DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
Food and Drug Administration
Silver Spring, MD 20993

August 21, 2006

Dear Members, Speakers and Guests:

Thank you for your willingness to participate in the September 21, 2006 Cardiovascular and Renal Drugs Advisory Committee meeting regarding Trasylol® (aprotinin injection).

Trasylol is a proteinase inhibitor drug approved for use among certain patients undergoing coronary artery bypass grafting for the reduction of perioperative blood loss and the need for blood transfusion. This committee meeting is a follow-up to a Public Health Advisory (PHA) issued by the FDA on February 8, 2006. This PHA followed the publication of two observational clinical studies that suggested Trasylol use in clinical practice is associated with important safety concerns. The FDA PHA recommended that physicians should carefully monitor patients for toxicity and promptly report the toxicity. The PHA also noted that 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.

Partially in response to the concerns raised by the published data, additional information has been submitted to the FDA by the Trasylol sponsor. This information will be discussed at the Committee meeting along with the published data. FDA anticipates posing questions relating to the following major topics:

- An assessment of the clinical meaningfulness of the findings from the two published observational clinical studies.
- Perspectives regarding the clinical benefit associated with a reduction in the need for blood transfusion among certain patients undergoing coronary artery bypass grafting, especially in light of current surgical procedures and transfusion practices.
- Perspectives regarding the occurrence of hypersensitivity reactions and the options to lower the risk for these reactions.
- Considerations of potential product label alterations, or other options, to address safety and/or efficacy concerns, in light of current surgical and transfusion practices.

We are providing you an Integrated Executive Summary (attached).

We look forward to your participation and to a productive meeting on September 21, 2006.

Sincerely,

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FDA Advisory Committee Briefing Document
Safety Update
Prepared by the Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
August 21, 2006

Trasylol® (aprotinin injection)
NDA # 20-304; Sponsor: Bayer Pharmaceuticals Corporation

Contents

Executive Summary

Introduction

Trasylol is an intravenously administered proteinase inhibitor drug manufactured from bovine lung. Trasylol has anti-fibrinolytic properties and was initially approved in the United States in 1993 for use among certain patients undergoing coronary artery bypass grafting (CABG). The drug dosage is stated in terms of "KIU" or kallikrein inhibitor units. Notable drug labeling supplements to the application were approved in 1994 and 1998.

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

This Advisory Committee meeting is convened to discuss published clinical data and recently submitted safety information pertaining to the risks and benefits of Trasylol. Specifically, the following topics are the focus of the meeting:

- The findings from two publications of observational clinical studies that assess Trasylol effects.

  -Mangano, D., et. al. The Risk Associated with Aprotinin in Cardiac Surgery. New England Journal of Medicine. 354(4):353-65; January, 2006.

  -Karkouti, K., et. al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion. 46(3): 3:327-38; March, 2006.

- Post-marketing reports of hypersensitivity reactions to Trasylol.

These topics are presented for discussion in order to optimize the usage of Trasylol through potential label modifications or other regulatory mechanisms, including the collection of additional clinical data.

At the Committee meeting, the published clinical data will be presented and discussed by the publication authors. It is important to note that the publication authors assume responsibility for the accuracy, integrity and interpretation of the published clinical data. Hence, the potential strengths and limitations of this type of information should be considered during any evaluation of its usage for regulatory considerations.

The post-marketing reports of hypersensitivity reactions to Trasylol consist of sponsor-verified clinical data submitted to the Trasylol drug application, via submissions consistent with routine post-marketing safety reporting to the FDA.

Trasylol Regulatory History

Summarized below are the most notable aspects of the FDA regulatory actions regarding Trasylol.

1. Original approval: 1993

FDA approved Trasylol in December, 1993 for the relatively limited indication of:

"prophylactic use to reduce perioperative blood loss and the need for transfusion in patients undergoing cardiopulmonary bypass in the course of repeat coronary artery bypass grafting (CABG) surgery. Trasylol is also indicated in selected cases of primary coronary bypass graft surgery where the risk of bleeding is especially high (impaired hemostasis, e.g., presence of aspirin or other coagulopathy) or where transfusion is unavailable or unacceptable. This selected use of Trasylol in primary CABG patients is based on the risk of renal dysfunction and on the risk of anaphylaxis (should a second procedure be needed)."

This approval specifically cited the use of "Regimen A" in the dosage and administration section of the label. Regimen A has subsequently been referred to as "full dose" or the "high dose" regimen. Regimen A consists of a 1 mL test dose (10,000 KIU), a loading dose of 2 million KIU, a "pump prime" dose of 2 million KIU and an intra-operative constant infusion dose of 500,000 KIU/hr.

In support of the original approval, the sponsor submitted clinical data from two confirmatory clinical studies conducted among patients undergoing CABG along with a supportive clinical study that examined the use of Trasylol among patients undergoing cardiac valvular surgery. In addition to "Regimen A," these studies also used a Trasylol "Regimen B" which has subsequently been referred to as "half dose" or "low dose" regimen. Regimen B consists of exactly one-half the dose of Regimen A, following the test dose (i.e., 1 million KIU loading dose, 1 million KIU pump prime dose and a constant intra-operative infusion at 250,000 KIU/hr).

The studies supporting the original approval are summarized in Table 1.

Table 1. Studies submitted in support of the original approval

Study #	Design	Safety n	Regimen	Control	Procedure
D-89-004	R, DB, SC	171	A & B	Placebo	Repeat CABG
D-89-005	R, DB, MC	212	A & B	Placebo	Valvular surgery
D-89-006	R, DB, MC	216	A only	Placebo	Primary and repeat CABG

R = randomized; DB = double blind; SC = single center; MC = multi-center

In the two CABG studies, fewer patients receiving Trasylol required any donor blood when compared to patients receiving placebo. In general, the risk for use of donor blood was reduced by half subsequent to the administration of Trasylol. The major efficacy findings for the groups of subjects undergoing repeat CABG are shown in Table 2.

Table 2. Major efficacy findings in support of the original approval: comparison of the numbers of patients who required donor blood transfusion

Study	Regimen A	Regimen B	Placebo
D-89-004	22/53 (42%)*	23/49 (47%)*	40/52 (77%)
D-89-006	7/23 (30%)*	not studied	23/32 (72%)

*$p \leq 0.002$ compared to placebo

Except for renal data, the safety data generally showed similar adverse event rates among the study groups, including mortality rates. The findings were notable for the observation that 3% of patients experienced "kidney failure" following Trasylol administration while "kidney failure" was reported for 1% of placebo patients. The incidence of "renal dysfunction" was also increased among patients receiving Trasylol when compared to placebo (23% versus 12%). However, the available data supported a determination that the renal dysfunction was reversible.

The original approval findings also included the following observations that were included within the product label:

-An increase in the risk for both renal failure and mortality was detected in a case-controlled clinical study that examined Trasylol use among patients undergoing hypothermic circulatory arrest.

-Trasylol had been found to prolong the activated clotting time (ACT) as measured by the Hemochron method; hence the original review concluded that heparin administration during bypass surgery should be based upon ACT findings from a method that was not altered by the presence of Trasylol in the circulation.

