

Early Communication about an Ongoing Safety Review Aprotinin Injection (marketed as Trasylol)

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

On October 19, 2007, FDA was notified of the Data Safety Monitoring Board's (DSMB) recommendation to stop patient enrollment in the aprotinin (marketed as Trasylol by Bayer, Inc.) treatment group arm of the: *Blood conservation using antifibrinolytics: A randomized trial in a cardiac surgery population (BART)* study. The preliminary findings suggest that, compared to the antifibrinolytic drugs, epsilon-aminocaproic acid and tranexamic acid, aprotinin increases the risk of death.

The BART study was designed to test the hypothesis that aprotinin was superior to epsilon-aminocaproic acid and tranexamic acid in decreasing the occurrence of massive bleeding associated with cardiac surgery. The study had planned to enroll approximately 3,000 adult Canadian patients who were to undergo various types of cardiac surgery that placed them at high risk for bleeding.

Information from the interim analyses performed by the DSMB is limited, but FDA has been informed that:

- the 30- day mortality in the aprotinin group nearly had reached conventional statistical significance at the interim analysis, when compared to either epsilon-aminocaproic acid or tranexamic acid;
- a trend toward increased mortality in the aprotinin group had been observed throughout the study;
- the use of aprotinin was associated with less serious bleeding than either of the comparator drugs; however, more deaths due to hemorrhage had been observed among patients receiving aprotinin;
- the DSMB concluded that continued enrollment of patients into the aprotinin group was unlikely to significantly change the study findings.

Additional data collection and analyses must be performed to more thoroughly assess the findings from the BART study. However, these preliminary data support the findings from observational studies that also suggested increased risks for mortality when aprotinin was compared to other antifibrinolytic drugs. These observational studies were discussed at a September 12, 2007, joint meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees.

In light of the preliminary BART study findings, FDA anticipates re-evaluation of the overall risks and benefits of Trasylol. This re-evaluation may result in the need to revise the labeling or other regulatory actions. Until this process has been completed, healthcare providers who are considering use of Trasylol should be aware of the risks and benefits described in the labeling for Trasylol and the accumulating data suggesting Trasylol administration increases the risk for death compared to other antifibrinolytic drugs.

Trasylol is currently 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 (CABG) surgery who are at an increased risk for blood loss and blood transfusion.

This early communication is in keeping with FDA's commitment to inform the public about its ongoing safety reviews of drugs. FDA will work with the sponsor of the BART study and the manufacturer of Trasylol to fully evaluate the risks and benefits associated with the use of Trasylol. As soon as this process is complete, FDA will communicate the conclusions and recommendations to the public.

The FDA urges healthcare professionals to promptly report serious and unexpected adverse reactions associated with Trasylol to Bayer or to the FDA MedWatch reporting program, as described below.

- online at www.fda.gov/medwatch/report.htm
- by returning the postage-paid FDA form 3500 (available in PDF format at www.fda.gov/medwatch/getforms.htm) to 5600 Fishers Lane, Rockville, MD 20852-9787
- faxing the form to 1-800-FDA-0178
- by phone at 1-800-332-1088

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