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Assessment report

Antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid

Aminocaproic 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products containing aprotinin, aminocaproic acid and tranexamic acid should be maintained, varied, suspended or withdrawn.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

Antifibrinolytics[1] (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, become 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 data[2] 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 aminocaproic acid. For details on aprotinin and TXA 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 study[3] 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 Bental 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 disfavouring 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 thrombogenic 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. Aminocaproic acid

Aminocaproic acid has been authorised since 1963 as an injectable solution that can be used intravenously or orally. It is a lysine analogue which was used in several indications, including treatment of bleeding associated with hyperfibrinolysis; treatment and prophylaxis of postoperative bleeding; severe bleeding induced by a thrombolytic in anticoagulant and anti-haemorrhagic combined treatment, together with heparin; bleeding associated with haematopoietic disorders, among others. All indications were considered for this review.

Only one MAH submitted data for review. An overview of the evidence of therapeutic benefit of EACA from randomised clinical trials, observational studies and meta-analysis, including data that become 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. Haemorrhages associated to hyperfibrinolysis, such as those secondary to cirrhosis of the liver or early detachment of the placenta.

The study by *Gunawan and Runyon* (2006) analysed records of all patients admitted to the Ranchos Los Amigos Medical centre during 2001 and 2002 with abnormal ELT. Of 37 patients who received EACA due to bleeding, two showed no improvement and one died of liver failure within 24 hours of treatment. Of 16 patients without bleeding who received EACA, three showed no improvement. Two patients discontinued due to side-effects. *Northup* and *Caldwell* (2007) noted that once cirrhosis is established, specific therapeutic and prophylactic interventions need careful investigation. Therapeutic

agents such as aminocaproic acid, among others, 'have been used in specific circumstances. However, controlled clinical trials using these agents have been either non-existent or disappointing in efficacy'.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of EACA in haemorrhages associated with hyperfibrinolysis. The new efficacy data raises reasonable doubt on the efficacy of the product. In a study published in 2006, five patients showed no improvement and one died. A review available in 2007 indicated that results from trials have been either non-existing or 'disappointing in efficacy'.
The safety profile of EACA has evolved since its authorisation, and safety data has accumulated over the years. Leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Aminocaproic acid has also been associated with hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders; blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment and thrombotic complications.
In view of the identified serious limitations of the efficacy data for treatment of haemorrhages associated with hyperfibrinolysis including the new data on lack of efficacy and the adverse reactions profile (some of which serious) associated with the use of EACA, the CHMP considers that the benefit risk balance of EACA in this indication is not positive under normal conditions of use. The CHMP recommends its deletion from the product information.

B. Postsurgical haemorrhages in urology (surgery of the bladder and prostate), gynaecology (cervical surgery), obstetrics (post-partum and post-miscarriage haemorrhages), heart surgery (with or without bypass placement), gastroenterology, odonto-stomatology (dental extractions in haemophiliacs, thrombopathies, patients undergoing anticoagulant therapy and diabetics), ear, nose and throat (tonsil surgery and other rhinopharyngeal haemorrhages) and, in general, as treatment and prophylaxis of postsurgical haemorrhages in which an increase in local or general fibrinolysis is suspected.

B.1. Postsurgical haemorrhages in urology (surgery of the bladder and prostate)

Aminocaproic acid is used in urinary fibrinolysis associated with surgical bleeding in urology, particularly following prostatectomy and nephrectomy, and prospective studies were available to support the use in urology. *Miller* (1980) studied 100 patients undergoing transurethral prostactectomy or endoscopic bladder tumour resection allocated randomly to TXA or no-treatment control; the incidence of secondary haemorrhage after prostatectomy was reduced from 56% in the no-treatment control group to 24% in the treatment group. *Stefanini et al* (1990) administered 150 mg/kg/day of EACA for up to 21 days to 9 patients with macroscopic haematuria (for various reasons, one of which related to haematuria following prostate resection) which was controlled effectively without overt clinical reactions. In three patients where hepatic and renal function was monitored, no significant abnormalities were found.