-Although no anaphylactic reactions were reported in the initial confirmatory clinical studies, anaphylactic reactions had been reported in non-USA postmarketing experience for Trasylol.

At the time of the original Trasylol approval in 1993, FDA cited the potential therapeutic advance associated with the use of a drug that decreases the need for blood transfusion, especially in light of considerable concern regarding the infectious risks associated with allogeneic blood. Specifically, the FDA press release noted: "Aprotinin can reduce the risks of bypass surgery for some patients," said FDA Commissioner David A. Kessler, MD. "Fewer transfusions mean a much lower risk of infection or possible adverse reactions to the blood." Notably, donor blood HIV-antibody testing was initiated in 1985; hepatitis C antibody testing in 1990 and HIVp24 antigen testing in 1995.

2. Additional Dosage Regimen Supplement Approval: 1994

In 1994, the sponsor submitted clinical data from Study D-92-008 in order to support the inclusion of Regimen B within the label's dosage section. This study was a randomized, double-blinded, placebo-controlled study that examined Trasylol usage among patients undergoing repeat CABG. Three Trasylol dose regimens were examined: Regimen A, Regimen B and a "pump prime only" regimen that consisted of a dose of 2 million KIU added to the pump-prime only. Overall, 287 patients were enrolled and evaluated for safety. The efficacy evaluation was confined to 254 patients. The safety and efficacy

findings for Regimens A and B were similar to those detected in the earlier confirmatory clinical study that examined these dose regimens. The "pump prime" regimen did not demonstrate efficacy. Based upon this second confirmatory clinical study's findings, the product label was modified to cite the option of either Regimen A or B as an acceptable Trasylol dosage.

3. Broadened Indication and Additional Clinical Data Supplement Approval: 1998

In 1996, the sponsor submitted clinical data from three new confirmatory clinical studies in order to support a change in the product label's indication to cite the use of Trasylol among "patients undergoing cardiopulmonary bypass in the course of CABG surgery." This proposal was to broaden the indication to include all patients undergoing cardiopulmonary bypass for CABG, not solely use among patients undergoing repeat CABG or patients at high risk for bleeding during primary CABG surgery. Table 3 summarizes the three prospective clinical studies submitted in support of the new indication.

Table 3. Studies initially submitted in support of the broader indication

Study #	Design	safety n	Regimen	Control	Procedure
D-91-007	R, DB, SC	99	A & B	Placebo	Primary or repeat CABG
D-92-016	R, DB, MC	704	A, B, pump only	Placebo	Primary CABG
D-92-048	R, DB, MC	873	A	Placebo	Primary CABG

R = randomized; DB = double blind; SC = single center; MC = multi-center

In addition to these prospective studies, the submission included a report from a retrospective study (Study 25504) that reported Trasylol hypersensitivity findings from a group of 387 patients with at least two Trasylol exposures.

Study D-91-007 was a pilot, pharmacodynamic study performed at a single clinical site. Hence, this study was regarded as supportive to the other, more informative clinical studies. The study findings supported the efficacy of Trasylol in reducing blood transfusion requirements.

Study D-92-016 randomized patients with a broad risk of bleeding among placebo and three Trasylol dose regimens. In the study, patients were stratified at randomization based upon the risk for bleeding (high versus low, with predefined risk factors for bleeding) and on the perceived risk for perioperative myocardial infarction (high or low, with predefined criteria). Table 4 shows the major efficacy findings.

Table 4. Study D-92-016 efficacy

Variable	Regimen A n = 160	Regimen B n = 168	Pump Prime n = 159	Placebo n = 157
% requiring blood	33%	35%	33%	52%
Blood units, range	0 - 8	0 - 6	0 - 7	0 - 21

A notable Study D-92-016 observation was the finding that, among the 25% of patients at low risk for bleeding, no statistically significant difference was noted among the groups for the percentage of patients requiring blood transfusion.

Study D-92-016 safety findings showed a slight numeric excess in the rates of myocardial infarction, as denoted by the site investigators (Regimen A 5%; Regimen B 3%; Pump prime 5% and placebo 2%). A blinded adjudication of the myocardial infarction clinical data found only a numeric excess of infarctions in the pump prime group. The rates of post-operative serum creatinine elevations were similar among the study groups.

Study D-92-048 was an international study that randomized primary CABG patients with a broad risk for bleeding to either placebo or Trasylol Regimen A. The study assessed a primary endpoint of saphenous vein graft patency rates as determined by post-CABG coronary arteriography and a secondary endpoint comparison of donor blood transfusion requirements.

The study's primary endpoint result showed more patients with graft closure in the Trasylol group (15%) than in the placebo group (11%). However, the rates for myocardial infarction were similar (Trasylol 2.9% and placebo 3.8%) as were the death rates (Trasylol 1.4% and placebo 1.6%). Exploratory analyses showed the higher rates for graft occlusion were evidenced only at the non-USA sites.

The study showed a statistically favorable effect of Trasylol upon the need for blood transfusion (38% versus 54%) with the treatment effect evident in the subsets of patients either at high or low risk for bleeding.

Study D-92-048 safety findings revealed similar rates of adverse events between the Trasylol and placebo study groups, including similar rates of renal dysfunction.

Study 25504, the retrospective clinical study, suggested that the risk for anaphylaxis was 5% if the re-exposure occurred within six months of the initial exposure. The anaphylaxis risk was 0.9% per re-exposure if the re-exposure occurred after six months. Multiple re-exposures appeared to incrementally increase the risk for anaphylaxis.

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Following review of the clinical data from the three prospective clinical studies and the one retrospective clinical study, FDA issued a non-approvable letter for the supplemental application. The basis for this action related to the following observations: inconsistent primary endpoint subset findings in Study D-92-016; concern regarding the risk for anaphylaxis if patients had received Trasylol at primary CABG but subsequently required Trasylol at a repeat CABG; and study of only the Regimen A in Study D-92-048.

Subsequently, the sponsor highlighted data from two additional clinical studies (Studies SN0406 and SN0407 and submitted an exploratory reanalysis of Study D-92-048 and a proposal to add a black box warning to the product label regarding the risk for anaphylaxis. The additional clinical data included findings from 152 patients at low risk for bleeding who were undergoing primary CABG. Both studies demonstrated a reduction in the need for blood transfusion among patients receiving Trasylol (only the Regimen A was examined). The exploratory re-analysis of Study D-92-048 focused upon subsets of patients identified according to low risk for bleeding as well as USA versus non-USA sites.

FDA determined that the totality of the clinical data, in combination with the revision of the product label to include a black box warning regarding anaphylaxis was acceptable and the supplement was approved in August, 1998. This approved indication is the currently marketed indication.

Publications and Updated Safety and Efficacy Information

1. Publications, including FDA Comments:

Summarized below are highlights from 2006 publications and FDA public comments. Copies of the publications are provided in the Appendix. Some of these publications cite the use of tranexamic acid and aminocaproic acid, two drugs with anti-fibrinolytic activity. These two drugs are not FDA-approved for use during cardiac surgery. The FDA-approved indications for these two drugs are the following:

> -Tranexamic acid: for use "in patients with hemophilia for short term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction."
>
> -Aminocaproic acid: for "enhancing hemostasis when fibrinolysis contributes to bleeding."

