Summary Minutes of the Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee
September 12, 2007
Location: Hilton Washington DC North/Gaithersburg, the Ballrooms
620 Perry Parkway, Gaithersburg, MD

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

These summary minutes for the September 12, 2007 of the Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on ___**9-26-07**_____

I certify that I attended the September 12, 2007, meeting of the Cardiovascular and Renal Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration meeting and that these minutes accurately reflect what transpired.

R. Harrington MD

Mimi T. Phan, Pharm.D., R.Ph.
Acting Designated Federal Official

Robert A. Harrington, M.D.
Acting Chair

Meeting of the Cardiovascular & Renal Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee
September 12, 2007

Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA and the sponsor. The meeting was called to order by Robert Harrington, M.D (Acting Chair); the conflict of interest statement was read into the record by Mimi T. Phan, Pharm.D., R.Ph. (Acting Designated Federal Official). There were approximately one hundred and twenty (120) persons in attendance. There were four (4) speakers in the Open Public Hearing session.

Issue: The committee discussed clinical data for aprotinin injection (TRASYLOL, Bayer Pharmaceuticals), a product 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 transfusion. This discussion followed a September 27, 2006, FDA Public Health Advisory regarding a study of aprotinin injection safety.

Attendance:
CRDAC Committee Members Present (Voting):
Steven Findlay, MPH (Consumer Representative); Robert A. Harrington, MD, FACC (Acting Chair); Frederick J. Kaskel, MD, PhD; Michael Lincoff, MD, Emil P. Paganini, MD; FACC; John R. Teerlink, MD; Lynn Warner-Stevenson, MD

DSaRM Committee Members Present (Voting):
Susan R. Heckbert, MD, PhD; Timothy S. Lesar, PharmD

Special Government Employee Consultants (Voting):
Henry R. Black, MD; Alfred Cheung, MD; Stephanie Y. Crawford, PhD; Ruth S. Day, PhD; John E. Ellis, MD; James W. Gillett, PhD; Valluvan Jeevanandam, MD; Norman S. Kato, MD, FACC; James D. Neaton, PhD; Lewis S. Nelson, MD

Guest Speaker (Non-Voting):
Paul Corso, MD; Keyvan Karkouti, MSc, MD, FRCPC; Dennis T. Mangano, PhD, MD

FDA Participants (Non-Voting):
Mark Levenson, PhD; Gerald Dal Pan, MD; Richard Pazdur, MD; Rafel Dwaine Rieves, MD; George Shashaty, MD

Acting Designated Federal Official:
Mimi T. Phan, Pharm.D., R.Ph.

Open Public Hearing Speakers:
Niv Ad, MD (Inova Heart and Vascular Institute)
Anthony P. Furnary, MD (Providence St Vincent Hospital)
Bruce D. Spiess, MD, FAHA (Virginia Commonwealth University Medical Center);
Stanley Young (National Institute of Statistical Sciences)
The agenda was as follows:

Call to Order Introduction of Committee	**Robert A. Harrington, M.D.** Acting Chair, CRDAC
Conflict of Interest Statement	**Mimi T. Phan, Pharm.D., R.Ph.**

	Acting Designated Federal Officer, CRDAC
Opening Remarks	**Gerald Dal Pan, M.D.** Director, Office of Surveillance and Epidemiology (OSE), CDER, FDA
Trasylol (Aprotinin) NDA 20-304 Overview	**George Shashaty, M.D.** Medical Officer, Division of Medical Imaging and Hematology Products (DMIHP), Office of Oncology Drug Products (OODP), CDER, FDA
Coronary Artery Bypass	**Paul Corso, M.D.** Director, Cardiovascular Surgery Washington Hospital Center Washington, DC
A Propensity Score Comparison of Aprotinin vs. Tranexamic Acid Updated Analysis of a Large, Single Center Cardiac Surgery Database	**Keyvan Karkouti, M.D., F.R.C.P.C., M.Sc.** Clinical Studies Resource Centre Division of Clinical Investigations and Human Physiology Toronto General Research Institute
Safety of Aprotinin vs. Epsilon Aminocaproic Acid vs. Tranexamic Acid	**Dennis Mangano, M.D., Ph.D.** Principal Scientist/Founder/CEO Ischemia Research and Education Foundation

