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Assessment report

Antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid

Tranexamic acid

Procedure number: EMEA/H/A-1267

Referral under Article 31 of Directive 2001/83/EC

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 12 March 2010, Germany triggered a referral under Article 31 of Directive 2001/83/EC. The Committee for medicinal products for human use (CHMP) was requested to give its opinion on whether the marketing authorisations for medicinal products containing aprotinin, aminocaproic acid and tranexamic acid should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, was applicable.

2. Scientific discussion

2.1. Introduction

Antifibrinolytics¹ (e.g. aprotinin, aminocaproic acid and tranexamic acid), are a class of haemostatic agents used to prevent excessive blood loss. Aprotinin, a naturally occurring polypeptide, is an inhibitor of proteolytic enzymes. It has a broad action on proteolytic enzymes such as plasmin, trypsin, and kallikrein. The lysine analogues epsilon aminocaproic acid (EACA, also referred as aminocaproic acid) and tranexamic acid (TXA) inhibit more specifically the conversion of plasminogen to plasmin.

In 2006 concerns were raised over the safety of aprotinin as a result of the publication of observational studies (Mangano *et al* 2006, Karkouti *et al* 2006) and the preliminary results of a large observational cohort study (i3 Drug Safety, 2007). These found an increased risk in renal dysfunction and/or cardiovascular events in patients treated with aprotinin compared to those treated with EACA or TXA. In 2007 preliminary results of a randomised controlled clinical trial, the 'Blood conservation using antifibrinolytics: a randomised trial in a cardiac surgery population' (BART) study, became available. The BART was a prospective, randomised, blinded trial in patients undergoing a procedure for which cardiopulmonary bypass (CPB) was required. It was designed to determine whether aprotinin was superior to EACA and TXA in decreasing the rate of massive bleeding and the need for transfusions. The preliminary results of the BART study showed that although the use of aprotinin was associated with less serious bleeding than either of the comparator drugs, more deaths due to haemorrhage had been observed among patients receiving aprotinin. The BART study was discontinued due to the safety signal. In November 2007, based on the review of available data² at the time, including the preliminary results of the BART study, the CHMP concluded that the benefit/risk balance of aprotinin-containing medicinal products for systemic use was not favourable. The marketing authorisations for all aprotinin-containing medicines in the European Union were suspended with a condition for marketing authorisation holders (MAHs) to identify a patient population in which the efficacy of systemic aprotinin clearly outweighed its risks. In its 2007 review, the Committee also acknowledged the need to trigger an article 31 referral procedure in order to evaluate the totality of the information on the BART study, once the final report would be available.

Further to the publication of the final results of the BART study an overall review on the benefits and risks of antifibrinolytics was considered necessary. In March 2010 Germany triggered this article 31 referral to assess the benefits and risks of the antifibrinolytic drugs aprotinin, EACA and TXA in all its approved indications.

Several data sources informed the opinion of the Committee, including available data from clinical studies, published literature, spontaneous reports and other data submitted by MAH's of medicinal products containing aprotinin, EACA or TXA. A CHMP scientific advisory group (SAG) meeting was held in October 2011 and its views were considered in the framework of this review.

Separate opinions and conclusions were issued by the CHMP for the three antifibrinolytics (aprotinin, EACA and TXA). This document presents a summary on the BART study and the discussion and conclusions on TXA. For details on aprotinin and EACA please refer to their respective reports.

¹ Fibrinolysis is degradation of intravascular fibrin clots by action of plasmin that results from plasminogen hydrolysis.

² The initial 2007 review was handled under Article 107(2) of Directive 2001/83/EC.

2.2. Clinical aspects

2.2.1. BART study

The BART study³ was a prospective, multicentre, randomised double blinded trial involving 'high-risk' cardiac surgery patients, i.e., defined as surgical intervention with an average mortality of at least twice the norm for isolated primary coronary artery bypass graft (CABG) and a risk of repeat surgery exceeding 5%. The study was designed to compare the therapeutic use of aprotinin with EACA and TXA. The study was administered by the Ottawa Health Research Institute (OHRI), with patients enrolled at several centres across Canada.

The patient population was not limited to the approved indication and consisted of high-risk cardiac surgical patients requiring one of the following high-risk surgical interventions, either on an elective or urgent basis; all surgery had to be done on cardiopulmonary bypass (CPB):

- Re-operation for CABG;
- Re-operation for aortic valve replacement;
- Re-operation for mitral valve replacement or repair;
- Initial mitral valve replacement;
- Aortic and/or mitral valve replacement/repair with a CABG;
- Multiple valve replacement/repair (initial or re-operation);
- Ascending aortic artery procedures (including Bentall procedures, etc).

The protocol-specified primary outcome was massive postoperative bleeding. Secondary outcomes included allogeneic exposure to any blood product, fatal/life-threatening event (e.g. 30-day all-cause mortality, myocardial infarction (MI) and cerebrovascular accidents) and serious adverse events (e.g. dialysis-dependent renal failure, need for prolonged invasive mechanical ventilatory support (greater than 48 hours) or prolonged low output state (need for vasopressors, balloon pump, or ventricular assist device for more than 48 hours)).

In terms of efficacy, the results of the BART study demonstrated reduced incidence in massive post-operative bleeding and reduced need for transfusion of blood products when aprotinin was used as compared to EACA and TXA. Aprotinin was also superior to both EACA and TXA with respect to avoiding re-operation for bleeding and significant perioperative bleeding from chest tubes in CABG surgery.

