Food and Drug Administration
Center for Drug Evaluation and Research
Advisors and Consultants Staff Conference Room 1066
5630 Fishers Lane, Rockville, MD 20857

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting for
September 21, 2006

On September 21, 2006 the committee discussed clinical data for aprotinin injection (trade name, TRASYLOL), an approved product (NDA 020-304, Bayer Pharmaceuticals) with the indication 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.

These summary minutes for the September 21, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on September 25, 2006.

I certify that I attended the September 21, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, B.S.N.	William R. Hiatt, M.D.
Designated Federal Official	Committee Chair

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder06.html#CardiovascularRenal

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 21, 2006 at 5630 Fishers Lane, Room 1066, Rockville, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the sponsor and the FDA. The meeting was called to order by William R. Hiatt, M.D (Committee chair); the conflict of interest statement was read into the record by Cathy Groupe, R.N., B.S.N. (Designated Federal Official). There were approximately 125 persons in attendance. There were three speakers for the Open Public Hearing sessions.

Issue: The committee discussed clinical data for aprotinin injection (trade name, TRASYLOL), an approved product (NDA 020-304, Bayer Pharmaceuticals) with the indication 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. This discussion follows a February 8, 2006 FDA Public Health Advisory for the use of aprotinin injection

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
David L. DeMets, Ph.D.; Steven D. Findlay, M.P.H. (Consumer Representative); John M. Flack, M.D., M.P.H.; Robert A. Harrington, M.D., F.A.C.C.; William R. Hiatt, M.D. (Committee Chair); Frederick J. Kaskel M.D., Ph.D.; Michael A. Lincoff, M.D.; Ronald J. Portman, M.D.; John R. Teerlink, M.D.; Lynn Warner-Stevenson, M.D.

Special Government Employee Consultants (Voting):
Norman S. Kato, M.D.; Valluvan Jeevanandam, M.D.; Jeffrey R. Balser, M.D., Ph.D.; John E. Ellis, M.D.; Sean Hennessy, Pharm.D., Ph.D.; Susan R. Heckbert, M.D., Ph.D.; Alfred Cheung, M.D.; Emil Paganini, M.D., F.A.C.P, F.R.C.P.; Joseph J. Knapka, Ph.D.

Cardio-Renal Advisory Committee Members Absent:
John F. Neylan, MD (Industry Representative)

Participant Guest Speakers (Non-voting):
Dennis Mangano, M.D., Ph.D; Keyvan Karkouti, M.D.

FDA Participants:
Mark Avigan, M.D.; Richard Pazdur, M.D.; Dwaine Rieves, M.D.**;** Kathy M. Robie Suh, M.D., Ph.D.; Susan Lu, R.Ph .

Designated Federal Official:
Cathy A. Groupe, R.N., B.S.N.

Open Public Hearing Speakers:
S. Stanley Young; Bruce D. Spiess, M.D., F.A.H.A.; Linda Shore-Lesserson, M.D.

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The agenda was as follows:

Call to Order and Introductions	**William R. Hiatt, M.D.** Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy Groupe, B.S.N.** Executive Secretary Cardiovascular and Renal Drugs Advisory Committee

FDA Presentations:

Opening Remarks	**Dwaine Rieves, M.D.** Deputy Division Director, Division of Medical Imaging and Hematology Products, FDA
FDA Regulatory Overview	**Kathy M. Robie Suh, M.D., Ph.D.** Medical Officer, Division of Medical Imaging and Hematology Products, FDA
FDA OSE/Postmarket Reports	**Susan Lu, R.Ph .** Team Leader, Division of Drug Risk Evaluation, FDA
FDA Topics for Discussion	**Dwaine Rieves, M.D.**

Guest Speaker Presentations:

Dennis Mangano, M.D., Ph.D.

Break

Keyvan Karkouti, M.D.

Bayer Pharmaceuticals presentation:

Introduction and Overview	**Michael Rozycki, Ph.D.** Director, US Regulatory Affairs Bayer Pharmaceuticals Corporation
Methodological Considerations on the Two Recent Observational Studies of Aprotinin	**Robert Makuch, Ph.D.** Professor of Biostatistics Yale University School of Public Health
Review of Clinical Data	**Pamela Cyrus, M.D.** Vice President, US Medical Affairs Bayer Pharmaceuticals Corporation
Risk-Benefit Assessment	**Jerrold Levy, M.D.** Professor and Deputy Chair for Research Emory University School of Medicine Director of Cardiothoracic Anesthesiology Emory University Hospital, Department of Anesthesiology

Questions from the Committee

Lunch

Open Public Hearing

Committee Questions to Speakers

Committee Discussion of FDA Questions

Adjourn

The Committee members asked multiple questions of the guest presenters regarding the details of statistical methodology for the observational clinical studies. Several members noted that the analytical details of these observational studies were important considerations in interpretation of the meaningfulness of the findings. Several members expressed considerable concern that the author of the New England Journal of Medicine publication had not shared his database with independent reviewers, including FDA reviewers.

Questions to the Committee:

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.