SPONSOR PRESENTATION

Bayer Introduction	**Kemal Malik, M.D.** Head of Global Development and a Member of the Board of Management for Bayer HealthCare Pharmaceuticals
Safety of Aprotinin vs. Aminocaproic Acid During CABG Surgery	**Sebastian Schneeweiss, M.D., Sc.D.** Associate Professor Department of Epidemiology Harvard, School of Public Health
Trasylol® (aprotinin injection) Review of Clinical Data with a Focus on Specific Safety Events	**Pamela Cyrus, M.D.** Vice President, US Medical Affairs Bayer Pharmaceuticals Corporation
Aprotinin Studies: Weight of Evidence	**Robert W. Makuch, Ph.D.** Professor, Biostatistics Yale, School of Public Health
Trasylol® (aprotinin injection) Risks and Benefits from a Surgeon's Perspective	**Peter K. Smith, M.D.** Professor and Division Chief Thoracic and Cardiovascular Surgery Duke University Medical Center

FDA PRESENTATION

Aprotinin: Observational Studies	**Rita Ouellet-Hellstrom, Ph.D., M.P.H.** OSE, Division of Drug Risk Evaluation (DDRE) CDER, FDA
Statistical Review of the Observational Studies of Aprotinin Safety Part I: Methods, Mangano and Karkouti Studies	**Mark Levenson, Ph.D.** Statistical Reviewer, Office of Biostatistics, Division of Biometrics VI, CDER, FDA
Statistical Review of the Observational Studies of Aprotinin Safety Part II: The i3 Safety Study	**Chris Holland, M.S.** Statistical Reviewer, Office of Biostatistics, Division of Biometrics VI, CDER, FDA

Open Public Hearing

Committee Discussion and Questions to the CRDAC/DSaRM

Adjourn

Questions to the Committee:

1. VOTE: The Trasylol product label was modified in 2006 to change its indicated population from the relatively broad population of patients undergoing coronary artery bypass grafting (CABG) with cardio-pulmonary bypass (CPB) to CABG/CPB patients "who are at an increased risk for blood loss and blood transfusion." Modifications were also made to the label regarding warnings for anaphylaxis and renal dysfunction and also to contraindicate Trasylol use in patients with known or suspected use of Trasylol in the last 12 months.

Based upon the Trasylol risks and benefits evidenced in Bayer's controlled clinical studies and your consideration of the presented observational study data, do you recommend continued marketing authorization for Trasylol?

YES: 16 ***NO: 1*** ***Abstain: 1***
If yes, describe any necessary product label modifications or restrictions upon Trasylol distribution and proceed to questions # 2 and 3.

The committee encouraged the agency to work with the sponsor to come up with a better definition of the high risk population. Some committee members expressed options regarding programs to educate physicians and possible mechanisms to restrict the use of the drug. Several members expressed opinions that the label should be modified to highlight the specific patient populations (i.e. renal disease, MI, stroke, non-cardiac patients) at the highest risk.
(Please refer to the transcript for detail discussions)

2. VOTE: The i3 Drug Safety study and a published report in JAMA have suggested mortality disadvantages to the use of Trasylol, when compared to the use of no anti-fibrinolytic drug. Should these study findings (one or both studies) be described in product labeling?

YES: 6 ***NO: 11*** ***Abstain: 1***

If yes, discuss the conclusions to be drawn from these studies and provide suggestions regarding the emphasis or prominence for display of the information in the product label.

There was an extended discussion regarding the importance of inclusion of the information from the observational studies in the label. The majority of the panel voted no because they were concerned with the quality of this data.

(Please refer to the transcript for details of the discussions)

3. VOTE: Do you regard the performance of additional clinical studies to more thoroughly assess Trasylol safety, particularly with respect to mortality, as a pre-requisite to continued market authorization?

If yes, discuss the most important design considerations for these studies. For example, should a study be powered sufficiently to rule out a certain increase in mortality risk, where Trasylol is compared to no anti-fibrinolytic drug or to placebo or to both anti-fibrinolytic drug and placebo?
Question 3 was reworded to read:

3) Do you believe that there should be additional clinical studies including Randomize Controlled Trials (RCT) to further assess the risks and benefits of Trasylol?

YES: 17 ***NO: 0*** ***Abstain: 0***

The meeting adjourned for the day at approximately 5 p.m.