The CHMP noted that sufficient evidence is available from prospective trials to support the use of EACA in urology surgery.

B.2. Postsurgical haemorrhages in gynaecology (cervical surgery) and obstetrics (post post-partum and post-miscarriage haemorrhages)

Aminocaproic acid has been used to control profuse bleeding in patients with cervical carcinoma or other gynaecological malignancies, and lysine analogues have been used in missed abortion, secondary postpartum haemorrhage and threatened placental abruption. A review by *Verstraete* (1985) states the use of antifibrinolytics is logical in such patients, and broadly discusses the use of aprotinin and TXA as inhibitors of fibrinolysis, but which contains little direct data in support of use in postsurgical haemorrhage in gynaecology or obstetrics. *Bonnar et al* (1980) reviewed studies where EACA reduced menstrual bleeding and reduced fibrinolytic activity in women who had intra-uterine devices (IUDs) removed. It also discussed the use of EACA in the treatment of menstrual bleeding, bleeding in missed abortion and secondary postpartum haemorrhage, during pregnancy and in cervical and uterine carcinoma. *Grundsell et al* (1984) found a significant difference in the incidence of postpartum haemorrhage between patients undergoing conisation treated intraoperatively and postoperatively with either TXA or placebo. In the study by *Wellington K et al* (2003) it is stated that tranexamic acid may be considered as a first-line treatment for the initial management of idiopathic menorrhagia. A

consensus paper by *James et al* (2009) highlights that Von Willebrand disease is associated with abnormal reproductive tract bleeding, and that haemostatic treatment with TXA has equivalent or superior haemostatic efficacy and is generally better tolerated as compared to EACA.

The CHMP noted the evidence available on the use of EACA in gynaecology (cervical surgery), where most data available relate to the use of tranexamic acid. In addition, several new publications seem to indicate that in clinical practice, TXA may be a preferred first option in this indication. Having considered all available evidence the CHMP considers that the wording of the indication should be clarified to specify that EACA should be used in gynaecology in patients where TXA is not available or not tolerated.
Aminocaproic acid could also be used in obstetrics (post-partum and post-miscarriage haemorrhages). In this indication profuse bleeding from the uterus may continue despite the removal of retained products of conception and repair of soft tissue laceration (coagulation defect). The CHMP considered that the wording of the indication should thus be clarified to specify that EACA should be used after correction of the coagulation defect.

B.3. Postsurgical haemorrhages in heart surgery (with or without placement of bypass)

BART study
The BART study (see also section 2.2.1 BART study) compared aprotinin to the lysine analogues EACA (and TXA). In direct comparisons, aprotinin was superior to EACA (and TXA) for all components of the primary outcome except for the outcome death due to haemorrhage (see also section 2.2.2 Aprotinin). Aminocaproic 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 EACA is effective in reducing post-operative bleeding and in reducing the need for blood transfusions associated with cardiac surgery.

The CHMP noted that sufficient evidence is available from prospective trials to support the use of EACA in heart surgery.

B.4. Postsurgical haemorrhages in gastroenterology

The use of antifibrinolytic drugs in patients with gastrointestinal lesions that can cause bleeding is considered due to the high local concentration of fibrinolytic enzymes in the digestive tract. A meta-analysis of six randomised double-blind placebo controlled studies performed by *Henry and O'Connell* in patients peptic ulcers, mucosal erosions or other causes of bleeding treated with TXA (versus placebo), showed that treatment reduced recurrent bleeding by 20-30%, need for surgery by 30-40% and mortality by 40%. In addition, a study by *Cox et al* (1969) suggested that there was increased fibrinolytic activity after manual manipulation of the gut, which was inhibited by EACA.

The CHMP noted that although the level of evidence from prospective trials is limited, and some relate to other lysine analogues, such as TXA, EACA could be used in gastroenterology.