The committee agreed that the data are consistent with an association with aprotinin use and renal impairment, specifically for an increasing creatinine, however, most of the committee were not convinced that there was a definite increased risk of renal failure requiring dialysis. The committee also agreed overall that there was no association between aprotinin use and an increased risk of myocardial infarction, heart failure, stroke or encephalopathy. Additionally, the committee commented that these are short-term outcomes and we currently have little or no data on the long-termcardiovascular outcomes in these patients.

In terms of subgroup risks, some committee members suggested that the risk-benefit is most favorable in those highest risk patients such as those on anti-platelet therapy or who are undergoing complex surgery. The committee also point out, when discussing increased risks, that these are increased risks compared to no treatment or placebo, and not increased risk compared to other agents. The committee additionally cited the fact that the available data indicate there is no improvement in mortality with aprotinin use.

(See transcripts for detailed discussion)

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?

Test Dose:
The committee highlighted that nearly half of the reported patients with hypersensitivity reactions had reactions with the test dose alone. Some of the committee found little predictive value in the 'test dose' as a useful screening tool for identifying patients at high risk. Concerns raised included usage in non-cardiac settings such as hip replacement surgery, where CPB is not readily available to resuscitate the patient should a reaction occur. Recommendations were made to rename 'initial dose' as opposed to 'test dose' to alleviate any possible false sense of security in implementing this drug therapy.
Many other members of the committee, however, found the test dose of value, cautioning against any decision to abandon the test dose altogether. They emphasized its value, specifically in the surgical setting when given slowly enough to recognize early hypersensitivity signs [hypotension] and where CBP is readily available for rescue/resuscitation.

IgG Assay:
The committee recognizes that the IgG assay is a work in progress, but many found promise in the Sponsor's RiskMAPP for an IgG assay for identifying high risk patient. The committee applauded the sponsor on their efforts to exclude patients from aprotinin treatment, who would screen positive. An assay with a good negative predictive value would be beneficial as a screening tool, as long as it is coordinated and monitored closely in conjunction with the FDA, (i.e. defining under what clinical situations the assay should be used and how to interpret assay data). The assay should be tested extensively before recommended for routine clinical use.

Education:
The committee emphasized the need for education on having CPB rescue readily available for resuscitation. Concern was raised, though, in the complete reliance of using the medical history to identify high risk patients for a hypersensitivity reaction, as cases have been cited where such efforts failed to uncover a previous exposure to the drug.

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?

The committee had limited comments or recommendations on singling out subgroups that may be at higher risk for hypersensitivity reaction. Those 'redo' CABG patients, especially those within 6 months of originally surgery, were identified as a higher risk of hypersensitivity reaction. An additional suggestion was made for a national registry of patients who have received aprotinin, as a safety measure in identifying patient exposure to the drug.

(See transcripts for detailed discussion)

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.

A majority of the committee agree that patients that present for surgery today are even sicker than in the past, with proportionally more patients on anti-platelet therapy, re-operations, transplants, etc. The committee agreed that the need for a reduction in perioperative bleeding is as great as or greater than when the drug was first approved. The committee also cited that we have better transfusion practice and safer blood products today than in the past.

The committee recognized, though, that there should be caution in not routinely using the drug for everyone but rather, selecting out those patients [high risk] who will benefit the most from it. Recommendations were made for a guideline/consensus paper on the topic for future practice, in addition to the use of databases to pull information.

Recommendations were made that, because there is limited current and long-term data, Bayer should be encouraged to sponsor such prospective studies to gather this information. Others encouraged smaller trials and observational datasets to gather additional information about patient populations, drug usage and outcomes.
(See transcripts for detailed discussion)

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?

A suggestion was made to change the language from 'at increased risk' to 'at high risk' because this raised the question of increased risk compared to who? The majority of the committee cautioned in limiting usage to those patients undergoing repeat CABG. While there was discussion to expand the label to include other forms of cardiac surgery, there were no data to support any changes in the current label in terms of expanding aprotinin use to other forms of surgery.

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?**

YES: 18 ***NO: 0*** ***ABSTAINED FROM VOTING: 1***

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?"

Many of the committee members found the label language accurate. Most of committee agreed that there should be limited restriction in the language, for the use of the drug in repeat CABG patients, leaving these clinical decisions to the surgeon.

Labeling language was recommended that in addition to an 'increased risk of blood loss/blood transfusion' there should be language such as 'factors that put you at increased risk for the drug.'

The committee cited, as examples of those patients who at increased risk of blood loss/blood transfusion, those on anti-platelet therapy; redo CABGs; valve/transplant patients; uremic patients; and patients who are on nephrotoxc drugs.

Committee recommendations for package labeling included comments that there was no demonstration that aprotinin improves mortality (i.e. no data on improved outcome). Opinions varied however upon the appropriateness of including this type of "no mortality effect" statement in the product label.

Additionally, comments regarding the uncertainty about the value of the 'test dose' should be reflected in the package label (i.e. recommendation that a test dose be given in the complete absence of any data about patient history).

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?

One committee member abstained from voting, citing the limited data available to accurately identify who is at high risk for bleeding, which requires more research, and that a decision analysis regarding treatment versus no treatment is dependant upon that information. None of the committee voted 'No' to this question.

The committee adjourned at approximately 5:00 P.M.

(See transcript for detailed discussion)