Cardiovascular and Renal Drugs Advisory Committee Questions
September 21, 2006

1. (Safety) Discussion: Published reports (Transfusion 2006; 46:327-38; NEJM 2006; 354:353-65) and an updated Bayer safety review are generally consistent in the detection of an increased risk for renal dysfunction following aprotinin administration. However, the NEJM report described several other serious risks associated with aprotinin.

Please consider the conclusions from the publications and from Bayer's controlled clinical studies and discuss whether Trasylol usage, compared to no hemostatic therapy, is associated with increased risks for the following serious adverse events:

- Renal failure requiring dialysis
- Myocardial infarction
- Heart failure
- Stroke or encephalopathy

In your discussions, please comment upon whether any increased risks apply only to specific subsets of CABG/CPB patients; for example, patients undergoing repeat CABG versus initial CABG.

2. (Safety) Discussion: The identification of patients at high risk for Trasylol hypersensitivity reactions predominantly involves ascertainment of a history of any prior aprotinin exposure and the use of a "test dose" procedure. Bayer has proposed a risk minimization program focused upon healthcare provider education and the possible use of an IgG assay to detect prior aprotinin exposure. Please discuss the strengths and limitations of these procedures. In your discussion, please consider the following questions:

a. To what extent do you regard these procedures, especially the use of a "test dose," as acceptable measures to identify patients at high risk?

b. Please discuss whether the risks and consequences of hypersensitivity differ for subsets of patients; for example, patients undergoing repeat CABG versus initial CABG? Are the risks sufficiently high for some subsets of patients such that Trasylol should not be administered? If so, which types of patients?

3. (Efficacy) Discussion: Since Trasylol was originally approved in 1993, allogeneic blood transfusion practices in CABG surgery may have changed due to the wider use of autologous blood and changes in the clinical criteria for transfusion. Please discuss the importance of the Trasylol benefit of reduced perioperative bleeding and the need for blood transfusions, in the context of current cardiovascular surgical, anesthetic and blood transfusion practices.

4. (Safety and Efficacy) Bayer Pharmaceuticals has proposed modification of the Trasylol indication statement to the following: "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 increased risk for blood loss and blood transfusions."

a. Discussion: Please discuss the clinical considerations in identifying patients "who are at increased risk for blood loss and blood transfusion." For example, should this descriptor only apply to patients undergoing repeat CABG?

b. Vote: Highlights of Bayer's recent safety and efficacy data submissions to the FDA were presented at this meeting along with findings from two publications. FDA review of these data is on-going and may be importantly impacted by further analyses or additional information submitted to the Trasylol NDA. Nevertheless, the Committee's perspectives regarding the highlighted data will form an important component of the on-going FDA review. Based upon the presentations today, do you regard the totality of clinical data as supporting acceptable safety and efficacy for Trasylol usage among certain CABG/CPB patients?

c. Discussion: If your response to "b" is yes, please identify those patients in which the safety and efficacy data sufficiently support Trasylol usage. Specifically, does this population include the proposed CABG/CPB patients "who are at increased risk for blood loss and blood transfusion?"

d. Discussion: If your response to "b" is no, please provide recommendations regarding ways to obtain sufficient safety and efficacy data for Trasylol usage. For example would additional controlled clinical studies in specific CABG patients assist in more thoroughly assessing Trasylol risks and benefits?