B.5. Postsurgical haemorrhages in odonto-stomatology (dental extractions in haemophiliacs, thrombopathies, patients undergoing anticoagulant therapy and diabetics)

Evidence from randomised controlled trials show that EACA has efficacy in dental procedures in haemophilia (e.g. *Rizza* (1980)), along with data from uncontrolled studies of haemophiliacs where EACA was successfully used post-extraction (Stajcić [1985] and Cadorph [1990]) or where EACA was used pre- and post-extraction with haemostasis rated 'excellent' or 'good' (Djulbegovic [1996]). In another study in haemophiliacs (Cooksey et al 1966) of haemophiliacs treated with EACA pre- and post-operatively or with replacement factor only, postoperative hospital time was reduced from 18 to 7 days. Evidence for patients with other coagulopathies or diabetics is limited and a review by *Patatanian and Fugate* (2006) examined eight studies (seven with TXA, one with EACA) of locally-acting haemostatic agents in patients undergoing dental extractions and who were taking anticoagulants. The studies suggested patients receiving uninterrupted oral anticoagulation and using haemostatic mouthwashes had no greater (and sometimes lesser) bleeding compared with other treatment groups. However, in this recent review the authors note "EACA has limited evidence, with only one study

examining its use. The results shown with TXA should not be considered applicable to EACA, as the potencies of these therapies differ. However, in countries where TXA is not available, EACA appears to be a reasonable alternative. Additional studies of EACA mouthwash are needed to clearly define its safety, efficacy, optimal duration, and efficacy in other dental procedures".

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of EACA in *odonto-stomatology*. This included evidence from randomised controlled trials in dental procedures in haemophilia. Other available evidence includes a recent review of several studies by *Patatanian and Fugate* (2006) which concluded that EACA has limited evidence of efficacy and in odonto-stomatology, the results shown with TXA should not be considered applicable to EACA, as the potencies of these therapies differ. The new efficacy data raises reasonable doubt on the efficacy of the product.
The safety profile of EACA has evolved since its authorisation, and safety data has accumulated over the years. Leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Aminocaproic acid has also been associated with hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders; blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment and thrombotic complications.
In view of the identified serious limitations of the efficacy data for treatment in odonto-stomatology including the new data confirming the limited efficacy and the adverse reactions profile (some of which serious) in particular in patients with other coagulopaties than haemophilia (for which data on dental extractions is reassuring), the CHMP considers that the wording of the indication should be modified. The general term thrombopathies is misleading to the prescriber and the patient populations should specify that EACA can be used in odonto-stomatology (in dental extractions in haemophiliacs and patients undergoing anticoagulant therapy) in line with the development of knowledge within the medical community on the use of EACA in these patient populations.

B.6. Postsurgical haemorrhages in ear, nose and throat (tonsil surgery and other rhinopharyngeal haemorrhages)

A review produced by *Verstraete* (1985) states that the most common complication of tonsillectomy is bleeding and that systemic administration of antifibrinolytics has been evaluated in several trials (two with TXA). The review states also that there is little clinical use of EACA in this indication. The MAH then stated that prophylactic oral treatment with EACA in ear, nose and throat surgery is used to prevent excessive bleeding secondary to tonsil extraction, but no data was submitted to substantiate such statement.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of EACA in postsurgical haemorrhages in the ear, nose or throat. This included a review of available studies by *Verstraete* (1985), which questions the clinical role of EACA in this indication. The new efficacy data raises reasonable doubt on the efficacy of the product.
The safety profile of EACA has evolved since its authorisation, and safety data has accumulated over the years. Leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Aminocaproic acid has also been associated with hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders; blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment and thrombotic complications.
In view of the identified serious limitations of the efficacy data in postsurgical haemorrhages in the ear, nose or throat including the new data on efficacy and the adverse reactions profile (some of which serious) associated with the use of EACA, the CHMP considers that the benefit risk balance of EACA in this indication is not positive under normal conditions of use. The CHMP recommends its deletion from the product information.