Also included in the appendix is an abstract publication of an on-going clinical study that compares the usage of aprotinin to aminocaproic acid and tranexamic acid (the BART study, "Blood conservation using antifibrinolytics: randomized trial in high-risk cardiac surgery"). Only summary (non-comparative) information is available from this study.

New England Journal of Medicine publication: In January, 2006 Mangano, et.al. published a report of a multi-center observational clinical study that compared the use of aprotinin to the use of two other drugs with anti-fibrinolytic activities (aminocaproic acid and tranexamic acid) as well as the use of no anti-fibrinolytic drug. In this study, 4374 patients undergoing coronary revascularization were assessed following the assignment of each patient to the physician-prescribed anti-fibrinolytic drug regimen (patients were not randomized to the study drugs or the no drug regimen). In order to adjust for imbalances in baseline characteristics, the study authors used propensity-adjustment methodology in multivariable logistic regression analyses of important study outcomes among the study groups. The authors reported that, for patients undergoing "complex" or primary coronary artery surgery, aprotinin administration was associated with a doubling in the risk of renal failure requiring dialysis. Additionally, aprotinin administration to patients undergoing primary coronary artery surgery was associated with a 55 percent increase in the risk of myocardial infarction or heart failure and a 181 percent increase in the risk of stroke or encephalopathy. All three anti-fibrinolytic drugs were reported to reduce blood loss.

Transfusion publication: In March, 2006 Karkouti, et.al. published (following an earlier, on-line publication) a report of a single center observational clinical study that compared the use of aprotinin to tranexamic acid among high-transfusion risk patients. In this study, patients undergoing cardiac surgery with cardiopulmonary bypass were assessed following the assignment of each patient to the physician-prescribed anti-fibrinolytic drug (as in the prior publication, patients were not randomized to the study drugs). Using propensity scores, 449 patients who received aprotinin were matched to

449 patients who received tranexamic acid. The study reported that all adverse events occurred at similar rates, except for renal dysfunction which occurred in 24% aprotinin-exposed patients and 17% tranexamic acid patients.

FDA comments: In February, 2006 FDA issued a Public Health Advisory regarding Trasylol. In this Advisory, FDA anticipated a public discussion of the publication findings and also recommended that physicians who use Trasylol should:

> -carefully monitor patients for the occurrence of toxicity and report important findings to the drug manufacturer and FDA;
>
> -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.

2. Updated Safety and Efficacy Information:

Bayer, the holder of the Trasylol NDA has submitted updated safety and efficacy information pertaining to Trasylol clinical studies and post-marketing reports. This information, submitted over the past few months, includes integrated analyses from the world-wide safety experience in cardiac surgery as well as clinical study experience for the use of Trasylol in the prevention of bleeding associated with non-cardiac surgery. Bayer will summarize these findings at the Advisory Committee meeting and the details are not repeated here. Cited below is a brief summary of the sponsor's findings with a special notation regarding hypersensitivity reactions.

Integrated safety and efficacy information: Overall, the sponsor's updated analyses of safety and efficacy findings from the controlled clinical trial experience in CABG appear consistent with the previously reported findings.

The integrated efficacy analyses continue to show that Trasylol administration decreases the rate of blood transfusion among patients undergoing CABG with cardiopulmonary bypass.

Notable summary findings from the updated and integrated safety findings of the controlled clinical studies are:

- The global CABG studies show similar mortality rates between control patients and patients receiving full dose Trasylol during CABG (2.9% among 2249 Trasylol patients and 2.5% among 2164 control patients). In this patient population, congestive heart failure rates are also reported as similar (6.3% among Trasylol patients and 5.9% among placebo patients).

- Myocardial infarction rates in the clinical studies that rigorously ascertained the events showed similar rates (11% among 642 full dose Trasylol patients and 11% among 656 placebo patients).

- In the US CABG studies, the rate of renal failure was similar between control patients and patients receiving full dose Trasylol (1.9% among 862 Trasylol patients and 1.9% among 861 placebo patients). In these studies, renal dysfunction rates were 6.6% (57/862) for full dose Trasylol and 6.0% (52/861) for

placebo. More limited controlled data are available for comparisons of renal dysfunction among patients receiving full versus half dose Trasylol versus placebo, as follows: 9.1% (29/318) for full dose Trasylol; 7.6% (24/317) for half-dose Trasylol; 7.2% (23/319) for placebo.

- Analyses disclose very limited controlled clinical study data for patients with baseline serum creatinine values greater than 2 mg/dL (only 9 patients exposed to Trasylol versus 1 placebo patient, among US CABG patients).

Hypersensitivity reactions: The sponsor has supplied a summary of Trasylol-related hypersensitivity reports from 1984 through 2005. This analysis found a higher than anticipated reporting rate for reactions during 2005. Using Poisson analysis and estimates of product usage, the sponsor reports that spontaneous reports of hypersensitivity reactions increased from 2004 (21/409,783) to 2005 (54/471,922). This increase was mainly driven by an increase in the reporting rate of possibly associated non-fatal cases from the US. However, the number of reports of fatal hypersensitivity reactions increased from 4 in 2004 to 10 in 2005.

FDA has special concerns regarding the findings from the sponsor's summary of hypersensitivity reactions. These concerns relate specifically to the occurrence of fatal hypersensitivity reactions as well as to concerns regarding the utility of the "test" Trasylol dose procedure in light of the apparent failure to predict fatal hypersensitivity reactions. Notably, this test dose administration alone was reported to result in 19 deaths (included among a total of 51 deaths associated with Trasylol hypersensitivity reactions).

In response to the hypersensitivity reports, the sponsor has proposed a risk minimization plan that focuses upon additional physician education and outreach efforts regarding the risk for hypersensitivity reactions, specifically encouraging more in-depth history taking regarding any prior exposure to aprotinin. Additionally, Bayer proposes the development of a blood test for the detection of IgG antibodies to aprotinin. This test is proposed for use as a biomarker to detect patients who had previously been exposed to aprotinin. The blood test is currently in a developmental stage.

Summarized below are major observations regarding Trasylol hypersensitivity findings:

Incidence: The sponsor estimates a total exposure of 4.3 million patients to Trasylol from 1984 through 2005. To date, 304 cases of suspected hypersensitivity reactions were identified within the sponsor's global drug safety database. Independent adjudication of these 304 cases estimated that 284 of the cases were hypersensitivity reactions possibly associated with Trasylol (51 were fatal and 233 were non-fatal).

Risk factors: Given the limitations of the case reports, the following observations are especially notable:

-133/284 (47%) cases had documented previous exposure to Trasylol; of the 51 fatalities that were adjudicated and assessed as possibly associated, previous aprotinin exposure could be documented in 28 cases.

-90/107 (84%) cases in which the time of previous exposure was documented had received the drug in the previous six months.

-38/139 (27%) cases in which the test dose administration was documented experienced a hypersensitivity reaction despite a negative test dose result.

-the majority of cases in which the surgical procedure was documented were in the setting of procedures other than CABG surgery.

-aprotinin is contained with certain fibrin sealants, including Tisseel®, a product marketed in the US with an indication for "use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligation, and cautery is ineffective or impractical."

