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QUESTIONS AND ANSWERS ON THE EMEA RECOMMENDATION TO SUSPEND THE MARKETING AUTHORISATIONS FOR APROTININ-CONTAINING MEDICINES

The European Medicines Agency (EMA) has looked at the safety of medicines containing aprotinin. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of 'systemic' formulations of these medicines no longer outweigh their risks, and has recommended that all marketing authorisations for these medicines should be suspended throughout Europe. 'Systemic' formulations are those that affect the whole body, such as infusions (drips).

What is aprotinin?

Aprotinin-containing medicines are used to prevent the loss of blood. Aprotinin is an antifibrinolytic. This means that it stops the body breaking down blood clots. Medicines containing aprotinin can be used as an infusion during surgery to prevent the need for blood transfusion in patients undergoing a coronary artery bypass (when the arteries that supply blood to the heart are replaced by blood vessels taken from another part of the body).

Systemic medicines containing aprotinin have been available since 1974. They are authorised in Austria, Belgium, Bulgaria, the Czech Republic, Cyprus, Germany, Denmark, Greece, Estonia, Finland, France, Hungary, Lithuania, Luxembourg, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom, under the trade names Acset, Antagosan, Antilysin Spofa, Gordox, Pantinol, Traskolan, Trasylol and Trasynin.

Aprotinin can also be used locally during surgery, in sealants (glues), to help stop bleeding. These medicines are not affected by this recommendation.

Why was aprotinin reviewed?

On 5 November 2007, the German medicines regulatory authority suspended the marketing authorisations for the aprotinin-containing medicines Trasylol and Trasynin, used as an infusion during bypass surgery. This decision was triggered by the preliminary results of a study called the BART study, which was looking at the use of aprotinin in around 3,000 heart surgery patients to reduce post-operative bleeding.

This study was stopped early because it showed that, 30 days after surgery, there were more deaths in the group of patients receiving aprotinin than in the group receiving alternative antifibrinolytic treatments (aminocaproic acid or tranexamic acid). On the basis of this finding, the German authority concluded that the benefits of aprotinin in this indication no longer outweighed its risks, and that the marketing authorisations should be suspended. Bayer, the company that makes Trasylol and Trasynin, subsequently decided to remove these medicines from the market worldwide.

As required by Article 107 of Directive 2001/83/EC as amended, the German authority informed the CHMP of its action so that the Committee could consider whether the marketing authorisations for all systemic products containing aprotinin should be maintained, changed, suspended or withdrawn across the European Union (EU) and European Economic Area (EEA).

Which data has the CHMP reviewed?

The CHMP looked at the data that its Pharmacovigilance Working Party (PhVWP) had already been considering in the context of its monitoring of the safety of medicines. The PhVWP review has been looking at the information obtained from three 'observational' studies¹, which looked at the outcomes of patients undergoing heart surgery and treated with aprotinin.

In the current review, the CHMP has also taken the new information from the BART study into account. Since the BART study is the first 'randomised' study that compares the effects of aprotinin with other medicines in a head-to-head manner, its results are considered to be more reliable than those previously available. 'Randomised' means that patients were allocated to receive either aprotinin or another medicine in a random manner, to avoid bias in the results.

What are the conclusions of the CHMP?

The PhVWP review had already identified some concerns over the benefit-risk balance of systemic aprotinin-containing medicines, especially their possible effect on the kidneys and the heart. These concerns led to measures being put in place to minimise the risk associated with their use. All healthcare professionals were notified of these measures.

At its November 2007 meeting, the CHMP considered all the available evidence, including the negative findings of the BART study and their impact on the benefit- risk balance of systemic aprotinin. The CHMP concluded that the benefits of aprotinin used systemically no longer outweigh its risks. Therefore, the Committee recommended that the marketing authorisations of systemic medicines containing aprotinin be suspended in all European Union and European Economic Area markets.

A European Commission Decision on this opinion will be issued in due course. It should be noted that the use of systemic aprotinin in surgery will be suspended throughout the EU once the European Commission has made the CHMP recommendation legally binding.

What are the recommendations for patients and prescribers?

- Surgeons should re-assess the need for antifibrinolytics for the prevention of excessive blood loss during bypass surgery. Depending on the country, there may be other medicines that are authorised for use. These include medicines containing aminocaproic acid or tranexamic acid.
- Patients who have received medicines containing aprotinin during surgery and have any questions should speak to their surgeon or the doctor who is currently looking after them.

¹ Mangano D, Tudor J, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Eng J Med* (2006), 354:353-65, Mangano D *et al.*, Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* (2007), 297:471-479 and 'i3' safety study results, 2007