Information for Healthcare Professionals

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

FDA ALERT [02/2006, Updated 09/2006 and 12/2006]: This Alert highlights important revisions to the full prescribing information for Trasylol. The new labeling for Trasylol (December 2006) has a more focused indication for use, a new Warning about renal dysfunction, a revised Warning about anaphylactic reactions, and a new Contraindication. Trasylol is now indicated only for prophylactic use to reduce peri-operative blood loss and the need for blood transfusion in patients who are at *an increased risk for blood loss and blood transfusion* undergoing cardiopulmonary bypass in the course of coronary artery bypass grafting (CABG) surgery. Trasylol should be administered only in the operative setting where cardiopulmonary bypass can be started quickly. Trasylol should not be administered to any patient with a known or suspected exposure to aprotinin within the past 12 months.

FDA is evaluating additional recently submitted epidemiological safety study data (discussed below), in the context of all other safety and efficacy information available on aprotinin. This review may result in other actions, including additional changes to the full prescribing information (product labeling).

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

The new labeling for Trasylol has a more focused indication, a new Warning about renal dysfunction, a revised Warning about anaphylactic reactions, and a new Contraindication. The new labeling changes are summarized here:

Indication and Usage—more limited and focused

Trasylol is now indicated for use only in patients *who are at increased risk for blood loss and blood transfusion* in association with cardiopulmonary bypass in the course of coronary artery bypass grafting. It should be administered only in the operative setting where cardiopulmonary bypass can be rapidly initiated.

A new Warning about renal dysfunction

Trasylol administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period.

Stronger Warnings about anaphylactic reactions including a new Contraindication for previous aprotinin exposure

Anaphylactic reactions, including fatal reactions, are one of the important risks associated with Trasylol administration. As a consequence of the higher risk for anaphylactic reactions, administration of Trasylol to patients with a known or suspected exposure during the past 12 months is contraindicated.

The new full prescribing information is available here:<INSERT LINK TO NEW LABEL>

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Recommendations and Considerations for physicians:

- Consistent with clinical practice guidelines for patients undergoing CABG surgery, when administering Trasylol, carefully monitor your patient for the occurrence of toxicity, particularly to the kidneys, heart, or central nervous system.

- Limit 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.

- 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 information sheet.

- Monitor patients closely for anaphylactic reactions, even when administering a test dose of Trasylol. Anaphylactic reactions occur more frequently in patients who have been exposed previously to Trasylol or to other aprotinin-containing products (for example, fibrin glues such as Tissucol or Tisseel). The most frequently reported sign of hypersensitivity is hypotension.

Information for the patient:

When a decision to treat a patient with Trasylol has been made, physicians and other healthcare professionals should discuss the following with the patient:

- Because the patient has a higher chance for blood loss and blood transfusion during their upcoming cardiopulmonary bypass during their CABG surgery, they may receive Trasylol during their operation.

- The factors that increase the patient's chance for serious complications include previous treatment with Trasylol (especially within the past 12 months), prior heart surgery, known drug allergies, or known kidney disease.

- Previous treatment with Trasylol increases the chance of experiencing an anaphylactic allergic reaction, which can happen suddenly and can be life threatening or cause death.

- Trasylol can increase the patient's chance of serious kidney problems that could lead to a need for kidney dialysis after surgery. Treatment with Trasylol can also lead to kidney failure.

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Data Summary:

Two articles published in January 2006 reported the results of two new safety studies of Trasylol, which indicated a higher risk of death and serious and/or life-threatening renal and cardiac adverse events following treatment with Trasylol.

Results from a study published in the New England Journal of Medicine

A January 26, 2006, article published in the New England Journal of Medicine (NEJM) described the findings from an observational study of 4,374 patients (1,295 treated with Trasylol) scheduled for CABG surgery 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). The choice of treatment drug (or no treatment) was at physician discretion, rather than through random assignment. Aminocaproic acid and tranexamic acid are anti-fibrinolytic drugs approved by the FDA for indications other than prevention of blood loss in the CABG surgery setting.

In this study, imbalances in measured baseline characteristics suggested that Trasylol-treated patients may have been sicker at baseline than patients receiving other treatments. To adjust for these imbalances, 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).

Compared to those receiving no preventive drug therapy and after propensity adjustment, **primary patients** receiving Trasylol had a higher risk for dialysis or creatinine increase; myocardial infarction or heart failure; or stroke, encephalopathy or coma. Compared to those receiving no preventive drug therapy and after propensity adjustment, **complex patients** receiving Trasylol had a higher risk for dialysis or creatinine increase, but not for heart complications, stroke, encephalopathy or coma. 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 prospective study of 898 patients (449 treated with Trasylol) undergoing CABG surgery with cardiopulmonary bypass at a single center. These patients were selected from a larger group of 10,870 based on their propensity scores that adjusted for imbalances in measured baseline characteristics. Study patients received either Trasylol or tranexamic acid; the choice of treatment drug was made by the patient's treating physician drug rather than through random assignment. 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, especially in those with existing renal dysfunction. The two patient study groups had similar rates of other adverse events and of red blood cell transfusion.

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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 trials, 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.

Post-marketing Spontaneous Reports

Two hundred ninety-one cases of hypersensitivity possibly associated with Trasylol, including 52 cases with fatal outcomes, have been reported to Bayer. A test dose was administered in 139 of the 291 cases. A hypersensitivity reaction occurred with the test dose alone in 81 cases, including 19 fatal cases. Additionally, the test dose did not elicit a reaction among 38 cases (9 fatal) of anaphylaxis that occurred with a therapeutic dose.

A new study, reported to FDA on September 27, 2006

Following a September 21, 2006 discussion of the two published observational studies and other information at an FDA Cardiovascular and Renal Drugs Advisory Committee meeting, Bayer Pharmaceuticals informed FDA of another observational study they had performed using a contract research organization. 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, kidney failure, congestive heart failure and stroke.