A publication that cites a summary of 124 hypersensitivity reactions is included in the appendix. This publication cites several risk factors for hypersensitivity reactions, including ones similar to those the sponsor has identified. The publication authors propose that the risk for a hypersensitivity reaction is greatest within the first several months following an initial aprotinin exposure, as shown in the figure, below. In the figure, the number of hypersensitivity reactions is shown on the vertical axis and the time span between repeated aprotinin injections is shown on the horizontal axis.

The publication also outlines the concepts that suggest the detection of IgG antibodies to aprotinin may serve as a biomarker for prior exposure. The publication notes that the low concentration of IgE, as well as its relatively short half-life, may limit its usefulness in an assay that attempts to detect prior aprotinin exposure.

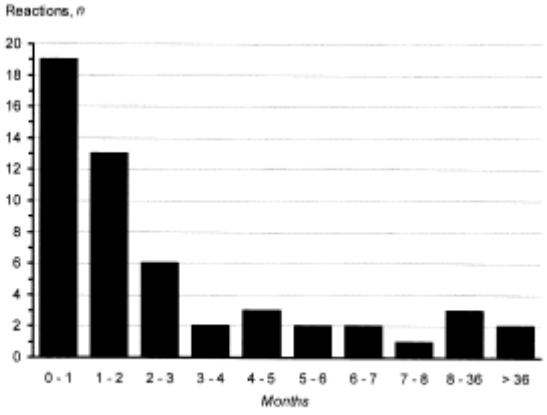

Fig 2. Time spans between repeated aprotinin exposures.

Test dose considerations: The product label cites the intravenous administration of a 10000 KIU (1 mL) intravenous "test dose" at least 10 minutes prior to the loading dose. The label notes that hypersensitivity reactions can range from skin eruptions, itching, dyspnea, nausea and tachycardia to fatal anaphylactic shock and physicians are to observe patients for the appearance of these signs and symptoms. To date, 19 patients are reported to have died after administration of the test dose alone.

Appendix: Publications

1. Mangano, D., et.al., The Risk Associated with Aprotinin in Cardiac Surgery. New England Journal of Medicine. 354(4):353-65; January, 2006.

2. Karkouti, K., et. al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion. 46(3): 3:327-38; March, 2006.

3. FDA Public Health Advisory, February, 2006.

4. Beierlein, W. Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. Annals of Thoracic Surgery; 79:741-8; 2005.

5. Fergusson, M., et.al, Incidence of massive bleeding in a blinded randomized controlled trial of antifibrinolytic drugs in high risk cardiac surgery. Anesth Analg. 102: SCA1-97; 2006.

FDA Public Health Advisory

Aprotinin Injection (marketed as Trasylol)

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.

Date created: February 8, 2006

Information for Healthcare Professionals
Aprotinin (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.
- 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.

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.

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

Topics for Committee Questions

FDA anticipates posing questions relating to the following major topics:

1. An assessment of the clinical meaningfulness of the findings from the two published observational clinical studies.

2. Perspectives regarding the clinical benefit associated with a reduction in the need for blood transfusion among certain patients undergoing coronary artery bypass grafting, especially in light of current surgical procedures and transfusion practices.

3. Perspectives regarding the occurrence of hypersensitivity reactions and the options to lower the risk for these reactions.

4. Considerations of potential product label alterations, or other options, to address safety and/or efficacy concerns, in light of current surgical and transfusion practices.

TRASYLOL®
(aprotinin injection)

01298181 12/03

Anaphylactic or anaphylactoid reactions are possible when Trasylol® is administered. Hypersensitivity reactions are rare in patients with no prior exposure to aprotinin. The risk of anaphylaxis is increased in patients who are re-exposed to aprotinin-containing products. The benefit of Trasylol® to patients undergoing primary CABG surgery should be weighed against the risk of anaphylaxis should a second exposure to aprotinin be required. (See WARNINGS and PRECAUTIONS).

DESCRIPTION

Trasylol® (aprotinin injection), $C_{284}H_{432}N_{84}O_{79}S_7$, is a natural proteinase inhibitor obtained from bovine lung. Aprotinin (molecular weight of 6512 daltons), consists of 58 amino acid residues that are arranged in a single polypeptide chain, cross-linked by three disulfide bridges. It is supplied as a clear, colorless, sterile isotonic solution for intravenous administration. Each milliliter contains 10,000 KIU (Kallikrein Inhibitor Units) (1.4 mg/mL) and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide is used to adjust the pH to 4.5-6.5.

CLINICAL PHARMACOLOGY

Mechanism of Action: Aprotinin is a broad spectrum protease inhibitor which modulates the systemic inflammatory response (SIR) associated with cardiopulmonary bypass (CPB) surgery. SIR results in the interrelated activation of the hemostatic, fibrinolytic, cellular and humoral inflammatory systems. Aprotinin, through its inhibition of multiple mediators [e.g., kallikrein, plasmin] results in the attenuation of inflammatory responses, fibrinolysis, and thrombin generation.

Aprotinin inhibits pro-inflammatory cytokine release and maintains glycoprotein homeostasis. In platelets, aprotinin reduces glycoprotein loss (e.g., GpIb, GpIIb/IIIa), while in granulocytes it prevents the expression of pro-inflammatory adhesive glycoproteins (e.g., CD11b).

The effects of aprotinin use in CPB involves a reduction in inflammatory response which translates into a decreased need for allogeneic blood transfusions, reduced bleeding, and decreased mediastinal re-exploration for bleeding.

Pharmacokinetics: The studies comparing the pharmacokinetics of aprotinin in healthy volunteers, cardiac patients undergoing surgery with cardiopulmonary bypass, and women undergoing hysterectomy suggest linear pharmacokinetics over the dose range of 50,000 KIU to 2 million KIU. After intravenous (IV) injection, rapid distribution of aprotinin occurs into the total extracellular space, leading to a rapid initial decrease in plasma aprotinin concentration. Following this distribution phase, a plasma half-life of about 150 minutes is observed. At later time points, (i.e., beyond 5 hours after dosing) there is a terminal elimination phase with a half-life of about 10 hours.

Average steady state intraoperative plasma concentrations were 137 KIU/mL (n=10) after administration of the following dosage regimen: 1 million KIU IV loading dose, 1 million KIU into the pump prime volume, 250,000 KIU per hour of operation as continuous intravenous infusion (Regimen B). Average steady state intraoperative plasma concentrations were 250 KIU/mL in patients (n=20) treated with aprotinin during cardiac surgery by administration of Regimen A (exactly double Regimen B): 2 million KIU IV loading dose, 2 million KIU into the pump prime volume, 500,000 KIU per hour of operation as continuous intravenous infusion.

Following a single IV dose of radiolabelled aprotinin, approximately 25-40% of the radioactivity is excreted in the urine over 48 hours. After a 30 minute infusion of 1 million KIU, about 2% is excreted as unchanged drug. After a larger dose of 2 million KIU infused over 30 minutes, urinary excretion of unchanged aprotinin accounts for approximately 9% of the dose. Animal studies have shown that aprotinin is accumulated primarily in the kidney. Aprotinin, after being filtered by the glomeruli, is actively reabsorbed by the proximal tubules in which it is stored in phagolysosomes.

