

Bayer Responds to BART Study Article and Editorial Published in NEJM

May 14, 2008, Leverkusen, Germany; West Haven, Connecticut, USA – Bayer is aware that an article and accompanying editorial have been published in the May 14, 2008 on-line edition of the *New England Journal of Medicine* regarding the efficacy and safety of Trasylol (aprotinin injection), a Bayer drug used in patients at an increased risk of blood loss and blood transfusion while undergoing coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB). Trasylol, currently under temporary market suspension worldwide, continues to be available in some countries under special access programs as reviewed and agreed to with the relevant regulatory bodies in those markets.

The article authored by Dr. Dean Fergusson, M.H.A., Ph.D, Paul C. Hebert, M.D., M.H.Sc. (lead investigators of the Canadian-based BART study) et al, is entitled “A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery”. The editorial, entitled, The Aprotinin Story – Is BART the Final Chapter?” is authored by Wayne A. Ray, Ph.D and C. Michael Stein, M.B., Ch.B.

The BART study was a randomized clinical trial in patients undergoing one of the following high-risk cardiac surgical procedures for which cardiopulmonary bypass was required: repeat cardiac surgery, isolated mitral-valve replacement, combined valve and CABG surgery, multiple valve replacement or repair, and surgery of the ascending aorta or aortic arch procedures. The primary objective of the BART study was to determine if aprotinin is superior to epsilon-aminocaproic acid and tranexamic acid in terms of massive postoperative bleeding in the initial 24 hours following surgery.

Dr. Fergusson’s article concludes that “Despite the possibility of a modest reduction in the risk of massive bleeding, the strong and consistent negative mortality trend associated with aprotinin, as compared with the lysine analogues, precludes its use in high-risk cardiac surgery.”

In the editorial, the opinion of Drs.’ Ray and Stein is that, “...although the existence of a class of patients who would benefit from aprotinin is not impossible, it seems highly unlikely,” and also recommends that “...the benefits of aprotinin with regard to clinical end points [in such a subset population] would need to be confirmed by an adequately powered clinical trial before further unrestricted use of the drug.”

In the next days Bayer expects to receive from Health Canada redacted data from the BART trial that are the basis of this article and accompanying editorial and we will work with the BART investigators to provide more detail and clarity if needed. When received, with the additional help of independent experts, we will undertake a thorough review and analysis of these and any other relevant published materials, and will work with health authorities to

determine what impact, if any, the BART data and any other new data will have on the benefit-risk profile of Trasylol. During this process any actions relevant to the worldwide temporary marketing suspension and/or restricted access programs for Trasylol will be discussed.

During this process of data examination and analysis Bayer will also undertake additional steps in certain markets where special access programs for Trasylol are now available to assure that Trasylol is used within the approved requirements of these programs.

At the time of the worldwide marketing suspension, (November 2007), in markets where special access programs were under development, some regulatory authorities did not require that existing stocks of Trasylol be actively recalled from the supply chain. Consistent with our goal that Trasylol now be used within the approved requirements of the various special access programs, Bayer has informed the regulatory authorities in these markets that it will now remove residual quantities of Trasylol that may remain in the supply chain. (Where local regulatory authorities direct Bayer to leave quantities of Trasylol in the market to supply special access, named patient or compassionate use programs we will do so.) Additionally, we will proactively share the BART paper, the NEJM editorial and our initial interpretation of these materials with all physicians and investigators who have been using or will use Trasylol under these special access programs.

Bayer will continue to carefully review this article, the editorial and (when available) the underlying data on which the authors have based their conclusions and continue to discuss both the restricted access programs for Trasylol and the worldwide temporary marketing suspension of the drug with regulatory authorities. When further conclusions are reached, Bayer will communicate publicly.

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 cardio-pulmonary bypass 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 full prescribing information..

About Bayer HealthCare Pharmaceuticals Inc.

Bayer HealthCare Pharmaceuticals Inc. is the U.S.-based pharmaceuticals business of Bayer HealthCare LLC, a subsidiary of Bayer AG. Bayer HealthCare is one of the world's leading, innovative companies in the healthcare and medical products industry, and combines the activities of the Animal Health, Consumer Care, Diabetes Care, and Pharmaceuticals divisions. In the United States, Bayer HealthCare Pharmaceuticals comprises the following business units: Women's Healthcare, Diagnostic Imaging, General Medicine, which includes Cardiology and Primary Care and Specialty Medicine, which includes Hematology, Oncology and Multiple Sclerosis. The company's aim is to discover and manufacture products that will improve human health worldwide by diagnosing, preventing and treating diseases.

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