Malta, 1 February 2007

Circular No. P01/2007

Dear Healthcare Professional,

Re: Follow-up Information on the Safety of Trasylol® (Aprotinin)

Aprotinin (marketed as Trasylol®) is an intravenously administered proteinase inhibitor drug with anti-fibrinolytic properties which is manufactured from bovine lung.

As detailed in the Medicines Authority Circular P03/2006[1], on January 26, 2006, *The New England Journal of Medicine* published an article[2] reporting an association of aprotinin with increased risk of cardiovascular events (myocardial infarction or heart failure), cerebrovascular events such as stroke, encphalopathy or coma and renal dysfunction or failure in patients undergoing coronary artery bypass grafting surgery (CABG). Another publication[3] suggests an association between aprotinin administration and renal toxicity among patients undergoing cardiac surgery with cardiopulmonary bypass. More recently, the preliminary findings from a new observational study by Bayer was submitted. Existing hospital data from 67,000 records of patients undergoing coronary artery bypass graft surgery were examined. 30,000 of the patients were treated with Trasylol® and 37,000 were treated with alternate products. Using complex epidemiological and statistical methods, the report suggested that patients receiving Trasylol® were at increased risk for death, serious kidney damage, congestive heart failure and stroke. These studies, along with other studies in the literature review indicate a higher risk of death and serious and/or life-threatening renal and cardiac adverse events following treatment with Trasylol®.

These findings have triggered an international review of the safety of aprotinin. The Medicines Authority in collaboration with the health authorities in other Member States is also conducting its own review of these reports along with other reports in the literature as well as adverse event reports.

[1] http://www.medicinesauthority.gov.mt/pub/ma_circular_p03-2006.pdf

[2] Mangano, D. T., Tudor, I. C., Dietzel, C. (2006). The Risk Associated with Aprotinin in Cardiac Surgery. *NEJM* 354:353-365

[3] Karkouti K et al. A propensity score case-control of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; 46(3):327-338.

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The prescribing information for Trasylol® has recently been revised by the Food and Drug Administration (FDA), US.[4] The new labeling has a more focused indication, a new warning that Trasylol® administration increases the risk of renal dysfunction and may increase the need for dialysis in the perioperative period and stronger warnings about anaphylactic reactions. In addition, due to the higher risk for anaphylactic reactions, re-administration of Trasylol® to patients with a known or suspected exposure during the past 12 months is contraindicated.

In January 2007, the Medicines Authority participated in discussions at the Pharmacovigilance Working Party (PhVWP) held at the European Medicines Agency (EMEA) regarding the safety profile of Trasylol®. It was agreed that the Summary of Product Characteristics (SmPC) and other product information of this medicinal product should be updated with a warning on the occurrence of hypersensitivity reactions associated with the use of Trasylol®, upon receiving confirmation from the license holder of Trasylol® about the availability in all Member States of an immunological test to be performed prior to the administration of aprotinin. The PhVWP was also informed that a bedside test that could be performed on the day of the surgery, thus providing a more rapid response should become available in 2008. Furthermore, the PhVWP recommended the introduction of the testing procedure to be accompanied by adequate communication to doctors and hospitals.

With regard to the issues of increased risk of myocardial infarction, renal failure and stroke associated with use in cardiac surgery, the PhVWP is awaiting the final report of a study being carried out to investigate these adverse reactions for discussion at future meetings. The Medicines Authority will notify health care providers and patients in a timely fashion as new information becomes available.

In the meantime, prescribers are advised to weigh the benefits against the risks of aprotinin when prescribing to patients, as is common practice when prescribing all medicinal products. Adverse Drug Reactions (ADRs) associated with this medicinal product should be promptly reported to the Medicines Authority by filling in an ADR reporting form. This may be accessed on: http://www.medicinesauthority.gov.mt/pub/adr.doc.

Should you require any further information please contact the Medicines Authority on 23439000 or by e-mail at: postlicensing.mru@gov.mt.

[4] http://www.fda.gov/bbs/topics/NEWS/2006/NEW01529.html