Aprotinin is slowly degraded by lysosomal enzymes. The physiological renal handling of aprotinin is similar to that of other small proteins, e.g., insulin.

CLINICAL TRIALS

Repeat Coronary Artery Bypass Graft Patients:

Four placebo-controlled, double-blind studies of Trasylol® were conducted in the United States; of 540 randomized patients undergoing repeat coronary artery bypass graft (CABG) surgery, 480 were valid for efficacy analysis. The following treatment regimens were used in the studies:

Trasylol® Regimen A (2 million KIU IV loading dose, 2 million KIU into the pump prime volume, and 500,000 KIU per hour of surgery as a continuous intravenous infusion); Trasylol® Regimen B (1 million KIU IV loading dose, 1 million KIU into the pump prime volume, and 250,000 KIU per hour of surgery as a continuous intravenous infusion); a pump prime regimen (2 million KIU into the pump prime volume only); and a placebo regimen (normal saline). All patients valid for efficacy in the above studies were pooled by treatment regimen for analyses of efficacy.

In this pooled analysis, fewer patients receiving Trasylol®, either Regimen A or Regimen B, required any donor blood compared to the pump prime only or placebo regimens. The number of units of donor blood required by patients, the volume (milliliters) of donor blood transfused, the number of units of donor blood products transfused, the thoracic drainage rate, and the total thoracic drainage volumes were also reduced in patients receiving Trasylol® as compared to placebo.

Efficacy Variables: Repeat CABG Patients
Mean (S.D.) or % of Patients

VARIABLE	PLACEBO REGIMEN N=156	Trasylol® PUMP PRIME REGIMEN† N=68	Trasylol® REGIMEN B** N=113	Trasylol® REGIMEN A** N=143
% OF REPEAT CABG PATIENTS WHO REQUIRED DONOR BLOOD	76.3%	72.1%	48.7%	46.9%
UNITS OF DONOR BLOOD TRANSFUSED	3.7 (4.4)	2.5 (2.4)	2.2 (5.0)*	1.6 (2.9)*
mL OF DONOR BLOOD TRANSFUSED	1132 (1443)	756 (807)	723 (1779)*	515 (999)*
PLATELETS TRANSFUSED (Donor Units)	5.0 (10.0)	2.1 (4.6)*	1.3 (4.6)*	0.9 (4.3)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.9 (3.5)	0.0 (0.0)*	0.5 (4.0)	0.1 (0.8)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	1.3 (2.5)	0.5 (1.4)*	0.3 (1.1)*	0.2 (0.9)*
THORACIC DRAINAGE RATE (mL/hr)	89 (77)	73 (69)	66 (244)	40 (36)*
TOTAL THORACIC DRAINAGE VOLUME (mL)[a]	1659 (1226)	1561 (1370)	1103 (2001)*	960 (849)*
REOPERATION FOR DIFFUSE BLEEDING	1.9%	2.9%	0%	0%

† The pump prime regimen was evaluated in only one study in patients undergoing repeat CABG surgery. Note: The pump prime only regimen is not an approved dosage regimen.

* Significantly different from placebo, $p<0.05$
(Transfusion variables analyzed via ANOVA on ranks)

** Differences between Regimen A (high dose) and Regimen B (low dose) in efficacy and safety are not statistically significant.

[a] Excludes patients who required reoperation

Primary Coronary Artery Bypass Graft Patients:

Four placebo-controlled, double-blind studies of Trasylol® were conducted in the United States; of 1745 randomized patients undergoing primary CABG surgery, 1599 were valid for efficacy analysis. The dosage regimens used in these studies were identical to those used in the repeat CABG studies described above (Regimens A, B, pump prime, and placebo). All patients valid for efficacy were pooled by treatment regimen.

In this pooled analysis, fewer patients receiving Trasylol® Regimens A, B, and pump prime required any donor blood in comparison to the placebo regimen. The number of units of donor blood required by patients, the volume of donor blood transfused, the number of units of donor blood products transfused, the thoracic drainage rate, and total thoracic drainage volumes were also reduced in patients receiving Trasylol® as compared to placebo.

Efficacy Variables: Primary CABG Patients
Mean (S.D.) or % of Patients

VARIABLE	PLACEBO REGIMEN N=624	Trasylol® PUMP PRIME REGIMEN† N=159	Trasylol® REGIMEN B** N=175	Trasylol® REGIMEN A** N=641
% OF PRIMARY CABG PATIENTS WHO REQUIRED DONOR BLOOD	53.5%	32.7%*	37.1%*	36.8%*
UNITS OF DONOR BLOOD TRANSFUSED	1.7 (2.4)	0.9 (1.6)*	1.0 (1.6)*	0.9 (1.4)*
mL OF DONOR BLOOD TRANSFUSED	584 (840)	286 (518)*	313 (505)*	295 (503)*
PLATELETS TRANSFUSED (Donor Units)	1.3 (3.7)	0.5 (2.4)*	0.3 (1.6)*	0.3 (1.5)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.5 (2.2)	0.0 (0.0)*	0.1 (0.8)*	0.0 (0.0)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	0.6 (1.7)	0.2 (1.7)*	0.2 (0.8)*	0.2 (0.9)*
THORACIC DRAINAGE RATE (mL/hr)	87 (67)	51 (36)*	45 (31)*	39 (32)*
TOTAL THORACIC DRAINAGE VOLUME (mL)	1232 (711)	852 (653)*	792 (465)*	705 (493)*
REOPERATION FOR DIFFUSE BLEEDING	1.4%	0.6%	0%	0%*

† The pump prime regimen was evaluated in only one study in patients undergoing primary CABG surgery. Note: The pump prime only regimen is not an approved dosage regimen.

* Significantly different from placebo, $p<0.05$
(Transfusion variables analyzed via ANOVA on ranks)

** Differences between Regimen A (high dose) and Regimen B (low dose) in efficacy and safety are not statistically significant.

Additional subgroup analyses showed no diminution in benefit with increasing age. Male and female patients benefited from Trasylol® with a reduction in the average number of units of donor blood transfused. Although male patients did better than female patients in terms of the percentage of patients who required any donor blood transfusions, the number of female patients studied was small.

A double-blind, randomized, Canadian study compared Trasylol® Regimen A (n=28) and placebo (n=23) in primary cardiac surgery patients (mainly CABG) requiring cardiopulmonary bypass who were treated with aspirin within 48 hours of surgery. The mean total blood loss (1209.7 mL vs. 2532.3 mL) and the mean number of units of packed red blood cells transfused (1.6 units vs 4.3 units) were significantly less ($p<0.008$) in the Trasylol® group compared to the placebo group.

In a U.S. randomized study of Trasylol® Regimen A and Regimen B versus the placebo regimen in 212 patients undergoing primary aortic and/or mitral valve replacement or repair, no benefit was found for Trasylol® in terms of the need for transfusion or the number of units of blood required.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Hypersensitivity to aprotinin.

