NOTICE TO HOSPITALS
Health Canada Endorsed Important Safety Information on
TRASYLOL® [aprotinin]

Bayer HealthCare
Pharmaceuticals

March 27, 2007

FINAL

To: Hospital Chief of Medical Staff

Please distribute to relevant Departments of General Surgery, Thoracic Surgery, pediatric Cardiothoracic Surgery, Cardiothoracic Surgery, Hepatology, Surgical Oncology, Orthopedic Surgery, Anesthesiology, Critical Care Anesthesiology, Nephrology, Internal Medicine, Hospital Pharmacy, and/or other Departments as required and **post this Notice** in an appropriate location in your institution.

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Subject: **Association of Trasylol® (aprotinin) with hypersensitivity reactions and renal dysfunction**

Bayer Inc. (Bayer) would like to inform you of important new safety information regarding Trasylol® (aprotinin). Trasylol® is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in those patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery who are at increased risk for blood loss and blood transfusion requirement.

Based on postmarket and clinical study data, the Canadian Product Monograph (CPM) for Trasylol® has been updated to include additional safety information with respect to the authorized indication, contraindications, the risk of hypersensitivity reactions, and the risk of renal dysfunction:

- **The authorized indication for Trasylol® is restricted to those patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery who are at increased risk for blood loss and blood transfusion.**

- **Trasylol® administration may cause fatal and nonfatal 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. As a result, Trasylol® should only be administered in operative settings where cardiopulmonary bypass can be rapidly initiated.**

- **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. As a result, administration of Trasylol® to patients with a known or suspected previous aprotinin exposure during the last 12 months is contraindicated.**

- **Trasylol® administration increases the risk of 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.**

Hypersensitivity Reactions

The risk for fatal and nonfatal anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure. Hence, a thorough history to account for any prior aprotinin exposure must be sought prior to Trasylol® administration.

An analysis of all spontaneous reports from the Bayer Global database covering a period from 1985 to March 2006 revealed that of 291 possibly associated spontaneous cases of hypersensitivity (fatal: n=52 and nonfatal: n=239), 47% (138/291) of hypersensitivity cases had documented previous exposure to Trasylol®. Of the 138 cases with documented previous exposure, 110 had information on the time of the previous exposure. Ninety-nine (99) of the 110 cases had previous exposure within the prior 12 months.

Administration of Trasylol®, especially to patients who have received any aprotinin-containing products in the past, requires a careful risk/benefit assessment because of the increased risk of hypersensitivity reactions. Although the majority of cases of anaphylaxis occur upon re-exposure within the first 12 months, there are also single case reports of anaphylaxis occurring upon re-exposure after more than 12 months.

Hypersensitivity reactions often manifest as anaphylactic/anaphylactoid reactions with hypotension the most frequently reported sign of the hypersensitivity reaction. Other symptoms of a hypersensitivity reaction include pruritis, rash, asthma, and nausea. The hypersensitivity reaction can progress to 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. Even when a second exposure to Trasylol® has been tolerated without symptoms, a subsequent administration may result in severe hypersensitivity/anaphylactic reactions.

Before initiating treatment with Trasylol®, 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 (eg, epinephrine, corticosteroids).
2) Administration of the initial (test) dose and loading dose should be done only when the patient is intubated and when conditions for rapid cannulation and initiation of cardiopulmonary bypass are present.
3) Delay the addition of Trasylol® into the pump prime solution until after the loading dose has been safely administered.

Renal Dysfunction

Data from Bayer's global pool of placebo-controlled studies in patients undergoing coronary artery bypass graft (CABG) surgery showed that the incidence of serum creatinine elevations >44.2 µmol/L (0.5mg/dL) above pretreatment levels was statistically higher at 9.0% (185/2047) in the Trasylol® group compared with 6.6% (129/1957) in the placebo group, with an odds ratio of 1.41 (1.12-1.79). In the majority of instances, postoperative renal dysfunction was not severe and was reversible. However, renal dysfunction may progress to renal failure and the incidence of serum creatinine elevations >176.8 µmol/L (2.0 mg/dL) above baseline was slightly higher in the Trasylol® group (1.1% vs 0.8%).

Careful consideration of the balance of risks and benefits is therefore advised before administering Trasylol® to patients with pre-existing impaired renal function (creatinine clearance <60 mL/min), or to those with other risk factors for renal dysfunction (such as perioperative administration of aminoglycosides or products that alter renal function).

Additional safety information and information regarding the proper use of Trasylol® can be found in the revised CPM. The CPM as well as this Notice to Hospitals can be found on the Canadian Bayer HealthCare website at: www.bayerhealth.com. In addition, this Notice to Hospitals can be found on the Health Canada website at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html.

Bayer and Health Canada continue to actively review information pertaining to the use of Trasylol®. The information currently under review at Bayer includes preliminary findings from an observational study that was reported to regulatory authorities following a public discussion of Trasylol® safety at a September 21, 2006 US FDA Advisory Committee meeting. This study used complex statistical and epidemiological methods, and the association of Trasylol® with the safety concerns described in this study is the subject of ongoing review by both Bayer and Health Canada.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported postmarketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious and/or unexpected adverse reactions in patients receiving Trasylol®should be reported to Bayer Inc. or Health Canada at the following addresses:

Bayer Inc.
77 Belfield Road
Toronto, Ontario M9W 1G6
Tel: 1-800-265-7382
Fax: 1-866-232-0565

Any suspected adverse reaction can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

For other inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate (MHPD)
E-mail: mhpd_dpsc@hc-sc.gc.ca
Tel: (613) 954-6522
Fax: (613) 952-7738

If you wish to request further information, please contact Bayer HealthCare, Medical Information at 1-800-265-7382.

Sincerely,

Shurjeel H. Choudhri, MD, FRCPC
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Bayer Inc.