B.7. Postsurgical haemorrhages in which an increase in local or general fibrinolysis is suspected

Two general reviews by *Goodnough and Shander* (2006) and *Bolliger et al* (2010) refer to the routine use of TXA and EACA in blood management, but do not provide direct evidence of efficacy. A review by *Henry et al* (2008) concluded that antifibrinolytics provide reductions in blood loss and the need for

transfusion however, the authors acknowledge the need for large head-to-head comparative trials in different surgical settings, with evidence available mostly for TXA, questioning the use of EACA. *Downand et al* (2003) performed a retrospective analysis of extracorporeal membrane oxygenation (ECMO) patients given EACA from 1991-2001 and found a significant reduction in surgical site bleeding but not intracranial haemorrhage, compared with no EACA treatment. Available evidence exists of the use of EACA in specific types of postsurgical haemorrhages in which an increase in local or general fibrinolysis is suspected.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of EACA in postsurgical haemorrhages in which an increase in local or general fibrinolysis is suspected. Although it is recognised that there is evidence of efficacy in postsurgical haemorrhage caused by local or general fibrinolysis following specific types of surgery, a general indication covering all clinical postsurgical situations is misleading to the prescriber and patient. The CHMP therefore proposed a modification of the wording of the indication to specify the types of surgical procedures where EACA is indicated, such as urology (surgery of the bladder and prostate), gynaecology (cervical surgery), in patients where tranexamic acid is not available or not tolerated, obstetrics (post-partum and post-miscarriage haemorrhages) after correction of the coagulation defect, heart surgery (with or without bypass placement), gastroenterology and odonto-stomatology (dental extractions in haemophiliacs, patients undergoing anticoagulant therapy).

C. Intense haemorrhages induced by thrombolytics (streptokinase, etc.), in combined anticoagulant and anti-haemorrhage treatments, together with heparin.

Two non-clinical studies by *Westlund et al* (1982) and *Lin et al* (2000) suggest that EACA is a specific antidote to bleeding caused by fibrinolytic agents (e.g. streptokinase, etc.). There is also a consensus on the use of EACA as an antidote as this is listed in the product information for streptokinase, for use in emergency or life-threatening situations.

The CHMP noted there is a consensus within the medical community on the use of EACA as an antidote in life-threatening haemorrhages induced by thrombolytics, such as streptokinase. The CHMP noted also that EACA is contraindicated when there is evidence of an active intravascular clotting process, and this is listed under the contraindication and warning sections of the summary of product characteristics. These sections of the product information correctly address that EACA should not be used in disseminated intravascular coagulation (DIC) without the concomitant administration of heparin. The reference of combined anticoagulant and anti-haemorrhage treatments in the indication is misleading and it noted that in general antifibrinolytics should not be used for DIC ('Guidelines for the diagnosis and management of DIC', *Levi* 2009). The CHMP considered that the wording of the indication should thus be clarified and refer only that EACA can be used in life-threatening haemorrhages induced by thrombolytics, such as streptokinase.

D. Haemorrhages associated to haematological processes (haemophilia, thrombopathies, aplastic anaemia, polycytaemia, fulminating purpura and thrombopenic purpura, leukaemia, hypo- or afibrinogenaemia, etc.).