Regarding safety, the preliminary results of the BART study had shown that 30-day all-cause mortality in the aprotinin arm was increased in comparison to EACA or TXA. Results were not statistically significant but the trend of an increased mortality in the aprotinin arm was reported as consistent throughout the study.

A new analysis of originally recorded data was undertaken for 30-day all-cause mortality, including all randomised subjects for whom data was available. The relative risk (RR) calculated by the MAH of aprotinin containing medicinal products was 1.48 (95% CI 0.95-2.29, $p=0.08$) for aprotinin compared with EACA and 1.38 (95% CI 0.90-2.12, $p=0.14$) for aprotinin compared with TXA. Neither of these results was statistically significant. The numerical difference in mortality between treatment arms was mostly observed during the first 5 days. There were no clear differences for mortality between treatment arms after this period.

Other serious adverse events of interest included as secondary outcomes - stroke, MI and renal failure/dysfunction - did not show any significant differences between the three treatment groups. Although there was no increase in the risk for renal dysfunction or renal failure associated with the use of aprotinin compared to both EACA and TXA, there was an increase in the proportion of patients with a doubling of serum creatinine levels in the aprotinin group.

The new analysis of data available further to finalisation and publication of the final study results also showed that aprotinin prolongs certain measures of blood clotting time. Patients treated with aprotinin had higher recorded values for partial thromboplastin time (PTT) than patients treated with EACA and TXA. In addition, the new analysis also indicated that less heparin had been used in the aprotinin arm compared to EACA and TXA arms, in particular in sites with reported 30-day mortality (compared to sites with no reported mortality). This new evidence raised doubts if the observed trend for differences in mortality disfavours the aprotinin group could be explained by under-heparinisation and inadequate use of the appropriate method to maintain adequate anticoagulation. In addition, analysis

³ BART study: Blood conservation using antifibrinolytics: a randomised trial in a high-risk cardiac surgery population, Fergusson *et al* (2008), New England Journal of Medicine.

of cause of death for 5-day mortality seemed to also indicate an association between site and mortality, with only a few sites accounting for most of the numerical difference between treatments.

The BART study results did not indicate a clear difference between the risks or benefits of EACA compared to TXA.

During the review of the final results and new analysis of the BART study by the CHMP, concerns were raised regarding aspects of the trial methodology, including unplanned interim analysis, the unjustified exclusion of patients from the outcome analyses, the lack of important data on anticoagulant monitoring and an apparent change in the definition of components of the primary outcome. In addition, subgroup analysis indicated that in some centres with higher mortality rates for aprotinin compared with EACA or TXA, patients treated with aprotinin had lower heparinisation or excessive amounts of protamine had been used.

A scientific advisory group (SAG) meeting was held, mainly to discuss the final results and new analysis of the BART trial and provide views on the use of aprotinin in CABG. The impact of aprotinin in the reduction of massive bleeding was considered of clinical relevance by the SAG. Although the link between blood loss and mortality has not been proven, bleeding less would result in fewer complications, fewer transfusions and less time spent in hospital, which was considered clinically relevant.

Regarding heparinisation, the SAG considered that the use of non-appropriate activated clotting tests at some of the centres might have influenced the level of heparinisation of patients, i.e., under-heparinisation of patients randomised to aprotinin, resulting in differences in outcome of cardiovascular surgery in terms of mortality and morbidity at different centres. In addition, the increase in mortality could also be influenced by differences in baseline patient characteristics and centre variability. Overall the SAG considered that the BART study had major flaws, such as the unexplained exclusion of patients from the final study results, underlying differences in baseline characteristics between the study groups which were not homogenous in spite of randomisation, and the reduced level of heparinisation in the aprotinin arm which would increase the risk of thrombotic events in this group. Therefore the SAG experts agreed that the BART data and the signal of increased mortality in the aprotinin arm were not considered reliable.

The CHMP noted that since its initial review in 2007, more data has become available, in particular the final study results, and more importantly new analysis of the BART study. These new data have now made it possible to identify the major flaws of the BART study, which were not identifiable before.

2.2.2. Tranexamic acid

Tranexamic acid is a lysine analogue authorised since 1969. It was used in several indications, including bleeding or haemorrhage caused by local or general fibrinolysis in surgery, hepatology, urology, gynaecology and obstetrics, in ENT (ear, nose, and throat) and dentistry. Other indications included a use in hereditary angioneurotic oedema, in disseminated intravascular coagulation (DIC), in ophthalmology, in dermatology and in leukaemia. All indications were considered for this review.

Several MAHs submitted data for review. An overview of the evidence of therapeutic benefit of TXA from randomised clinical trials, observational studies and meta-analysis, including data that became available since the granting of the initial marketing authorisation was considered for the assessment. Only relevant information for the discussion is presented per indication hereinafter.

Efficacy

A. Cardiovascular surgery

BART study

The BART study (see also section 2.2.1 BART study) compared aprotinin to the lysine analogues TXA (and EACA). In direct comparisons, aprotinin was superior to TXA (and EACA) for all components of the primary outcome except for the outcome death due to haemorrhage (see also section 2.2.2 Aprotinin). Tranexamic acid had not previously been associated with an increased risk of mortality and this has remained unchanged post-publication of the BART study.

Other randomised trials and observational studies

Available evidence from other randomised clinical trials and meta-analysis of randomised trials reviewed suggest that TXA is effective in reducing post-operative bleeding and in reducing the need for blood transfusions associated with major surgery, cardiac surgery and after traumatic injury.