WARNINGS

Anaphylactic or anaphylactoid reactions are possible when Trasylol® is administered. Hypersensitivity reactions are rare in patients with no prior exposure to aprotinin. Hypersensitivity reactions can range from skin eruptions, itching, dyspnea, nausea and tachycardia to fatal anaphylactic shock with circulatory failure. If a hypersensitivity reaction occurs during injection or infusion of Trasylol®, administration should be stopped immediately and emergency treatment should be initiated. It should be noted that severe (fatal) hypersensitivity/anaphylactic reactions can also occur in connection with application of the test dose. Even when a second exposure to aprotinin has been tolerated without symptoms, a subsequent administration may result in severe hypersensitivity/anaphylactic reactions.

Re-exposure to aprotinin: In a retrospective review of 387 European patient records with documented re-exposure to Trasylol®, the incidence of hypersensitivity/anaphylactic reactions was 2.7%. Two patients who experienced hypersensitivity/anaphylactic reactions subsequently died, 24 hours and 5 days after surgery, respectively. The relationship of these 2 deaths to Trasylol® is unclear. This retrospective review also showed that the incidence of a hypersensitivity or anaphylactic reaction following re-exposure is increased when the re-exposure occurs within 6 months of the initial administration (5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months). Other smaller studies have shown that in case of re-exposure, the incidence of hypersensitivity/anaphylactic reactions may reach the five percent level.

Before initiating treatment with Trasylol® in a patient with a history of prior exposure to aprotinin or products containing aprotinin, the recommendations below should be followed to manage a potential hypersensitivity or anaphylactic reaction: 1) Have standard emergency treatments for hypersensitivity or anaphylactic reactions readily available in the operating room (e.g., epinephrine, corticosteroids). 2) Administration of the test dose and loading dose should be done only when the conditions for rapid cannulation (if necessary) are present. 3) Delay the addition of Trasylol® into the pump prime solution until after the loading dose has been safely administered.

Additionally, administration of H1 and H2 blockers 15 minutes before the test dose may be considered.

PRECAUTIONS

General: *Test Dose:* All patients treated with Trasylol® should first receive a test dose to assess the potential for allergic reactions. The test dose of 1 mL Trasylol® should be administered intravenously at least 10 minutes prior to the loading dose. However, even after the uneventful administration of the initial 1 mL test-dose, the therapeutic dose may cause an anaphylactic reaction. If this happens the infusion of aprotinin should immediately be stopped, and standard emergency treatment for anaphylaxis be applied. It should be noted that hypersensitivity/ anaphylactic reactions can also occur in connection with application of the test-dose. (see WARNINGS)

Allergic Reactions: Patients with a history of allergic reactions to drugs or other agents may be at greater risk of developing a hypersensitivity or anaphylactic reaction upon exposure to Trasylol®. (see WARNINGS)

Loading Dose: The loading dose of Trasylol® should be given intravenously to patients in the supine position over a 20-30 minute period. Rapid intravenous administration of Trasylol® can cause a transient fall in blood pressure. (see DOSAGE AND ADMINISTRATION).

Use of Trasylol® in patients undergoing deep hypothermic circulatory arrest: Two U.S. case control studies have reported contradictory results in patients receiving Trasylol® while undergoing deep hypothermic circulatory arrest in connection with surgery of the aortic arch.

The first study showed an increase in both renal failure and mortality compared to age-matched historical controls. Similar results were not observed, however, in a second case control study. The strength of this association is uncertain because there are no data from randomized studies to confirm or refute these findings.

Drug Interactions: Trasylol® is known to have antifibrinolytic activity and, therefore, may inhibit the effects of fibrinolytic agents.

In study of nine patients with untreated hypertension, Trasylol® infused intravenously in a dose of 2 million KIU over two hours blocked the acute hypotensive effect of 100mg of captopril.

Trasylol®, in the presence of heparin, has been found to prolong the activated clotting time (ACT) as measured by a celite surface activation method. The kaolin activated clotting time appears to be much less affected. However, Trasylol® should not be viewed as a heparin sparing agent. (see Laboratory Monitoring of Anticoagulation During Cardiopulmonary Bypass).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies to evaluate the carcinogenic potential of Trasylol® or studies to determine the effect of Trasylol® on fertility have not been performed.

Results of microbial *in vitro* tests using *Salmonella typhimurium* and *Bacillus subtilis* indicate that Trasylol® is not a mutagen.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats at intravenous doses up to 200,000 KIU/kg/day for 11 days, and in rabbits at intravenous doses up to 100,000 KIU/kg/day for 13 days, 2.4 and 1.2 times the human dose on a mg/kg basis and 0.37 and 0.36 times the human mg/m^2 dose. They have revealed no evidence of impaired fertility or harm to the fetus due to Trasylol®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mother: Not applicable.

Pediatric Use: Safety and effectiveness in pediatric patient(s) have not been established.

Geriatric Use: Of the total of 3083 subjects in clinical studies of Trasylol®, 1100 (35.7 percent) were 65 and over, while 297 (9.6 percent) were 75 and over. Of patients 65 years and older, 479 (43.5 percent) received Regimen A and 237 (21.5 percent) received Regimen B. No overall differences in safety or effectiveness were observed between these subjects and younger subjects for either dose regimen, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Laboratory Monitoring of Anticoagulation during Cardiopulmonary Bypass: Trasylol® prolongs whole blood clotting times by a different mechanism than heparin. In the presence of aprotinin, prolongation is dependent on the type of whole blood clotting test employed. If an activated clotting time (ACT) is used to determine the effectiveness of heparin anticoagulation, the prolongation of the ACT by aprotinin may lead to an overestimation of the degree of anticoagulation, thereby leading to inadequate anticoagulation. During extended extracorporeal circulation, patients may require additional heparin, even in the presence of ACT levels that appear adequate.

In patients undergoing CPB with Trasylol® therapy, one of the following methods may be employed to maintain adequate anticoagulation:

1) ACT - An ACT is not a standardized coagulation test, and different formulations of the assay are affected differently by the presence of aprotinin. The test is further influenced by variable dilution effects and the temperature experienced during cardiopulmonary bypass. It has been observed that Kaolin-based ACTs are not increased to the same degree by aprotinin as are diatomaceous earth-based (celite) ACTs. While protocols vary, a minimal celite ACT of 750 seconds or kaolin-ACT of 480 seconds, independent of the effects of hemodilution and hypothermia, is recommended in the presence of aprotinin. Consult the manufacturer of the ACT test regarding the interpretation of the assay in the presence of Trasylol®.

2) Fixed Heparin Dosing - A standard loading dose of heparin, administered prior to cannulation of the heart, plus the quantity of heparin added to the prime volume of the CPB circuit, should total at least 350 IU/kg. Additional heparin should be administered in a fixed-dose regimen based on patient weight and duration of CPB.

3) Heparin Titration - Protamine titration, a method that is not affected by aprotinin, can be used to measure heparin levels. A heparin dose response, assessed by protamine titration, should be performed prior to administration of aprotinin to determine the heparin loading dose. Additional heparin should be administered on the basis of heparin levels measured by protamine titration. Heparin levels during bypass should not be allowed to drop below 2.7 U/mL (2.0 mg/kg) or below the level indicated by heparin dose response testing performed prior to administration of aprotinin.

Protamine Administration - In patients treated with Trasylol®, the amount of protamine administered to reverse heparin activity should be based on the actual amount of heparin administered, and not on the ACT values.