The review by *Rizza et al* (1980) on the use of antifibrinolytic agents in haemophiliac patients was described, and details of studies in other haematopoietic disorders were provided. In *Rizza et al* (1980), aprotinin was given in the joint and EACA was given systemically at the time of operation along with fresh frozen plasma in haemophiliac patients undergoing synovectomies. The author concluded that "the weight of published evidence suggests that EACA and TXA have no significant effect in the prophylactic treatment of haemophilia". Evidence is available on the current accepted use of EACA in haemorrhages associated to other haematological processes. *Gardner and Helmer* (1980) studied 13 patients with amegakaryocytic thrombocytopenia, treated with EACA from 3 days to 13 months, in which 4 patients on long-term treatment had marked decreases in the number of required platelet transfusions. *Garewal and Durie* (1985), performed an uncontrolled study in which one course of EACA was given to nine acutely ill patients with thrombocytopenia of various aetiologies. The authors concluded that EACA is safe and useful in the management of thrombocytopenia including that occurring during leukaemic induction. In the study by *Kalmadi et al* (2006), 77 patients with thrombocytopenic haemorrhage were treated with EACA (uncontrolled), 51 (66%) patients achieved a complete response and 13 (17%) patients achieved a partial response, resulting in a decrease in platelet and red blood cell transfusions.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of EACA in haemorrhages associated to haematological processes. This included evidence from randomised controlled trials in haemophilia by *Rizza* (1980), which indicate that EACA has no significant effect in the treatment of haemophilia. The new efficacy data raises reasonable doubt on the efficacy of the product. More recent reviews by *Gardner and Helmer* (1980) and *Kalmadi et al* (2006) confirm the clinical use of EACA in haematological processes, such as thrombocytopenia, thrombopenic purpura and leukaemia.
The safety profile of EACA has evolved since its authorisation, and safety data has accumulated over the years. Leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Aminocaproic acid has also been associated with hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders; blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment and thrombotic complications.
In view of the identified serious limitations of the efficacy data for treatment of haemorrhages associated to haematological processes including the new data on lack of efficacy and the adverse reactions profile (some of which serious) associated with the use of EACA, the CHMP considers that the use in haemophilia is not positive under normal conditions of use (other than in haemophiliacs undergoing dental extraction, which is covered by the odonto-stomatology indication), thus its reference should be removed from the product information. Furthermore, the correct 'thrombopathies' terms should be listed to guide physicians in the current accepted use of EACA within the medical community. A modification of the wording to reflect thrombocytopenia, thrombopenic purpura and leukaemia was recommended by the CHMP, considering the now known safety profile of EACA in particular regarding blood disorders and thrombotic complications.

E. Other indications: essential haematuria in haemophilic patients and secondary to other conditions; intense menstruations, menorrhagia and haemorrhagic metropathies; angioneurotic oedema; epistaxis; haemoptysis secondary to tuberculosis or lung cancer.

Evidence is available on the use of EACA in hereditary angioedema and menorrhagia or related conditions.
Based on data from different studies, concerns were raised over the use of EACA in haemophiliac patients experiencing haematuria. Due to the risk of renal colic derived from ureteric obstruction by an insoluble clot, use of antifibrinolytic agents should be avoided in these patients. Data in the US also advise against the use of EACA in haematuria of upper urinary tract origin, due to the risks of clots in the renal pelvis or ureters. *Allon* (1990) and *de Santris et al* (2002) addressed haematuria secondary to sickle cell disease. *Stefanini et al* (1990) documented the successful treatment with EACA in nine patients with haematuria of various causes for up to 21 days treatment. Concerns were also raised over the use of EACA in epistaxis. This included a review of available studies by *Verstraete* (1985), which questions the clinical role of EACA in haemorrhages of ear, nose or throat (see also B.6. Postsurgical haemorrhages in ear, nose and throat, above). Haemoptysis can be caused by a number of different diseases, including lung cancer and tuberculosis. A systematic review of randomised trials found that EACA use in surgery-related bleeding have limited or contradictory evidence of efficacy (Erstad BL, 2001); furthermore in most studies patients with e.g. cancer were excluded. Recent reviews also considered that controlled studies of these drugs are lacking in the cancer setting (Pereira et al, 2004), raising doubts on whether EACA should be used to treat haemoptysis secondary to tuberculosis or lung cancer.

The CHMP noted the available scientific data, including evidence from new studies, on the efficacy of EACA in these indications. Concerns were raised with the use of EACA in the indication of haematuria and the CHMP considered that the indication warrants revision, as the new data indicates that the use in haematuria of upper urinary tract should be avoided. It was also noted that the evidence by *Rizza* (1980) indicates that EACA has no significant effect in the treatment of haemophilia (see also D. Haemorrhages associated to haematological processes, above). Therefore the CHMP proposes that the indication should capture the use in non-surgical haematuria of the lower urinary tract, such as haematuria secondary to cystitis, among others. A modification of the indication was thus proposed by the CHMP.
Evidence is also available regarding the use of EACA in intense menstruations, menorrhagia, haemorrhagic metropathies and angioneurotic oedema.
The safety profile of EACA has evolved since its authorisation, and safety data has accumulated over the years. Leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure are adverse events which can be serious and have been reported, but these risks have not been

considered in the current authorised product information. Aminocaproic acid has also been associated with hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders; blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment and thrombotic complications.
In view of the identified serious limitations of the efficacy data for treatment of epistaxis and haemoptysis secondary to tuberculosis or lung cancer including the current medical knowledge regarding its use in these settings, and the adverse reactions profile (some of which serious) associated with the use of EACA, the CHMP considers that the benefit risk balance of EACA in epistaxis and haemoptysis secondary to tuberculosis or lung cancer is not positive under normal conditions of use. The CHMP recommends the deletion of these indications from the product information.