The CHMP noted that sufficient evidence is available from prospective trials to support the use of TXA in haemorrhage due to cardiovascular surgery.

B. Hepatology

Tranexamic acid is authorised in the treatment of haemorrhagic syndrome related to hepatic cirrhosis, gastro- duodenal ulceration or hepatic diseases in several member states. Evidence is available from randomised clinical trials which assessed the effect of TXA in patients with suspected or verified upper gastrointestinal bleeding, and the results from these individual trials were reviewed in subsequent meta-analyses. Evidence is also available from randomised placebo controlled and comparator trials on the safety and efficacy of TXA for the reduction of perioperative bleeding and the risk of blood transfusion during liver resection or transplantation.

The CHMP noted that sufficient evidence is available on the use of TXA in the reduction of bleeding for hepatic diseases, upper gastro-intestinal bleeding and bleeding linked to hepatic transplantation. The CHMP proposes the maintenance of the indication in gastro-intestinal bleeding and abdominal surgery.

C. Ear, nose and throat (ENT), including dentistry

Available evidence, including from randomised clinical trials, suggests that TXA is effective in the prevention and treatment of haemorrhages due to ENT surgery. Limited studies, also discuss the use in special populations, such as in haemophilia, and *Taparia M et al* (2002) described the occurrence of pulmonary embolism in a study of patients with congenital and acquired coagulation disorders. It was also noted that there was one non medically-confirmed case reporting blindness. The child had haemophilia and was taking tranexamic acid 500mg twice daily to treat epistaxis. The event recovered completely following discontinuation of the product. *Walton et al* (2002) reported that another lysine analogue has been known to precipitate acute renal failure in patients with even mild haemophilia.

The CHMP noted the available scientific data, including evidence from new studies, on the use of TXA in the treatment of haemorrhagic syndromes caused by ear, nose and throat surgery (adenoidectomy and tonsillectomy), and in dentistry too. Tranexamic acid can be useful to treat mucosal bleeding or prevent bleeding for procedures such as dental extraction, avoiding the need for blood products.

The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. In haemophilia, pulmonary embolism and temporary blindness have been reported. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting. Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported.

In view of the identified serious limitations of the efficacy data for treatment of haemophilia including the new data and the adverse reactions profile (some of which serious) associated with the use of TXA, the CHMP considers that the benefit risk balance of TXA in this indication is not positive under normal conditions when specific reference is made to haemophilia. A modification of the wording of the indication to read Ear, nose, throat surgery (adenoidectomy, tonsillectomy, dental extractions) was proposed by the CHMP.

D. Urology

Tranexamic acid is authorised in haemorrhages resulting from different clinical settings in urology in the EU, and administration of TXA has been known to reduce blood loss in this setting (*Dunn*, 1999 and

Rannikko, 2004). In clinical trials, TXA was shown to reduce the incidence of secondary bleeding (24% for TXA and 56% for no antifibrinolytic group) and the number of readmissions for haemorrhagic complications. The treatment is not known to reduce the need for blood transfusions and therefore was not given routinely (*Dunn, Mahdy*). Furthermore, in a large randomised trial (*Rannikko*), short term TXA treatment significantly reduced the operative blood loss associated with transurethral resection of prostate. However, TXA did not influence the number of patients requiring a blood transfusion. It was noted that in case of haematuria from the upper urinary tract, there is a risk for urethral obstruction.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of TXA in urology. Different wordings covering the same settings were available in different member states and the CHMP considers that a clear harmonised wording is more helpful to physicians and patients. In order to achieve this, the CHMP proposes a modification of the indication to be inclusive of the different conditions which can be encountered and read that TXA can be used in all 'haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract'. In addition, a warning should be added regarding haematuria from the upper urinary tract in the appropriate section of the product information, as this is a known risk of TXA administration in particular in this clinical setting.

E. Gynaecology and obstetric

Tranexamic acid has been shown to be effective in treatment of menorrhagia and metrorrhagia (*Lethaby*, 2008) and is authorised for these indications across the EU. Some of the data available refer to oral use. It may be considered among first-line treatments for the initial management of idiopathic menorrhagia, especially for patients in whom hormonal treatment is either not recommended or not wanted (*Kadir*, 2006; *Wellington*, 2003; *Fraser*, 2008). Its use in this setting is also recommended by the National Institute for Health and Clinical Excellence (NICE) guidelines.

The CHMP noted the available scientific data, including evidence from new studies and the consensus within the medical community on the use of TXA in menorrhagia and metrorrhagia. The use of TXA is widely recommended and the CHMP considered there is sufficient evidence of the use of TXA in these indications.

Tranexamic acid is authorised in haemorrhages resulting from different clinical settings in gynaecology in the EU. Randomised controlled studies on the use of TXA for the prevention and treatment of postpartum haemorrhage are available (*Gai* (2002), *Gohel* (2007), *Yang* (2001)). Data from meta-analysis of randomised trials and observational studies (*Ferrer*, 2009 and *Lindonff*, 1993) also show that TXA decreased postpartum blood loss after delivery and caesarean section. However, the number of women treated was low and the trials were non-blinded. The results of a literature search for clinical trials of TXA and abruption-placenta do not find any randomised, controlled trials of TXA for the treatment of haemorrhagic bleeding associated with placental abruption. However, some data are available from limited case studies. Regarding conisation of the cervix, a review of available literature did not reveal any double-blind, placebo-controlled trials of TXA for the treatment of haemorrhage following conisation of the cervix. However, a prospective, randomised trial of 360 women compared peri- and postoperative treatment with TXA with no treatment for the prevention of postoperative haemorrhage after laser conisation or laser miniconisation of the cervix (*Grundsell*, 1984) with incidence of post-operative haemorrhage significantly reduced in those treated with TXA compared to no treatment.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of TXA in gynaecology. Different wordings covering the same settings were available in different member states and the CHMP considers that a clear harmonised wording is more helpful to physicians and patients. In order to achieve this, the CHMP proposes a modification of the indication to be inclusive of the different conditions which can be encountered and read that TXA can be used in all 'gynaecological surgery or disorders of obstetric origin'.

