Annex II

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

Scientific conclusions

Overall summary of the scientific evaluation of referral on antifibrinolytics Tranexamic 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 tranexamic acid.

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.

Detailed grounds for re-examination submitted by the marketing authorisation holder

One MAH for tranexamic acid containing medicinal products 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 was 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.

Having considered the data presented, the CHMP noted that there are ongoing PK studies in children that could provide valuable information. The final study results of these clinical trials should be considered before recommending the need of additional studies. Therefore, the CHMP concluded 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.

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

Whereas

Figure: 1. The Committee considered the procedure under Article 31 of Directive 2001/83/EC, for aprotinin, aminocaproic acid and tranexamic acid (see Annex I).

Figure: 2. The Committee considered all data provided by the MAHs in writing, including data available from literature reviews.

Figure: 3. 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.

Figure: 4. 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.

Figure: 5. 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.

Figure: 6. 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.