Information for Healthcare Professionals

Aprotinin injection
(marketed as Trasylol)

FDA ALERT [2/2006]: FDA is issuing this alert to provide notice of two recently published studies reporting serious renal and cardiovascular toxicity following Trasylol administration to patients undergoing coronary artery bypass grafting surgery (CABG). An observational study published on January 26, 2006 in *The New England Journal of Medicine* (NEJM), reported that Trasylol may be associated with increased risk of cardiovascular events (myocardial infarction or heart failure), cerebrovascular events such as stroke, encephalopathy or coma, and renal dysfunction or failure. Another publication (*Transfusion*, on-line edition, January 20, 2006) has reported that Trasylol administration may increase the risk for renal toxicity (dysfunction or failure). Neither study was randomized, and both compared Trasylol to products that are not FDA approved for use in the management of cardiac surgery patients.

FDA is evaluating these observational studies in the context of the pre-marketing clinical studies supporting the safety and efficacy of Trasylol and the post-marketing reports submitted to the MedWatch program.

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

Considerations:

Physicians should consider the following:

- Consistent with clinical practice guidelines for patients undergoing CABG, physicians who use Trasylol should carefully monitor for the occurrence of toxicity, particularly to the kidneys, heart, or central nervous system.

- 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 the benefit outweighs the potential risks.

Report serious adverse events to
FDA's MedWatch reporting system by completing a form on line at
http://www.fda.gov/medwatch/report.htm,
by faxing (1-800-FDA-0178),
by mail using the postage-paid address form provided on line
(5600 Fishers Lane, Rockville, MD 20853-9787),
or by telephone (1-800-FDA-1088).
Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570
Druginfo@fda.hhs.gov

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- Physicians should promptly report serious and unexpected adverse events associated with Trasylol to the drug manufacturer (Bayer), or to the FDA MedWatch program, as described at the end of this alert advisory.

Data Summary:

Trasylol is indicated "for prophylactic use to reduce peri-operative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery."

New Study Results from the NEJM

A January 26, 2006 NEJM publication described the findings from an observational study of 4,374 patients (1,295 treated with Trasylol) scheduled for CABG at multiple centers in multiple countries. Baseline and outcome data were prospectively collected from patients who were prescribed either no preventive drug therapy for blood loss or one of three drugs intended to prevent blood loss (Trasylol, aminocaproic acid or tranexamic acid). Patients were not randomized to these treatments. Instead, the choice of study drug (or no treatment) was at physician discretion. Aminocaproic acid and tranexamic acid are anti-fibrinolytic drugs approved by the FDA for indications other than prevention of blood loss in the CABG setting. The following information provides the major findings from the NEJM publication.

- Certain imbalances in baseline characteristics suggest that Trasylol-treated patients may have been sicker at baseline than patients receiving other treatments. To adjust for imbalances in baseline characteristics, the study authors used complex statistical methodology involving propensity scores. The study classified patients as primary (the surgery was elective and involved only coronary artery revascularization or angioplasty, with no history of cardiac or vascular surgery) or complex (all other patients).

- After propensity adjustment, **primary patients** receiving Trasylol had increased risk for the following outcomes when compared to patients who received no preventive drug therapy:

  - a renal event (dialysis or increase in creatinine), $p = 0.006$
  - either myocardial infarction or heart failure, $p = 0.01$

- stroke, encephalopathy, or coma, p = 0.02

- After propensity adjustment, **complex patients** receiving Trasylol had an increased risk for a renal event (dialysis or increase in creatinine, p = 0.004) compared to patients who received no preventive drug therapy. Myocardial infarction, heart failure and stroke risk were not increased among these patients.

- Risks for adverse renal events increased with the administered Trasylol dose.

- All three drug therapies (Trasylol, aminocaproic acid or tranexamic acid) were reported to reduce blood loss to similar extents.

New Study Results from *Transfusion*

A January 20, 2006 *Transfusion* (on-line edition) publication described the findings from an observational study of 898 patients (449 treated with Trasylol) undergoing CABG with cardiopulmonary bypass at a single center. Baseline and outcome data were obtained from a prospectively developed database for these patients. Patients received either Trasylol or tranexamic acid. Patients were not randomized to these treatments. Instead, the choice of study drug was at physician discretion. The 898 patients studied were a subset of a larger group of 10,870 patients selected on the basis of propensity scores to adjust for imbalances in measured baseline characteristics. Major findings from the *Transfusion* publication were:

- In general, the measured baseline characteristics were similar between the two patient groups in the study.

- The rate of renal dysfunction was higher among patients receiving Trasylol than among patients receiving tranexamic acid. The association between Trasylol and renal dysfunction was especially evident in patients with existing renal dysfunction.

- The rates of other adverse events were similar between the two study groups.

- The rate of red blood cell transfusion was similar for the two patient groups.

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Premarketing Studies

The premarketing clinical studies supporting Trasylol safety and efficacy enrolled a total of approximately 3,000 patients (2,002 treated with Trasylol). The studies, including six placebo-controlled trails, consistently showed that Trasylol decreased peri-operative blood loss and the need for blood transfusion. The risks for serious renal and cardiovascular adverse events and deaths were similar between patients receiving Trasylol and those receiving placebo. One study of approximately 800 subjects showed that patients receiving Trasylol had higher rates of coronary graft occlusion than patients receiving a placebo; however, this altered coronary patency was not associated with differences in myocardial infarction and mortality risk between the two study groups. The major pre-market safety signal was a risk for anaphylaxis, especially among subjects re-exposed to Trasylol. The Trasylol label carries a black box warning relating to anaphylaxis.

Implications:

The FDA will work with the authors of the reports and the manufacturer of Trasylol to evaluate the risks and benefits associated with use of Trasylol among patients undergoing cardiopulmonary bypass for CABG surgery. The FDA will notify health care providers and patients in a timely fashion as new information becomes available. Physicians should carefully monitor patients for the occurrence of toxicity and promptly report toxicity to Bayer, the Trasylol manufacturer, or to the FDA MedWatch program.