F. Hereditary angioneurotic oedema

Hereditary angioedema (HAE) is a disorder caused by mutations of the C1 esterase-inhibitor gene in which there are intermittent and unpredictable acute attacks of oedema. These may involve the larynx, oropharynx, face, gastrointestinal mucosa, extremities, or genitalia: gastrointestinal attacks can cause incapacitating colic, vomiting, and diarrhoea and can result in unnecessary abdominal surgery, and laryngeal attacks may be life-threatening. Available evidence on the efficacy of TXA refers to short-term use and results are primarily restricted to small, retrospective or observational studies, and case

reports. However, the assessment criteria has developed and currently effective use of TXA would be in long-term prophylaxis in order to prevent attacks of HAE. Long-term effectiveness or risk of TXA has not been established (*Agostini, 1978*). Sixteen patients needing continuous prophylaxis because of frequency and severity of attacks were treated with tranexamic acid. In four patients this treatment was ineffective and the drug was withdrawn after 2 months. A remission or reduction in the frequency or severity of attacks was observed in 12 patients treated for a period ranging from 8 to 34 months. The results of 2 double-blind, placebo-controlled, cross-over trials of oral or intravenous TXA for the treatment of hereditary angioneurotic oedema were reported in the 1970s (*Blohmé; Sheffer*). These were very small studies, with a duration between 1 and 13 months depending of the patients. Seven patients had “complete or almost complete” cessation of attacks on treatment as compared to placebo, four patients had attenuation and TXA was ineffective in one patient. Six patients did not enter in the cross-over period. *Munch and Weeke, 1985*, provide a controlled, double-blind cross-over study in ten patients with frequent attacks of non-hereditary angioedema, which is not the claimed indication. In four patients itching was a major accompanying complaint which was relieved in three. Concerns on diarrhoea and abdominal discomfort were more pronounced during tranexamic acid treatment and necessitated dose reduction in one patient. Treatment with TXA has mostly been used anecdotally, but efficacy in this scenario is uncertain.

The CHMP noted the available scientific data, including evidence from new small short term studies, on the efficacy of TXA in HAE. However, the CHMP considered that hereditary angioneurotic oedema is a chronic condition necessitating long term prophylaxis, which has not been proven for TXA. The new understanding of efficacy raises reasonable doubt on the efficacy of the product.

The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting. Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported.

In view of the identified serious limitations of the efficacy data for treatment of HAE including the absence of data on the effective long-term treatment of HAE, and the adverse reactions profile (some of which serious) associated with the use of TXA, the CHMP considers that the benefit risk balance of TXA in this indication is not positive under normal conditions of use. The CHMP recommends its deletion from the product information.

G. Leukaemia

Evidence from two randomised, placebo controlled trials and one retrospective analysis on the use of TXA in the prevention and treatment of haemorrhages in association with leukaemia is available. *Shpilberg (1994)* included patients with myeloid leukaemia but during the induction chemotherapy phase no difference could be made between TXA and placebo on bleeding events, severity of bleeding and the number of transfusions received. These events were statistically different during the consolidation phase but the demonstration was made only on 10 and 8 patients per arm. In the *Avvisati (1989)* study, a small number of patients was included and the study reported that patients receiving TXA had less haemorrhagic episodes, and needed less packed red cell transfusion and platelet concentrate transfusions. A retrospective study by *Rodeghiero (1990)* addressed the use of TXA in the prevention of bleeding in patients with promyelocytic leukaemia. The authors concluded that the study was not able to demonstrate any beneficial effects of antifibrinolytics in reducing the incidence of early deaths or increased survival. In addition the authors noted that the value of the results reported by *Avvisati et al* from the small study limiting the administration of TXA to the first 6 days of chemotherapy should be evaluated in a large prospective study. *Hashimoto et al (1994)* reported a fatal thromboembolism in a patient with acute promyelocytic leukaemia after receiving all-trans retinoic acid and tranexamic acid. *Pereira et al (2004)*, addressed the management of bleeding in patients with advanced cancer. The authors noted that a systematic review (*Erstad BL et al, 2001*) of randomised trials found that haemostatic medications, such as TXA used for reducing surgery-related bleeding have limited or contradictory evidence of efficacy. Large controlled studies of these drugs are lacking in the cancer setting.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of TXA in leukaemia. This included evidence from randomised controlled trials and retrospective studies which show that TXA has limited or contradictory evidence of efficacy, and no beneficial effect was observed in reducing the incidence of early deaths or increased survival. The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting. Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported. In view of the identified serious limitations of the efficacy data for treatment of leukaemia including the new data and the adverse reactions profile (some of which serious) associated with the use of TXA, the CHMP considers that the benefit risk balance of TXA in this indication is not positive under normal conditions of use. The CHMP recommends its deletion from the product information.

