

## FDA Public Health Advisory

### Aprotinin Injection (marketed as Trasylol)

**This information is not current. The FDA has issued new information about this safety issue, please see <http://www.fda.gov/cder/drug/infopage/aprotinin/default.htm>**

On January 26, 2006, *The New England Journal of Medicine* (NEJM) published an article by Mangano et al. reporting an association of Trasylol (aprotinin injection) with serious renal toxicity and ischemic events (myocardial infarction and stroke) in patients undergoing coronary artery bypass grafting surgery (CABG). Another publication (*Transfusion*, on-line edition, January 20, 2006, Karkouti, et al.) suggests an association between aprotinin administration and renal toxicity among patients undergoing cardiac surgery with cardiopulmonary bypass. FDA is evaluating these studies, along with other studies in the literature and reports submitted to the FDA through the MedWatch program, to determine if labeling changes or other actions are warranted.

While FDA is continuing its evaluation, we are providing the following recommendations to healthcare providers and patients:

- Physicians who use Trasylol should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or central nervous system and promptly report adverse event information to Bayer, the drug manufacturer, or to the FDA MedWatch program, as described at the end of this advisory.
- Physicians should consider limiting Trasylol use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

The study reported in the NEJM was an observational study of patients undergoing CABG who received either Trasylol, one of two other drugs intended to decrease peri-operative bleeding (aminocaproic acid or tranexamic acid), or no specific drug treatment.

A limitation of the study was that patients were not assigned at random to receive the treatments, but rather had their treatment chosen by their physician as part of their standard medical care. Consequently, patients receiving Trasylol may have been at higher risk to begin with for these serious adverse events compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility prevents a direct assessment of whether Trasylol altered the risk for serious adverse events. The study investigators used statistical procedures (multivariable logistic regression and propensity-score adjustment) to try to adjust for known differences between the treatment groups. Using these procedures, their study concluded that Trasylol was associated with more adverse outcomes. Other findings in the study suggested that patients receiving higher Trasylol dosages were at greater risk than those receiving lower dosages.

The study reported in the on-line edition of *Transfusion* was also an observational study that used statistical methodology to compare outcomes from patients undergoing CABG. The patients in this study received, at physician direction, either Trasylol or another drug intended to decrease the risk for perioperative bleeding. This study suggested that Trasylol administration increased the risk for renal dysfunction. This study has some of the same limitations as the NEJM publication.

In pre-marketing clinical studies conducted among approximately 3,000 patients undergoing CABG, the risks and benefits of Trasylol were determined in clinical studies that randomized patients to either a placebo or Trasylol. In these studies, the risks for serious renal toxicity and cardiovascular events were determined to be similar between patients receiving Trasylol and those receiving placebo. However, in one study assessing coronary graft patency, Trasylol administration was associated with an increased risk of graft closure. The FDA will work with the authors of the publications and the manufacturer of Trasylol to carefully evaluate the risks and benefits associated with use of Trasylol in CABG. The FDA anticipates the public presentation of the recently reported information and other data at an advisory committee in the near future. The FDA will notify health care providers and patients in a timely fashion as new information becomes available.

The FDA urges health care providers and patients to report adverse event information to FDA via the MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by the Internet at <http://www.fda.gov/medwatch/index.html>.

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Date created: February 8, 2006, updated November 5, 2007