



**Bayer HealthCare**  
Pharmaceuticals

**IMPORTANT TRASYLOL SAFETY INFORMATION**

November 5, 2007

Dear Health Care Professional:

Bayer HealthCare would like to update you on important information concerning the availability of Trasylo<sup>®</sup> (aprotinin injection).

Today, following consultation with the German Federal Institute for Drugs and Medical Devices (BfArM), the U.S. Food and Drug Administration (FDA), Health Canada, and other health authorities, Bayer announced that it will temporarily suspend worldwide marketing of Trasylo<sup>®</sup> (aprotinin injection) until final results from the Canadian BART trial can be compiled, received and evaluated. The company elected to take this global action following direction from the German BfArM and requests from the FDA, Health Canada and other regulators that Bayer temporarily suspend Trasylo marketing in their respective countries until final BART data were available. The BART study is an independent randomized, controlled trial being conducted in high-risk cardiac surgery patients.

Once the complete BART dataset is available, Bayer will work with health authorities to evaluate whether these data have any impact on the positive benefit-risk assessment for Trasylo. At that time the temporary marketing suspension will be reevaluated.

The U.S. FDA, Health Canada and other health authorities have indicated their interest in working with Bayer to create a program for use during the temporary suspension under which physicians in these markets might request and receive Trasylo for treatment of certain surgical patients with an established medical need. The company will work with the FDA, Health Canada, and any other authorities who wish to institute similar programs, to outline appropriate patient profiles and the specific details.

The BART Trial – a randomized, controlled trial being conducted in high-risk cardiac surgery patients – was halted after a planned periodic data analysis indicated reduced bleeding but also an increase in all-cause mortality (that almost reached conventional statistical significance for 30-day mortality) for patients in the aprotinin treatment arm compared to patients who received either aminocaproic acid or tranexamic acid. Bayer, the FDA, German BfArM, Health Canada and other regulatory authorities released information to the public

regarding the halt of the trial, and Bayer posted guidance to physicians and health care providers regarding the use of Trasylol® (aprotinin injection).

Since October 25, the agencies have continued to work with Bayer to evaluate appropriate next steps. Given the limited and preliminary nature of information available to date from the BART study, these are challenging and complex decisions. Bayer has been informed that data are now being collected from centers throughout Canada and a final data analysis will be undertaken by BART investigators -- a process that is expected to take up to eight weeks, or perhaps longer.

Once more complete information is available from BART investigators and a thorough evaluation can be conducted by Bayer and global health authorities, the company will communicate publicly regarding any further actions that may be undertaken in response to the analysis of that information.

Until these issues are resolved Bayer has temporarily suspended marketing of Trasylol and halted all shipments on a world-wide basis. In the next days information concerning the temporary market suspension will be communicated to physicians, health care providers, hospital pharmacists and distributors in each respective market.

Bayer has posted information on this decision and this letter to Health Care Professionals to Bayer's websites [www.trasylol.com](http://www.trasylol.com), [www.pharma.bayer.com](http://www.pharma.bayer.com), [www.bayerscheringpharma.de/trasylol/en](http://www.bayerscheringpharma.de/trasylol/en), [www.bayerhealthcare.com/trasylol/en](http://www.bayerhealthcare.com/trasylol/en). Additionally, public information has been issued by the FDA, German BfArM, Health Canada and other health authorities. Subsequently, also in agreement with the various health authorities, Bayer will issue letters to health care providers in each market outlining the specific details of the temporary market suspension in their respective countries.

If you wish to request further information, please contact your local Bayer HealthCare Medical Department.

Sincerely

A handwritten signature in black ink, appearing to read "Kemal Malik", with a long horizontal flourish extending to the right.

Kemal Malik, MD  
Head of Global Development, Member of the Board of Management  
Bayer HealthCare Pharmaceuticals

## **About Trasylol®**

**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 who are at an increased risk for blood loss and blood transfusion.**

**Trasylol administration may cause fatal anaphylactic or anaphylactoid reactions. Fatal reactions have occurred with an initial (test) dose as well as with any of the components of the dose regimen. Fatal reactions have also occurred in situations where the initial (test) dose was tolerated. The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure and a history of any prior aprotinin exposure must be sought prior to Trasylol administration. The risk for a fatal reaction appears to be greater upon re-exposure within 12 months of the most recent prior aprotinin exposure. Trasylol should be administered only in operative settings where cardiopulmonary bypass (CPB) can be rapidly initiated. The benefit of Trasylol to patients undergoing primary CABG surgery should be weighed against the risk of anaphylaxis associated with any subsequent exposure to aprotinin.**

**[\(See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS in the prescribing information.\)](#)**

### **Safety Considerations**

**Trasylol is contraindicated in patients with a known or suspected aprotinin exposure during the last 12 months. Aprotinin may also be a component of some fibrin sealant products.**

In clinical studies, hypersensitivity and anaphylactic reactions were rare (<0.1%) in patients with no prior exposure to Trasylol.

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

This risk may be especially increased for patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function.

The incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was statistically higher in the full-dose aprotinin group (9.0%) compared with placebo (6.6%).

The incidence of serum creatinine elevations >2.0mg/dL above baseline was slightly higher in the full-dose aprotinin group (1.1% vs. 0.8%).

In clinical trials Trasylol® did not increase the risk of the following perioperative events: myocardial infarction, congestive heart failure, hepatic dysfunction and mortality.

**For Trasylol contraindications, warnings and precautions see prescribing information.**