H. Haemorrhagic complications of fibrinolytic therapy

Tranexamic acid is authorised in the treatment of haemorrhage linked to a fibrinolytic agent, for example streptokinase or urokinase, in several member states. Although no randomised clinical trials are available to support this indication, several pharmacological and clinical studies have already demonstrated the efficacy of TXA in stopping haemorrhages which concurs during thrombolytic treatment. It is also noted that the use of TXA is listed in the streptokinase's product information, among others.

The CHMP noted that TXA is considered an antidote for use in haemorrhages induced by thrombolytics, such as streptokinase. Therefore the use in haemorrhage due to the administration of a fibrinolytic agent should be maintained in the product information.

I. Disseminated intravascular coagulopathy

Clinical data is available in the literature (e.g. *Ontachi Y et al*, 2005 and *Koseki et al*, 2007) and mostly describes individual cases when TXA has been used in disseminated intravascular coagulopathy (DIC). However, efficacy data are contradictory and inhibition of fibrinolysis should not be given routinely to patients with on-going DIC because it is required to clear microthrombi, a consequence of the condition. In addition, recently available European and United States guidelines for DIC management (the British Committee for Standards in Haematology guidance (*Levi*, 2009)) indicate that in general patients with DIC should not be treated with antifibrinolytic agents. This evidence reflects the development within the expert medical community of the use of TXA in this indication. The Indian Paediatrics guidance (*Marwaha*) also states that the hazard of antifibrinolytics therapy is that continuously forming microthrombi will not be lysed. It is therefore noted that it is potentially dangerous to use TXA in case of DIC where it can give rise to serious thrombosis or serious systemic thrombotic complications, e.g., DIC itself.

The CHMP noted the available scientific data, including evidence from new studies and existing guidelines, on the efficacy of TXA for haemorrhage associated with DIC. No other robust evidence is available on the efficacy and safety of TXA in DIC and no prospective studies, pooled analysis or meta-analysis were identified.

The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting.

Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported.

In view of the identified serious limitations of the efficacy data for treatment of DIC including the consensus within the medical community that it should not be used in DIC patients, and the adverse reactions profile (some of which serious) associated with the use of TXA, in particular thromboembolic events and disseminated intravascular coagulation itself, the CHMP considers that the benefit risk balance of TXA in this indication is not positive under normal conditions of use. The CHMP recommends its deletion from the product information. Other sections of the product information, such as contraindications, warnings, adverse events should also be updated to appropriately inform physicians and patients of the identified risks.

J. Allergic dermatoses

In the double blind controlled study by *Laurberg* (1977), the author reported the ineffectiveness of TXA in treatment of chronic urticaria, as no difference was observed between patients treated with TXA and placebo. In addition, a position paper by *T. Zuberbier* (2009) states that some treatment alternatives, such as TXA, have been shown to be ineffective and should no longer be used.

The CHMP noted the available scientific data, including evidence from new studies and an existing position paper, on the efficacy of TXA in allergic dermatoses. No other robust evidence is available on the efficacy of TXA in allergic dermatoses and no prospective studies, pooled analysis or meta-analysis were identified.

The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting. Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported.

In view of the identified serious limitations of the efficacy data for treatment of allergic dermatoses including the new data and the development of the opinion within the medical community that TXA should no longer be used in this indication, and the adverse reactions profile (some of which serious) associated with the use of TXA, the CHMP considers that the benefit risk balance of TXA in this indication is not positive under normal conditions of use. The CHMP recommends its deletion from the product information.

K. Ophthalmology

Evidence on the use of TXA in hyphema is available in studies such as *Rahamani and Jahadi* (1999), *Uusitalo et al* (1981), but the number of patients enrolled is very limited. A retrospective study (*Kearns*, 1991) in patients with traumatic hyphema concluded that the use of antifibrinolytic agents does not appear to be necessary in such a population. A review by *Gharaibeh et al* (2011) concluded that although evidence is limited, it appears that patients with traumatic hyphema who receive TXA are less likely to experience secondary haemorrhaging. The authors also note that usually a combination of interventions/medicinal products are used in this setting and further research to assess the additive effect of these interventions might be of value. In a study by *Albiani et al* (2008) patients were treated with TXA plus topical steroids or topical steroids alone and the results showed that there was no significant difference in rebleed rate between the two groups. *Sheppard et al* also noted that TXA has been associated with nausea, vomiting, hypotension and visual abnormalities, which are of particular concern for these patients. A study by *Walton et al* (2002) reported a branch retinal artery occlusion 5 days after starting TXA. Central retinal vein occlusion has also been associated with tranexamic acid use. Tranexamic acid also delays the clearance of hyphemas. In most published studies, use of these medications has not conferred a definite visual benefit in association with the reduced frequency of secondary haemorrhage. This fact, combined with known potential risk, among others, has led experts to avoid the use of these medications.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of TXA in hyphema. This included evidence from randomised controlled trials and retrospective studies which show that TXA has limited and contradictory evidence of efficacy, and no definite visual benefit was observed. The new efficacy data raises reasonable doubt on the efficacy of the product in hyphema.

The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting. Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported.

In view of the identified serious limitations of the efficacy data for treatment of hyphema including the new data, and the adverse reactions profile (some of which serious) associated with the use of TXA, in particular the visual disturbances reported, the CHMP considers that the benefit risk balance of TXA in this indication is not positive under normal conditions of use. The CHMP recommends its deletion from the product information.

