Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations for aminocaproic acid containing medicinal products presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of referral on antifibrinolytics Aminocaproic acid containing medicinal products (see Annex I)

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.

Grounds for amendment of the marketing authorisations of aminocaproic acid containing medicinal products listed in Annex I

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC, for aprotinin, aminocaproic acid and tranexamic acid (see Annex I).

- The Committee considered all data provided by the MAHs in writing, including data available from literature reviews.

- 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 for which the amendments to the product information are set out in annex III of the opinion.