In conclusion, the CHMP proposes the modification of the indication to capture intense menstruation, menorrhagia and haemorrhagic metropathies, non-surgical haematuria of the lower urinary tract and angioneurotic oedema.

Posology

The CHMP noted the available scientific data on the recommended posology. New information on the licensed dosing regimens was mainly based on *Verstraete* (1985), who stated that due to the short half-life of EACA, relatively high doses are needed to sustain an effective plasma concentration of 0.01 mmol/L.
In adults, the following is noted when EACA is administered via the intravenous (IV) route: the desired blood level is reached with an initial dose of 4 to 5 g by slow intravenous infusion (over one hour), followed by a continuous infusion of 1 g/hour. If treatment needs to be extended, the maximum dose over 24 hours should not normally exceed 24 g. EACA may be given by mouth in an initial dose of 4 to 5 g, followed by 1 to 1.25 g every hour. According to *Verstraete*, the oral dose of EACA should be 0.1 g/kg bodyweight every 6 hours; for a patient weighing 60 kg, this schema represents a daily dose of 24 g.
Regarding children, new information was also available from the American hospital formulary service (AHFS) detailed monograph of EACA, which states that although safety and efficacy of EACA in children have not been established, the drug has been given by intravenous infusion to children at a dosage of 100 mg/kg or 3 g/m^2 during the first hour, followed by continuous infusion at the rate of 33.3 mg/kg per hour or 1 g/m^2 per hour; total dosage should not exceed 18 g/m^2 (600 mg/kg) in 24 hours.
The CHMP considered that the posology section should reflect the most current knowledge within the medical community and reflected in published literature on maximum dose for adult (24g in 24 hours) and paediatric (600mg/kg in 24 hours) populations. A modification to include the maximum doses was thus proposed for the posology section for both IV and oral administration.

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.

Safety

Data from spontaneously reported cases and published literature was analysed. Recent publications such as *Biswas et al* (1980)*, Glick et al* (1981)*, Geltzeiler & Schwartz*, (1984), *Palmer et al* (1986) *Pitts et al* (1986), , *Kutner et al* (1987), *Rabinovici et al* (1989), *Yien et al* (1992), *Wymenga & van der Boon* (1998), *Budris et al* (1999), *Thompson et al* (2008), *Berenholtz et al* (2009), *Greilich et al* (2009) and *Muttler et al* (2009) were also considered in the review. Skin eruption or rash, dry ejaculation, myopathy, myalgia, haematuria, proteinuria, renal failure, intrarenal obstruction via glomerular capillary thrombosis and high anion gap metabolic acidosis were among the mostly reported adverse events.

Aminocaproic 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 EACA use are hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders. Blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment, and thrombotic complications related with the use of EACA have also been reported. Special attention should be given when administering EACA, in particular in the cases of thromboembolic events, haematuria, skeletal muscle and neurological effects.

The CHMP noted that the product information for EACA did not reflect the latest safety information available from spontaneous reports and published literature. In addition, the CHMP also noted the available data reflected in the product information in the United States of America, which includes, among others, general reactions such as oedema, headache and malaise; hypersensitivity reactions; cardiovascular reactions, including hypotension, peripheral ischemia and thrombosis; gastrointestinal reactions such as abdominal pain, diarrhoea and vomiting; haematological reactions such as agranulocytosis, coagulation disorder, leukopenia and thrombocytopenia; musculoskeletal disorders such as increased creatine phosphokinase, muscle weakness, myalgia, myopathy, myosistis, rhabdomyolysis; neurological reactions such as confusion, convulsion, delirium, dizziness, hallucinations, intracranial hypertension, stroke and syncope; respiratory reactions such as dyspnea, nasal congestion, pulmonary embolism; skin reactions such as pruritus and rash; special senses reactions such as tinnitus, vision decreased, watery eyes, and urogenital reactions such as BUN (blood urea nitrogen) increased and renal failure. The CHMP requested that new identified risks, such as leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure be added to the list of undesirable effects. Its frequencies are unknown and cannot at present be established. This was also reflected in the product information.