Posology

Several differences in the presentation of the posology section (e.g. different administration schemes) were identified across member states. To better inform prescribers, the CHMP proposed a posology divided in standard treatment of local fibrinolysis and general fibrinolysis for adults, rather than a list of posology per individual indication, which covers all the recommended posology and is also in line with available evidence from all studies performed with TXA. Therefore the most appropriate scheme posology reflected in the product information is as follows for adult patients:

1. Standard treatment of local fibrinolysis:

0.5 g (1 ampule of 5 ml) to 1 g (1 ampule of 10 ml or 2 ampules of 5 ml) TXA by slow intravenous injection (= 1 ml/minute) two to three times daily;

2. Standard treatment of general fibrinolysis:

1 g (1 ampule of 10 ml or 2 ampules of 5 ml) TXA by slow intravenous injection (= 1 ml/minute) every 6 to 8 hours, equivalent to 15 mg/kg body weight.

The full product information contains additional information on posology, including recommended posology in special populations, such as renal and hepatic impairment, and in paediatric populations, as available.

Efficacy in paediatrics

A review of the paediatric utilisation of TXA was finalised in Europe in 2009 in the framework of article 45 of Regulation 1901/2006. Based on the overall data, modifications to the product information were proposed to reflect available paediatric data, which excludes neonates and infants aged less than 12 months. These modifications were considered in the framework of the review and the product information reflects available paediatric data.

Safety

Data from spontaneously reported cases and published literature was analysed. It was noted that thromboembolic events, including interaction with oestrogens have been reported. Tranexamic acid should be administered with care in patients receiving oral contraceptives because of this increased risk of thrombosis. In addition, TXA should be contraindicated in acute venous or arterial thrombosis. In patients with a history of thromboembolic diseases or in those with increased incidence of thromboembolic events in their family history (patients with a high risk of thrombophilia), TXA should only be administered if there is a strong medical indication after consulting a physician experienced in haemostaseology and under strict medical supervision. Accordingly, patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with TXA. Therefore, TXA should

be contraindicated in fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Disturbances of colour vision have been reported, in particular with long term TXA treatment. Special care should be taken with pathological ophthalmic changes, particularly with diseases of the retina. It was noted that in case of haematuria from the upper urinary tract, there is a risk for urethral obstruction.

Tranexamic acid had not previously been associated with an increased risk of mortality and this has remained unchanged post-publication of the BART study. Safety data have accumulated over the years and the most common side effects of TXA use are gastrointestinal, such as nausea, diarrhoea and vomiting. Dermatitis allergic, convulsions, visual disturbances, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported.

The CHMP noted that the product information did not contain all relevant safety information available from spontaneous reports and published literature. The CHMP requested that thromboembolic events, including interaction with oestrogens be listed in the product information. Acute venous or arterial thrombosis constitutes a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. In this regard, the warning section should be updated on disseminated intravascular coagulation. A warning on visual disturbances and the need to monitor patients on long term use of TXA was proposed. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision should also be added. The frequencies of the additional adverse effects (thromboembolic, visual) are unknown and cannot at present be established. This was reflected in the product information.

Adequate monitoring of adverse drug reactions reported, including through periodic safety update reports should continue.

Data from spontaneously reported cases were discussed. Rare cases of hepatic veno-occlusive disease have been reported. As for other adverse events, reports of hepatic veno-occlusive disease and visual impairment should be closely monitored by the MAHs through periodic safety update reports. No additional information was considered of relevance and no new concerns were raised.

Discussion on tranexamic acid

Tranexamic acid is a lysine analogue authorised for several indication since 1969. Data from randomised clinical trials and observational studies, including meta-analysis were provided, when available. The CHMP was satisfied that evidence is available on the efficacy of TXA in patients from one year of age in haemorrhage caused by local or general fibrinolysis. This includes specifically use in haemorrhage caused by general or local fibrinolysis such as menorrhagia and metrorrhagia; gastrointestinal bleeding; haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract; use in Ear, nose, throat surgery (adenoidectomy, tonsillectomy, dental extractions); use in gynaecological surgery or disorders of obstetric origin; thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery; and use in management of haemorrhage due to the administration of a fibrinolytic agent.

The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting. Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported.

Tranexamic acid has not previously been associated with an increased risk of mortality and this has remained unchanged post-publication of the BART study.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of TXA in other indications. Modifications to some of the indications were proposed, in order to bring them in line with current scientific knowledge on the use of TXA. In view of the identified serious limitations of the efficacy data, the available new evidence and/or current medical knowledge on the use of TXA, and considering the adverse reactions profile (some of which serious) associated with the use of TXA, the CHMP considers that the benefit risk balance of TXA in patients with congenital bleeding disorders (such as haemophilia), hereditary angioneurotic oedema, leukaemia, disseminated intravascular coagulopathy, allergic dermatoses and hyphema is not positive under normal conditions of use.

The CHMP considered that the clinical parts of the product information warranted revision to ensure that the information to healthcare professionals and patients is up-to-date. In particular, focus should be given to the revised indications, an update on the posology, an update on contraindications, a warning on DIC, visual impairment, thromboembolism, haematuria, convulsions and amendments to the list of undesirable effects to include thromboembolism and visual disturbances including impaired colour vision.

2.3. Risk management plan

The CHMP did not require the MAHs for medicinal products containing TXA to submit a risk management plan.

