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Questions and answers on the review of antifibrinolytic medicines (aprotinin, aminocaproic acid and tranexamic acid)

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

On 14 February 2012, the European Medicines Agency completed a review of the antifibrinolytic medicines aprotinin, aminocaproic acid and tranexamic acid. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines outweigh their risks and recommended that the EU-wide suspension of the marketing authorisation for aprotinin-containing medicines that has been in place since 2008 be lifted. The CHMP set out conditions for the reintroduction of aprotinin medicines onto the market and also made recommendations on the use of aminocaproic acid and tranexamic acid.

On 19 June 2012, following a re-examination, the CHMP confirmed its initial conclusions but decided to remove a requirement for a pharmacokinetic study with tranexamic acid. The CHMP was informed of ongoing pharmacokinetic studies which are to be finalised and assessed by national authorities.

What are antifibrinolytics?

Antifibrinolytics are medicines used to prevent excessive blood loss. They have been used for several decades in patients undergoing certain dental or surgical operations as well as other patients at risk of complications from bleeding.

Antifibrinolytics work by preventing fibrinolysis, the natural process by which blood clots are broken down. They work by reducing the activity of an enzyme called plasmin that is responsible for breaking up the fibres in blood clots. In patients at risk of significant bleeding, antifibrinolytics ensure that blood clots are not broken down too rapidly, which helps to reduce blood loss.

Aminocaproic acid and tranexamic acid are the commonly used antifibrinolytics in the EU. Aprotinin had been approved in several EU countries for patients undergoing heart bypass surgery but was suspended in the EU by the European Commission in February 2008.

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Why were antifibrinolytics reviewed?

On 5 November 2007, the German medicines regulatory authority (BfArM) suspended the marketing authorisations for aprotinin-containing medicines in Germany. This decision was triggered by the early results of a study (the BART study) that showed a higher number of deaths 30 days after heart surgery among patients given aprotinin compared with patients given other antifibrinolytic treatments (aminocaproic acid and tranexamic acid). The suspension in Germany led to an EU-wide review by the CHMP which recommended the suspension of aprotinin throughout the EU on 21 November 2007.[1] At the time of its recommendation, the CHMP had envisaged a further review once final data from the BART study became available.

The current CHMP review was initiated at the request of the German medicines agency to take into account further data and analyses from the BART study and other sources that have become available since 2007. On 12 March 2010, the German medicines agency asked the CHMP to carry out a full assessment of the benefits and risks of aprotinin, as well as those of aminocaproic acid and tranexamic acid, and to issue an opinion on their authorisation in the EU.

Which data has the CHMP reviewed?

The CHMP reviewed data from the BART study, including additional data and analyses that became available since 2007. The Committee also looked at data from other clinical studies, the published literature, spontaneous reports of side effects and data submitted by companies that market antifibrinolytics. During the review, the CHMP took advice from a scientific advisory group, consisting of experts in cardiovascular and bleeding disorders.

What are the conclusions of the CHMP?

The CHMP revisited its previous recommendation on aprotinin, taking into account the new information from the BART study. New analyses showed flaws in the way the study was carried out, which cast doubt on the previous conclusions. The way additional blood-thinning treatments (such as heparin) were used in the study was inconsistent and sometimes inappropriate, and this could have contributed to higher than expected rates of deaths in patients on aprotinin. There were also problems with the way data from some patients were excluded from the initial analyses and with the lack of appropriate monitoring of blood-thinning medicines the patients were taking.

The results from the BART study were not replicated in other studies, and when data from several studies (excluding BART) were analysed together, the results did not show that aprotinin is linked to a higher risk of death compared with other antifibrinolytics. The CHMP therefore concluded that the benefits of aprotinin outweigh its risk in appropriately managed patients undergoing isolated heart bypass surgery (not combined with other heart surgery), and recommended that the suspension of aprotinin medicines in the EU be lifted for this revised indication.

The CHMP also recommended important changes to the prescribing information for aprotinin medicines, including restricting their use to isolated heart bypass surgery in adults at high risk of major blood loss and the inclusion of a warning on the risk of giving patients too little heparin ('under heparinisation'). Furthermore, the CHMP advised that careful consideration be given to benefits and risks of aprotinin, and the availability of alternative treatments. A registry will be set up in the EU to monitor the use of aprotinin, and the CHMP has approved a risk management plan for aprotinin medicines.

[1] Questions and answers on the suspension of aprotinin

The amended prescribing information on aprotinin medicines for doctors can be found here.

The CHMP's review of aminocaproic acid and tranexamic acid, which are currently on the market in the EU, did not reveal any new safety concerns. As these medicines have been authorised since the 1960s, the CHMP reviewed the available evidence on their benefits in various conditions and made recommendations to harmonise the conditions for which these medicines should be used in the EU.

The amended prescribing information on aminocaproic acid for doctors can be found here. The amended information for tranexamic acid can be found here.

What are the recommendations for patients and prescribers?

- When aprotinin becomes available again, prescribers are advised to note the revised indication and to adhere closely to the updated prescribing advice.
- A registry will be set up in EU monitor the pattern of use of aprotinin. Prescribers will be sent information on how to use the registry.
- Prescribers should follow the new harmonised recommendations for the use of aminocaproic acid and tranexamic acid.
- Patients with any question should speak to their doctor or pharmacist.

The Committee has agreed with the companies marketing these medicines on a letter to be sent out to relevant healthcare professionals in the EU explaining the changes to the prescribing information.

The European Commission issued a decision for aminocaproic acid on 10 October 2012.

The European Commission issued a decision for tranexamic acid on 10 October 2012.

The European Commission issued a decision for aprotinin on 18 September 2013.