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

Discussion on aminocaproic acid

Aminocaproic acid is a lysine analogue authorised for several indications since 1963. 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 EACA in patients of all ages in haemorrhage caused by local or general fibrinolysis. This includes specifically use in postsurgical haemorrhage in urology (surgery of the bladder and prostate); gynaecology (cervical surgery), in patients where tranexamic acid is not available or not tolerated; obstetrics (post-partum and post-miscarriage haemorrhages) after correction of the coagulation defect; heart surgery (with or without bypass placement); gastroenterology; odonto-stomatology (dental extractions in haemophiliacs, patients undergoing anticoagulant therapy); use in life-threatening haemorrhages induced by thrombolytics (streptokinase, etc.); use in haemorrhages associated with thrombocytopenia, thrombopenic purpura, leukaemia; use in nonsurgical haematuria of the lower urinary tract (secondary to cystitis, etc.); use in intense menstruations, menorrhagia and haemorrhagic metropathies; and use in angioneurotic oedema.

The safety profile of EACA has evolved since its authorisation, and safety data has accumulated over the years. Leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure are adverse events which can be serious and have been reported, but these risks have not been considered in the current authorised product information. Aminocaproic acid has also been associated with hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders; blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment and thrombotic complications.
Aminocaproic 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 EACA 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 EACA. In view of the identified serious limitations of the efficacy data, the available new evidence and/or current medical knowledge on the use of EACA, and considering the adverse reactions profile (some of which serious) associated with the use of EACA, the CHMP considers that the benefit risk balance of EACA in haemorrhages associated with hyperfibrinolysis, such as those secondary to cirrhosis of the liver or early detachment of the placenta; in postsurgical haemorrhages in the ear, nose or throat (tonsil surgery and other rhinopharyngeal haemorrhages); in (a generalised indication of) postsurgical haemorrhages in which an increase in local or general fibrinolysis is suspected; haemorrhages associated with haematological conditions such as aplastic anaemia, polycythaemia, fulminating purpura and hypo or afibrinogenaemia; in combined anticoagulant and anti-haemorrhage treatments together with heparin; in epistaxis and haemoptysis secondary to tuberculosis or lung cancer, 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 and amendments to the list of undesirable effects to include leukopenia, thrombocytopenia, BUN increased and renal failure.

2.3. Risk management plan

The CHMP did not require the MAHs for medicinal products containing EACA 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 EACA.

Aminocaproic acid

The safety profile of EACA has evolved since its authorisation, and safety data has accumulated over the years. Leukopenia, thrombocytopenia, BUN (blood urea nitrogen) increased and renal failure are adverse events which can be serious and have been reported, but these risks had not been considered in the current authorised product information. Aminocaproic acid has also been associated with hypotension, nasal and conjunctival congestion, gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain), dizziness, headache, tinnitus and ejaculation disorders; blood disorders (agranulocytosis, coagulation disorders), muscular damage, convulsions, anaphylactic reactions, renal impairment, and thrombotic complications. The results of the BART trial did not have a negative impact on the benefit risk profile of EACA. EACA had not previously been associated with an increased risk of mortality and this has remained unchanged post-publication of the BART study. The CHMP recommended that information on leukopenia, thrombocytopenia, BUN increased and renal failure should be appropriately reflected through warnings and recommendations in the product information.