2.4. Overall benefit/risk assessment

Antifibrinolytics (e.g. aprotinin, aminocaproic acid and tranexamic acid), are a class of haemostatic agents used to prevent excessive blood loss. Aprotinin, a naturally occurring polypeptide, is an inhibitor of proteolytic enzymes. It has a broad action on proteolytic enzymes such as plasmin, trypsin, and kallikrein. The lysine analogues epsilon aminocaproic acid (EACA, also referred as aminocaproic acid) and tranexamic acid (TXA) inhibit more specifically the conversion of plasminogen to plasmin.

In March 2010 Germany triggered an article 31 referral to assess the benefits and risks of the antifibrinolytic drugs aprotinin, EACA and TXA in all their approved indications. The marketing authorisations for aprotinin were suspended when concerns over its safety were raised in a previous review in 2007. The preliminary results of a randomised controlled clinical trial, the 'Blood conservation using antifibrinolytics: a randomised trial in a cardiac surgery population' (BART) study, had shown that although the use of aprotinin was associated with less serious bleeding than either of the comparator drugs, an increase in 30 day all-cause mortality had been observed among patients receiving aprotinin compared to patients taking other medicines. These concerns echoed those of a few published observational studies. The marketing authorisations of EACA and TXA were not affected by the initial 2007 review.

Several data sources informed the opinion of the Committee, including available data from clinical studies, published literature, spontaneous reports and other data submitted by marketing authorisation holders (MAHs) of medicinal products containing aprotinin, EACA or TXA. A CHMP scientific advisory group (SAG) meeting was held in October 2011 and its views were considered by the CHMP in the framework of this review.

Separate opinions and conclusions were issued by the CHMP for the three antifibrinolytics (aprotinin, EACA and TXA). This document presents the conclusions on TXA.

Tranexamic acid

The safety profile of TXA has evolved since its authorisation, and safety data has accumulated over the years. Thromboembolic events, including interaction with oestrogens have been reported. Acute venous or arterial thrombosis should constitute a contraindication. The same is applicable for fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding. Haematuria and the risk for urethral obstruction should also be included as warnings. In addition, information on convulsions and visual disturbances including impaired colour vision are adverse events which can be serious and have been reported, but these risks had not been considered in the current authorised product information. Tranexamic acid has also been associated with gastrointestinal adverse events, such as nausea, diarrhoea and vomiting.

Dermatitis allergic, vascular disorders, such as malaise with hypotension, with or without loss of consciousness and arterial or venous thrombosis, and hypersensitivity reactions including anaphylaxis have been reported. The results of the BART trial did not have a negative impact on the benefit risk profile of TXA. Tranexamic acid had not previously been associated with an increased risk of mortality and this has remained unchanged post-publication of the BART study. The CHMP identified that information on disseminated intravascular coagulation, visual disturbances including impaired colour vision, thromboembolism, haematuria and convulsions should be appropriately reflected through warnings and recommendations in the product information.

Tranexamic acid is a lysine analogue authorised for several indication since 1969. Data available from randomised clinical trials and observational studies, including meta-analysis were considered. In addition to cardiac surgery, the CHMP considered that sufficient evidence is available on the safety and efficacy of TXA in other indications, including in patients undergoing dental or surgical procedures or at risk of complications from bleeding. For some conditions modifications to the wording were proposed, in order to bring them in line with current scientific knowledge on the use of TXA. In view of the identified serious limitations of the efficacy data, the available new evidence and/or current medical knowledge on the use of TXA, and considering the adverse reactions profile (some of which serious) associated with the use of TXA, the CHMP considered that some of these indications should be removed. A list of indications for which the CHMP considered that the benefit risk balance remains positive is presented below.

The product information was modified to ensure that the information to healthcare professionals and patients is up to date. In particular the therapeutic indications were updated to reflect current scientific knowledge on the use of TXA; other changes to the product information were inclusion information on disseminated intravascular coagulation, visual disturbances including impaired colour vision, thromboembolism, haematuria and convulsions as warnings and recommendations. The latest quality review of documents templates were taken into account during this review.

Taking into account all the available information on safety and efficacy, the Committee agreed on the variation of the marketing authorisation with the balance of the risks and benefits considered positive in the following revised indications for TXA:

Prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year.

Specific indications include:

- *Haemorrhage caused by general or local fibrinolysis such as:*
- *Menorrhagia and metrorrhagia,*
- *Gastrointestinal bleeding,*
- *Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract,*
- *Ear Nose Throat surgery (adenoidectomy, tonsillectomy, dental extractions),*
- *Gynaecological surgery or disorders of obstetric origin,*
- *Thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery,*
- *Management of haemorrhage due to the administration of a fibrinolytic agent.*

2.5. Changes to the product information

The CHMP considered all available evidence and recommended a harmonisation of the product information for all products affected by this review. Tranexamic acid is a product authorised for many years in Europe through national procedures. All indications were under the scope of this procedure. Considering that the most updated clinical and safety information should be available to all patients in Europe following this review, the product information was updated.

Tranexamic acid

The main changes to the SPC were sections 4.1 (modification of some indications and deletion of others to reflect available evidence); 4.2 (clarification on doses and limits from available literature evidence); 4.3 (update contraindication on acute venous or arterial thrombosis and fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding); 4.4 (update on warnings on DIC, visual impairment, thromboembolism, haematuria and convulsions); and 4.8 (inclusion of missing adverse events thromboembolic events and visual disturbances). Other clinical sections were revised for consistency

with the wording included and to bring the sections in line with the latest quality review of documents templates. The PL was updated accordingly with the changes proposed to the SPC.