ADVERSE REACTIONS

Studies of patients undergoing CABG surgery, either primary or repeat, indicate that Trasylol® is generally well tolerated. The adverse events reported are frequent sequelae of cardiac surgery and are not necessarily attributable to Trasylol® therapy. Adverse events reported, up to the time of hospital discharge, from patients in US placebo-controlled trials are listed in the following table. The table lists only those events that were reported in 2% or more of the Trasylol® treated patients without regard to causal relationship.

INCIDENCE RATES OF ADVERSE EVENTS (> = 2%) BY BODY SYSTEM AND TREATMENT FOR ALL PATIENTS FROM US PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Aprotinin (n = 2002) values in %	Placebo (n = 1084) values in %
Any Event	76	77
Body as a Whole		
Fever	15	14
Infection	6	7
Chest Pain	2	2
Asthenia	2	2
Cardiovascular		
Atrial Fibrillation	21	23
Hypotension	8	10

Myocardial Infarct	6	6
Atrial Flutter	6	5
Ventricular Extrasystoles	6	4
Tachycardia	6	7
Ventricular Tachycardia	5	4
Heart Failure	5	4
Pericarditis	5	5
Peripheral Edema	5	5
Hypertension	4	5
Arrhythmia	4	3
Supraventricular Tachycardia	4	3
Atrial Arrhythmia	3	3

Adverse Event	Aprotinin (n = 2002) values in %	Placebo (n = 1084) values in %
Digestive		
Nausea	11	9
Constipation	4	5
Vomiting	3	4
Diarrhea	3	2
Liver Function Tests Abnormal	3	2
Hemic and Lymphatic		
Anemia	2	8
Metabolic & Nutritional		
Creatine Phosphokinase Increased	2	1
Musculoskeletal		
Any Event	2	3
Nervous		
Confusion	4	4
Insomnia	3	4
Respiratory		
Lung Disorder	8	8
Pleural Effusion	7	9
Atelectasis	5	6
Dyspnea	4	4
Pneumothorax	4	4
Asthma	2	3
Hypoxia	2	1
Skin and Appendages		
Rash	2	2
Urogenital		
Kidney Function Abnormal	3	2
Urinary Retention	3	3
Urinary Tract Infection	2	2

In comparison to the placebo group, no increase in mortality in patients treated with Trasylol® was observed. Additional events of particular interest from controlled US trials with an incidence of less that 2%, are listed below:

EVENT	Percentage of patients treated with Trasylol N = 2002	Percentage of patients treated with Placebo N = 1084
Thrombosis	1.0	0.6
Shock	0.7	0.4
Cerebrovascular Accident	0.7	2.1
Thrombophlebitis	0.2	0.5
Deep Thrombophlebitis	0.7	1.0
Lung Edema	1.3	1.5
Pulmonary Embolus	0.3	0.6
Kidney Failure	1.0	0.6
Acute Kidney Failure	0.5	0.6
Kidney Tubular Necrosis	0.8	0.4

Listed below are additional events, from controlled US trials with an incidence between 1 and 2%, and also from uncontrolled, compassionate use trials and spontaneous post-marketing reports. Estimates of frequency cannot be made for spontaneous post-marketing reports *(italicized)*.

Body as a Whole: Sepsis, death, multi-system organ failure, immune system disorder, *hemoperitoneum*.

Cardiovascular: Ventricular fibrillation, heart arrest, bradycardia, congestive heart failure, hemorrhage, bundle branch block, myocardial ischemia, ventricular tachycardia, heart block, pericardial effusion, ventricular arrhythmia, shock, pulmonary hypertension.

Digestive: Dyspepsia, gastrointestinal hemorrhage, jaundice, hepatic failure.

Hematologic and Lymphatic: Although thrombosis was not reported more frequently in aprotinin versus placebo-treated patients in controlled trials, it has been reported in uncontrolled trials, compassionate use trials, and spontaneous post-marketing reporting. These reports of thrombosis encompass the following terms: thrombosis, occlusion, arterial thrombosis, *pulmonary thrombosis*, coronary occlusion, embolus, pulmonary embolus, thrombophlebitis, deep thrombophlebitis, cerebrovascular accident, cerebral embolism. Other hematologic events reported include leukocytosis, thrombocytopenia, coagulation disorder (which includes disseminated intravascular coagulation), decreased prothombin.

Metabolic and Nutritional: Hyperglycemia, hypokalemia, hypervolemia, acidosis.

Musculoskeletal: Arthralgia.

Nervous: Agitation, dizziness, anxiety, convulsion.

Respiratory: Pneumonia, apnea, increased cough, lung edema.

Skin: *Skin discoloration*.

Urogenital: Oliguria, kidney failure, acute kidney failure, kidney tubular necrosis.

Myocardial Infarction: In the pooled analysis of all patients undergoing CABG surgery, there was no significant difference in the incidence of investigator-reported myocardial infarction (MI) in Trasylol® treated patients as compared to placebo treated patients. However, because no uniform criteria for the diagnosis of myocardial infarction were utilized by investigators, this issue was addressed prospectively in three later studies (two studies evaluated Regimen A, Regimen B and Pump Prime Regimen; one study evaluated only Regimen A), in which data were analyzed by a blinded consultant employing an algorithm for possible, probable or definite MI. Utilizing this method, the incidence of definite myocardial infarction was 5.9% in the aprotinin-treated patients versus 4.7% in the placebo treated patients. This difference in the incidence rates was not statistically significant. Data from these three studies are summarized below.

Incidence of Myocardial Infarctions by Treatment Group Population:
All CABG Patients Valid for Safety Anaylsis

Treatment	Definite MI %	Definite or Probable MI %	Definite, Probable or Possible MI %
Pooled Data from Three Studies that Evaluated Regimen A			
Trasylol® Regimen A n = 646	4.6	10.7	14.1
Placebo n = 661	4.7	11.3	13.4
Pooled Data from Two Studies that Evaluated Regimen B and Pump Prime Regimen			
Trasylol® Regimen B n = 241	8.7	15.9	18.7
Trasylol® Pump Prime Regimen n = 239	6.3	15.7	18.1
Placebo n = 240	6.3	15.1	15.8

Graft Patency: In a recently completed multi-center, multi-national study to determine the effects of Trasylol® Regimen A vs. placebo on saphenous vein graft patency in patients undergoing primary CABG surgery, patients were subjected to routine postoperative angiography. Of the 13 study sites, 10 were in the United States and three were non-U.S. centers (Denmark (1), Israel (2)). The results of this study are summarized below.

