company to submit a type II variation.

The amended sections of the SPC discussed in this Final Assessment Report are presented below (text revisions highlighted in grey). The submission of a type II variation is required to implement the proposed SPC amendments.

Section 4.2 Posology and method of administration

(...)

In children, **for current approved indications as described in section 4.1**, the dosage is in the region of 20 mg/kg/day. **However, data on efficacy, posology and safety for these indications are limited.**

Injectable solution: The efficacy, posology and safety of Tranexamic acid in children undergoing cardiac surgery have not been fully established. Currently available data are limited and are described in section 5.1.

(...)

Section 4.3 Contra Indications

- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- Severe renal **insufficiency/impairment** (risk of accumulation)
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)

Section 4.4 Special Warnings and precautions for use

The indications and method of administration indicated above should be followed strictly:

- Intravenous injections should be given very slowly
- Tranexamic acid should not be administered by the intramuscular route.
- Due to the risk of cerebral oedema and convulsions, intrathecal ~~and/or~~ intraventricular injection and intracerebral application are contra-indicated. In patients with a history of convulsion, tranexamic acid should not be administered.
- In case of haematuria of renal origin, there is a risk of mechanical anuria due to formation of a ureteral clot.
- In renal insufficiency leading to a risk of accumulation, the dosage of tranexamic acid should be reduced according to the serum creatinine level :
 - serum creatinine between 120 and 250 $\mu\text{mol/l}$: TXA iv 10 mg/kg twice daily.
 - serum creatinine between 250 and 500 $\mu\text{mol/l}$: TXA iv 10 mg/kg once daily (every 24 hours).
 - serum creatinine > 500 $\mu\text{mol/l}$, TXA iv 10 mg/kg every other day (every 48 hours).
- ~~If the serum creatinine is between 120 and 250 $\mu\text{mol/l}$, intravenous administration of tranexamic acid is calculated on the basis of 10 mg/kg twice daily.~~
- ~~For concentrations between 250 and 500 $\mu\text{mol/l}$, this dose of 10 mg/kg should only be administered once every 24 hours.~~
- ~~When the creatinine level is above 500 $\mu\text{mol/l}$, this dose of 10 mg/kg should only be administered once every 48 hours.~~
- Before use of TXA, risk factors of thromboembolic disease should be investigated.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis.

Section 4.8 Undesirable Effects

Very rare adverse events have been reported :

- Gastro-intestinal disorders: digestive effects such as nausea, vomiting and diarrhoea.
- Cardio-vascular disorders :
 - malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration)
 - arterial or venous thrombosis at any sites
- Nervous system disorders: convulsions, particularly in case of misuse (see section 4.4 "Precautions and warnings")
- General disorders: hypersensitivity reactions including anaphylaxis

Section 5.1 Pharmacological properties

(...)

Injectable solution:

In children over one year old:

Literature review identified 12 efficacy studies in paediatric cardiac surgery which have included 1073 children, 631 having received TXA. Most of them were controlled versus placebo. Studied population was heterogenic in terms of age, surgery types, dosing schedules. Study results with TXA suggest reduced blood loss and reduced blood product requirements in paediatric cardiac surgery under cardiopulmonary bypass when there is a high risk of haemorrhage, especially in cyanotic patients or patients undergoing repeat surgery. The most adapted dosing schedule appeared to be:

- first bolus of 10 mg/kg after induction of anaesthesia and prior to skin incision,

- continuous infusion of 10 mg/kg/h or injection into the CPB pump prime at a dose adapted on the CPB procedure, either according to patient weight with a 10 mg/kg dose, either according to CPB pump prime volume,

- last injection of 10 mg/kg at the end of CPB.

While studied in very few patients, the limited data suggest that continuous infusion is preferable, since it would maintain therapeutic plasma concentration throughout surgery.

No specific dose-effect study or PK study has been conducted in children.

Section 5.2 Pharmacokinetic properties

(...)

Absorption

Peak plasma ATX concentration is obtained immediately after IV administration (500mg). Then concentration decreases until the 6th hour. Elimination half-life is about 3 hours.

Distribution

TXA is delivered in the cell compartment and the cerebrospinal fluid with delay. The distribution volume is about 33% of the body mass.

Elimination

TXA is excreted in urine as unchanged compound. 90% of the administered dose is excreted by the kidney in the twelve first hours after administration (glomerular excretion without tubular reabsorption). Plasma concentrations are increased in patients with renal insufficiency.