The CHMP considered that the indication for TXA should read:

‘Prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year.

Specific indications include:

- Haemorrhage caused by general or local fibrinolysis such as:
- Menorrhagia and metrorrhagia,
- Gastrointestinal bleeding,
- Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract,
- Ear Nose Throat surgery (adenoidectomy, tonsillectomy, dental extractions),
- Gynaecological surgery or disorders of obstetric origin,
- Thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery,
- Management of haemorrhage due to the administration of a fibrinolytic agent.’

For other detailed changes, please refer to the final approved SPC/PL attached to the Opinion.

2.6. Re-examination procedure

Following the CHMP conclusion and recommendations for antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid, one MAH submitted detailed grounds for the re-examination of the CHMP opinion. The re-examination was on tranexamic acid.

Detailed grounds for re-examination submitted by the MAH

One MAH expressed its disagreement with the CHMP opinion, focusing its grounds for re-examination on the following points:

- the MAH was not convinced that the fulfilment of a condition such as performing a pharmacokinetic study in children is an essential condition for the safe and effective use of tranexamic acid IV in adults. This PK study had been requested by the CHMP in the article 31 referral on antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid.
- The MAH informed that for children, some recent pharmacokinetic studies conducted with tranexamic acid in the paediatric population should provide relevant information. These studies results should be assessed when available.

CHMP conclusion on grounds for re-examination

The posology for TXA in paediatric patients was based on the outcome of a previous evaluation. It was mainly based on the dosing schedule tested by *Chauhan*, although it was noted that in most of the studies for TXA, the age range of paediatric patients was large and not stratified by age. It was fully recognised that there was a need for better defining PK in different age groups to better quantify the optimum treatment schedule for children.

The CHMP accepted that in the absence of new data, the conclusions of the previous reviews should be maintained, but noted that the current recommendations were based on limited data following literature review and on the posology already authorised in some member states. The CHMP noted that a PK study in paediatric population could be very helpful to better characterise the TXA profile in children. The CHMP requested that MAHs of TXA should perform a pharmacokinetic study to further investigate an appropriate paediatric regimen in children, given the lack of pharmacokinetic data in this patient population. A draft protocol was to be submitted to national competent authorities for assessment and approval.

During the re-examination the CHMP was informed that there are available/ongoing PK studies in children that could provide valuable information. The MAH proposed to wait for the final study results of these trials before considering the need of additional studies.

The CHMP considered that so far, well conducted dose-finding studies do not exist for any of the paediatric indications. The current posology recommendations for the already approved indications, although based on limited study data are supported by the extensive experience in a number of EU countries. Nevertheless, there are studies ongoing for which the results should be assessed by member states, when available, before a decision on the need for additional studies can be made.

Therefore, although additional studies to better define the optimal posology recommendation in children would be welcomed, in view of the ongoing studies, the CHMP considered that a PK study should not be requested as a condition at this point in time.

The MAHs are reminded that any new information on the use of TXA in children is considered valuable. The ongoing studies could provide some relevant PK data in different age stratum and some pharmacodynamic data, which is considered of interest. The MAHs should present this information to national competent authorities when final results for the studies become available.

3. Overall conclusion on tranexamic acid

Having considered the overall data provided by the MAHs in writing and data available from literature reviews, the CHMP concluded that

For tranexamic acid

The Committee considered that evidence from randomised clinical trials and observational studies support the use of tranexamic acid in patients undergoing dental or surgical procedures or at risk of complications from bleeding.

The Committee considered the available scientific data, including evidence from new studies, on the efficacy of TXA. The CHMP considered also the adverse reactions profile, including new adverse events (some of which serious) associated with the use of TXA.

In view of the identified serious limitations of the efficacy data, the available new evidence and/or current medical knowledge on the use of TXA, and considering the adverse reactions profile (some of which serious) associated with the use of TXA, the CHMP considered that for some of the therapeutic indications the benefits no longer outweigh the risks and therefore they should be removed.

The Committee considered that the product information should be updated. In particular, the therapeutic indications were updated to reflect current scientific knowledge on the use of TXA; other changes to the product information were inclusion information on disseminated intravascular coagulation, visual disturbances including impaired colour vision, thromboembolism, haematuria and convulsions as warnings and recommendations.

Therefore the CHMP concluded that the balance of risks and benefits for tranexamic acid is positive under normal conditions of use subject to the revision of the indications as follows:

prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year.

Specific indications include:

- Haemorrhage caused by general or local fibrinolysis such as:*
- Menorrhagia and metrorrhagia,*
- Gastrointestinal bleeding,*
- Haemorrhagic urinary disorders, further to prostate surgery or surgical procedures affecting the urinary tract,*
- Ear Nose Throat surgery (adenoidectomy, tonsillectomy, dental extractions),*
- Gynaecological surgery or disorders of obstetric origin,*
- Thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery,*
- Management of haemorrhage due to the administration of a fibrinolytic agent.*

On the basis of the above, the Committee recommended the variation to the terms of the marketing authorisation for the medicinal products containing tranexamic acid referred to in Annex I for which the amendments to the product information are set out in annex III of the opinion.

Having considered the detailed grounds for re-examination submitted by the MAH in writing, the CHMP considered that no additional conditions were necessary to ensure the safe and effective use of tranexamic acid.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.