Aminocaproic acid is a lysine analogue authorised for several indications since 1963. 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 EACA in other indications, including in patients undergoing dental or surgical procedures or at risk of complications from bleeding. For some indications modifications to the wording were proposed, in order to bring them in line with current scientific knowledge on the use of EACA. In view of the identified serious limitations of the efficacy data, the available new evidence and/or current

medical knowledge on the use of EACA, and considering the adverse reactions profile (some of which serious) associated with the use of EACA, 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 EACA; other changes to the product information were inclusion of information on leukopenia, thrombocytopenia, blood urea nitrogen increased and renal failure 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 EACA:

Aminocaproic acid is indicated for use in patients of all ages in haemorrhage caused by local or general fibrinolysis, including in
Postsurgical haemorrhages in:
- urology (surgery of the bladder and prostate)
- gynaecology (cervical surgery), in patients where tranexamic acid is not available or not tolerated
- obstetrics (post-partum and post-miscarriage haemorrhages) after correction of the coagulation defect
- heart surgery (with or without bypass placement)
- gastroenterology
- odonto-stomatology (dental extractions in haemophiliacs, patients undergoing anticoagulant therapy)
Life-threatening haemorrhages induced by thrombolytics (streptokinase, etc.).
Haemorrhages associated with thrombocytopenia, thrombopenic purpura, leukaemia.
Nonsurgical haematuria of the lower urinary tract (secondary to cystitis, etc.);
Intense menstruations, menorrhagia and haemorrhagic metropathies;
Angioneurotic oedema.

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. Aminocaproic 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.

Aminocaproic 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); and 4.8 (inclusion of missing adverse events leukopenia, thrombocytopenia, BUN increased and renal failure). 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 EACA should read:

‘Aminocaproic acid is indicated for use in patients of all ages in haemorrhage caused by local or general fibrinolysis, including in
Postsurgical haemorrhages in:
- urology (surgery of the bladder and prostate)
- gynaecology (cervical surgery), in patients where tranexamic acid is not available or not tolerated
- obstetrics (post-partum and post-miscarriage haemorrhages) after correction of the coagulation defect
- heart surgery (with or without bypass placement)
- gastroenterology
- odonto-stomatology (dental extractions in haemophiliacs, patients undergoing anticoagulant therapy)
Life-threatening haemorrhages induced by thrombolytics (streptokinase, etc.).

Haemorrhages associated with thrombocytopenia, thrombopenic purpura, leukaemia.
Nonsurgical haematuria of the lower urinary tract (secondary to cystitis, etc.);
Intense menstruations, menorrhagia and haemorrhagic metropathies
Angioneurotic oedema.'

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 and for more details please refer to the opinion and assessment report on tranexamic acid.

3. Overall conclusion on aminocaproic acid

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

For aminocaproic acid

The Committee considered that evidence from randomised clinical trials and observational studies support the use of aminocaproic 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 EACA. The CHMP considered also the adverse reactions profile, including new adverse events (some of which serious) associated with the use of EACA.

In view of the identified serious limitations of the efficacy data, the available new evidence and/or current medical knowledge on the use of EACA, and considering the adverse reactions profile (some of which serious) associated with the use of EACA, 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 EACA; other changes to the product information were inclusion of information on leukopenia, thrombocytopenia, blood urea nitrogen increased and renal failure as warnings and recommendations.

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

patients of all ages in haemorrhage caused by local or general fibrinolysis, including in
Postsurgical haemorrhages in:
- urology (surgery of the bladder and prostate)
- gynaecology (cervical surgery), in patients where tranexamic acid is not available or not tolerated
- obstetrics (post-partum and post-miscarriage haemorrhages) after correction of the coagulation defect
- heart surgery (with or without bypass placement)
- gastroenterology
- odonto-stomatology (dental extractions in haemophiliacs, patients undergoing anticoagulant therapy)
Life-threatening haemorrhages induced by thrombolytics (streptokinase, etc.).
Haemorrhages associated with thrombocytopenia, thrombopenic purpura, leukaemia.
Nonsurgical haematuria of the lower urinary tract (secondary to cystitis, etc.);
Intense menstruations, menorrhagia and haemorrhagic metropathies
Angioneurotic oedema.

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

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.