Incidence of Graft Closure, Myocardial Infarction and Death by Treatment Group

	Overall Closure Rates*		Incidence of MI**	Incidence of Death***
	All Centers n = 703 %	U.S. Centers n = 381 %	All Centers n = 831 %	All Centers n = 870 %
Trasylol®	15.4	9.4	2.9	1.4
Placebo	10.9	9.5	3.8	1.6
CI for the Difference (%) (Drug - Placebo)	(1.3, 9.6)†	(-3.8, 5.9)†	-3.3 to 1.5‡	-1.9 to 1.4‡

* Population: all patients with assessable saphenous vein grafts
** Population: all patients assessable by blinded consultant
*** All patients
† 90%; per protocol
‡ 95%; not specified in protocol

Although there was a statistically significantly increased risk of graft closure for Trasylol® treated patients compared to patients who received placebo (p=0.035), further analysis showed a significant treatment by site interaction for one of the non-U.S. sites vs. the U.S. centers. When the analysis of graft closures was repeated for U.S. centers only, there was no statistically

significant difference in graft closure rates in patients who received Trasylol® vs. placebo. These results are the same whether analyzed as the proportion of patients who experienced at least one graft closure postoperatively or as the proportion of grafts closed. There were no differences between treatment groups in the incidence of myocardial infarction as evaluated by the blinded consultant (2.9% Trasylol® vs. 3.8% placebo) or of death (1.4% Trasylol® vs. 1.6% placebo) in this study.

Hypersensitivity and Anaphylaxis: See WARNINGS.

Hypersensitivity and anaphylactic reactions during surgery were rarely reported in U.S. controlled clinical studies in patients with no prior exposure to Trasylol® (1/1424 patients or <0.1% on Trasylol® vs. 1/861 patients or 0.1% on placebo). In case of re-exposure the incidence of hypersensitivity/anaphylactic reactions has been reported to reach the 5% level. A review of 387 European patient records involving re-exposure to Trasylol® showed that the incidence of hypersensitivity or anaphylactic reactions was 5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months.

Laboratory Findings

Serum Creatinine: Data pooled from all patients undergoing CABG surgery in U.S. placebo-controlled trials showed no statistically or clinically significant increase in the incidence of postoperative renal dysfunction in patients treated with Trasylol®. The incidence of serum creatinine elevations > 0.5 mg/dL above pre-treatment levels was 9% in the Trasylol® group vs. 8% in the placebo group (p=0.248), while the incidence of elevations >2.0 mg/dL above baseline was only 1% in each group (p=0.883). In the majority of instances, postoperative renal dysfunction was not severe and was reversible. Patients with baseline elevations in serum creatinine were not at increased risk of developing postoperative renal dysfunction following Trasylol® treatment.

Serum Transaminases: Data pooled from all patients undergoing CABG surgery in U.S. placebo-controlled trials showed no evidence of an increase in the incidence of post-operative hepatic dysfunction in patients treated with Trasylol®. The incidence of treatment-emergent increases in ALT (formerly SGPT) > 1.8 times the upper limit of normal was 14% in both the Trasylol® and placebo-treated patients (p=0.687), while the incidence of increases > 3 times the upper limit of normal was 5% in both groups (p=0.847).

Other Laboratory Findings: The incidence of treatment-emergent elevations in plasma glucose, AST (formerly SGOT), LDH, alkaline phosphatase, and CPK-MB was not notably different between Trasylol® and placebo treated patients undergoing CABG surgery. Significant elevations in the partial thromboplastin time (PTT) and celite Activated Clotting Time (celite ACT) are expected in Trasylol® treated patients in the hours after surgery due to circulating concentrations of Trasylol®, which are known to inhibit activation of the intrinsic clotting system by contact with a foreign material (e.g., celite), a method used in these tests. (see Laboratory Monitoring of Anticoagulation During Cardiopulmonary Bypass).

OVERDOSAGE

The maximum amount of Trasylol® that can be safely administered in single or multiple doses has not been determined. Doses up to 17.5 million KIU have been administered within a 24 hour period without any apparent toxicity. There is one poorly documented case, however, of a patient who received a large, but not well determined, amount of Trasylol® (in excess of 15 million KIU) in 24 hours. The patient, who had pre-existing liver dysfunction, developed hepatic and renal failure postoperatively and died. Autopsy showed hepatic necrosis and extensive renal tubular and glomerular necrosis. The relationship of these findings to Trasylol® therapy is unclear.

DOSAGE AND ADMINISTRATION

Trasylol® given prophylactically in both Regimen A and Regimen B (half Regimen A) to patients undergoing CABG surgery significantly reduced the donor blood transfusion requirement relative to placebo treatment. In low risk patients there is no difference in efficacy between regimen A and B. Therefore, the dosage used (A vs. B) is at the discretion of the practitioner.

Trasylol® is supplied as a solution containing 10,000 KIU/mL, which is equal to 1.4 mg/mL. All intravenous doses of Trasylol® should be administered through a central line. **DO NOT ADMINISTER ANY OTHER DRUG USING THE SAME LINE.** Both regimens include a 1 mL test dose, a loading dose, a dose to be added while **recirculating** the priming fluid of the

cardiopulmonary bypass circuit ("pump prime" dose), and a constant infusion dose. To avoid physical incompatibility of Trasylol® and heparin when adding to the pump prime solution, each agent must be added **during recirculation** of the pump prime to assure adequate dilution prior to admixture with the other component. Regimens A and B (both incorporating a 1 mL test dose) are described in the table below:

	TEST DOSE	LOADING DOSE	"PUMP PRIME" DOSE	CONSTANT INFUSION DOSE
TRASYLOL® REGIMEN A	1 mL (1.4 mg, or 10,000 KIU)	200 mL (280 mg, or 2.0 million KIU)	200 mL (280 mg, or 2.0 million KIU)	50 mL/hr (70 mg/hr, or 500,000 KIU/hr)
TRASYLOL® REGIMEN B	1 mL (1.4 mg, or 10,000 KIU)	100 mL (140 mg, or 1.0 million KIU)	100 mL (140 mg, or 1.0 million KIU)	25 mL/hr (35 mg/hr, or 250,000 KIU/hr)

The 1 mL test dose should be administered intravenously at least 10 minutes before the loading dose. With the patient in a supine position, the loading dose is given slowly over 20-30 minutes, after induction of anesthesia but prior to sternotomy. In patients with known previous exposure to Trasylol®, the loading dose should be given just prior to cannulation. When the loading dose is complete, it is followed by the constant infusion dose, which is continued until surgery is complete and the patient leaves the operating room. The "pump prime" dose is added to the **recirculating** priming fluid of the cardiopulmonary bypass circuit, by replacement of an aliquot of the priming fluid, prior to the institution of cardiopulmonary bypass. Total doses of more than 7 million KIU have not been studied in controlled trials.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Discard any unused portion.

Renal and Hepatic Impairment: No formal studies of the pharmacokinetics of aprotinin in patients with pre-existing renal insufficiency have been conducted. However, in the placebo-controlled clinical trials conducted in the United States, patients with mildly elevated pretreatment serum creatinine levels did not have a notably higher incidence of clinically significant post-treatment elevations in serum creatinine following either Trasylol® Regimen A or Regimen B compared to administration of the placebo regimen. Changes in aprotinin pharmacokinetics with age or impaired renal function are not great enough to require any dose adjustment. No pharmacokinetic data from patients with pre-existing hepatic disease treated with Trasylol® are available.

HOW SUPPLIED

Size	Strength	NDC
100 mL vials	1,000,000 KIU	0026-8196-36
200 mL vials	2,000,000 KIU	0026-8197-63

STORAGE

Trasylol® should be stored between 2° and 25°C (36° - 77°F).

Protect from freezing.

Bayer HealthCare

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