**20th February 2012**

**Circular No. P05/2012**

Dear Healthcare Professional,

**Re: European Medicines Agency recommends lifting of the suspension of aprotinin**

The Medicines Authority would like to inform healthcare professionals that the European Medicines Agency has finalised a review and found that benefits of all antifibrinolytic medicines outweigh risks in a restricted range of indications and has recommended that the suspension of the marketing authorisations for aprotinin-containing medicines in the European Union (EU) be lifted. Aprotinin is authorised in Malta as Tisseel Kit, a powder and solution for sealant (topical use) 3000KIU/ml, as Trasylol solution for infusion 10,000KIU/ml and as Aprotinin injection 10,000KIU/50mls. Suspension of these products was imposed in 2008 as outlined in Medicines Authority circular **P19/2007**. Lifting of this suspension follows a full review of the benefits and risks of all antifibrinolytic medicines, which found that the results of the BART[1] study on which the suspension was based are unreliable.

Aprotinin is an antifibrinolytic medicine, which prevents excessive blood loss. It works by preventing the breakdown of fibrin, a protein found in blood clots. Prior to its suspension, aprotinin was authorised for patients undergoing heart bypass surgery.

The Agency's Committee for Medicinal Products for Human Use (CHMP) has now concluded that aprotinin's benefits in preventing blood loss outweigh its risks in patients undergoing isolated heart bypass surgery who are at high risk of major blood loss. It should only be used in this narrower

[1] The BART study results are available: Fergusson DA *et al.* (2008) A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 358(22): 2319-2331 (http://www.nejm.org/doi/full/10.1056/NEJMoa0802395).



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group of patients once the doctor has assessed the benefits and risks of treatment carefully and considered alternative treatments.

Aprotinin was suspended as a precautionary measure on the recommendation of the CHMP, following the preliminary results of the BART study, a randomised controlled trial in high-risk heart surgery patients. These results appeared to show an increased death rate in patients receiving aprotinin after 30 days compared to patients taking other medicines, and led to the early discontinuation of the study by its data safety monitoring board.

The current review was started after the publication of the final results of the BART study and looked at this study's results, as well as the results of other clinical studies, data from the scientific literature, reports of side effects and information submitted by the companies that market antifibrinolytic medicines. The CHMP also took the views of its scientific advisory group into account.

The Committee found that there were a number of problems with the way the BART study was conducted, which cast doubt on the previous conclusions. These included the imbalances in the way blood-thinning medicines such as heparin were used, inappropriate monitoring of the use of these medicines and how problems with the way that data from some patients were excluded from the initial analysis. The Committee found that the BART study's results were not replicated in other studies and that the overall data available showed that aprotinin's benefits are greater than its risks in the restricted indication.

As a condition of the lifting of the suspension, the Committee also recommended that doctors be warned of the risk of giving patients too little heparin, as well as the establishment of a registry to record information on the use of aprotinin in the EU. The Committee's opinion has now been forwarded to the European Commission for the adoption of a legally binding decision.

The review also included the antifibrinolytic medicines aminocaproic acid and tranexamic acid, which have been used since the 1960s in patients undergoing dental or surgical procedures or at risk of complications from bleeding. The Committee found no new safety concerns for these medicines. However, it noted that there is very limited information available on some of the conditions that these medicines are used to treat. Therefore, the Committee recommended a restricted list of conditions in which they should be used based on the currently available evidence.



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The Committee also requested that a study be carried out to gather more information on how tranexamic acid should be optimally dosed in children.

1. The CHMP concluded that the evidence supported the use of aminocaproic acid 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 gland), 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 or 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. The CHMP concluded that the evidence supported the use of tranexamic acid in the prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year, including 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 and 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.



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The Medicines Authority is in agreement with the full **press release** and the **question-and-answer** documents issued by the EMA. Healthcare professionals are encouraged to maintain vigilance on aprotinin-containing products. Suspected Adverse Drug Reactions may be reported using the Medicines Authority yellow card scheme or online at http://www.medicinesauthority.gov.mt/pub/adr.doc or to the marketing authorisation holder or their local representatives.

***Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.***



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