Summary Minutes of the Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee
September 11, 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 11, 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 10/03/07

I certify that I attended the September 11, 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.

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

Richard Platt, M.D., M.Sc.
Chair

Meeting of the Cardiovascular & Renal Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee
September 11, 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 Richard Platt, M.D (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 three hundred and fifty (350) persons in attendance. There were eight (8) speakers for the Open Public Hearing session.

Issue: The committees discussed updated information on the risks and benefits of erythropoeisis-stimulating agents (ARANESP, Amgen, Inc., EPGEN, Amgen, Inc. and PROCRIT, Amgen, Inc.) when used in the treatment of anemia due to chronic renal failure. This discussion followed a March 9, 2007, FDA Public Health Advisory regarding the use of these agents (http://www.fda.gov/cder/drug/advisory/RHE2007.htm).

Attendance:
CRDAC Committee Members Present (Voting):
Steven. Findlay, MPH (Consumer Representative); Frederick J. Kaskel, MD, PhD; Michael Lincoff, MD, FACC; John R. Teerlink, MD

DSaRM Committee Members Present (Voting):
Sean P. Hennessy, PharmD, PhD; Judith M. Kramer, MS, MS; Timothy S. Lesar, PharmD; Richard Platt, MD, MSc (Chair)

Special Government Employee Consultants (Voting):
Henry R. Black, MD; Alfred Cheung, MD; Stephanie Y. Crawford, PhD; Ruth S. Day, PhD; Lawrence G. Hunsicker, MD; Jeffrey Kopp, MD; Andrew Narva, MD; Chester B Good, MD; James D. Neaton, PhD; Lewis S. Nelson, MD; Malazia Y. Scott (Patient Representative)

Guest Speaker (Non-Voting):
Dennis J. Cotter, MSE; Miguel Hernan, MD; Ajay K. Singh, MD; Yi Zhang, DDS

FDA Participants (Non-Voting):
John Jenkins, MD; Richard Pazdur, MD; Rafel Dwaine Rieves, MD; Ann-Marie Trentacosti, MD; Ellis Unger, MD

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

Open Public Hearing Speakers:
Roberta Wager, RN, MSN (American Association of Kidney Patients)
Jonathan Himmelfarb, MD & Lynda Anne Szczech, MD, MSCE, FASN (American Society of Nephrology)
Friedrich K. Port, PhD & Robert A. Wolfe, PhD (Arbor Research Collaborative for Health)
Robert Provenzano (DaVita)
Michael J. Lazarus, MD (National Kidney Foundation)
Alan S. Kliger, MD (Renal Physicians Associations and American Society of Pediatric Nephrology)
Lori Hartwell (Renal Support Group)

The agenda was as follows:

Call to Order	**Richard Platt, M.D., M.Sc.**

Introduction of Committee	Chair, DSaRM
Conflict of Interest Statement	**Mimi Phan, Pharm.D., R.Ph.** Acting Designated Federal Officer, CRDAC
Introduction	**Dwaine Rieves, M.D.** Acting Director, Division of Medical Imaging and Hematology Products (DMIHP), OND, CDER, FDA
Anemia and Chronic Kidney Disease UPDATE	**Ajay K. Singh, M.D.** Clinical Director, Renal Division Director, Dialysis Services Assoc. Professor of Medicine, Brigham & Women's Hospital, Boston, MA
Medical Technology and Practice Patterns Institute (MTPPI) Epoetin Outcomes Research	**Dennis J. Cotter, M.S.E** President, MTPPI, Bethesda, MD
	Miguel Hernan, M.D. Associate Professor of Epidemiology Harvard University, School of Public Health Boston, MA
	Yi Zhang, D.D.S. Senior Analyst, MTPPI, Bethesda, MD

SPONSOR PRESENTATIONS

Amgen Introduction	**Paul Eisenberg, M.D., M.P.H., F.A.C.C.** Global Regulatory Affairs &Safety Amgen, Inc.
Clinical Perspective	**Allen R. Nissenson, M.D.** Professor of Medicine, Associate Dean, Director, Dialysis Program, David Geffen School of Medicine, UCLA
Benefit/Risk	**Preston Klassen, M.D., M.H.S.** Global Development, Amgen, Inc.
Benefit/Risk (continued)	**Jesse Berlin, Sc.D.** Pharmacoepidemiology, J&JPRD
	Preston Klassen, M.D., M.H.S. Global Development, Amgen Inc.
Risk Management	**Paul Eisenberg, M.D., M.P.H., F.A.C.C.** Global Regulatory Affairs &Safety Amgen Inc.

FDA PRESENTATIONS

Epoetin Alpha: FDA Overview of Patient	**Ann Marie Trentacosti, M.D.**

Reported Outcome (PRO) Claims	Study Endpoints and Labeling (SEALD), CDER, FDA
FDA Perspectives on Erythropoiesis-Stimulating Agents (ESAs) Anemia of Chronic Renal Failure: Hemoglobin Target and Dose Optimization	**Ellis F. Unger, M.D.** Acting Deputy Director for Science Office of Surveillance and Epidemiology (OSE) CDER, FDA

. **Open Public Hearing**

Committee Discussion and Questions to the CRDAC/DSaRM

Adjourn

Questions to the Committee:

1. VOTE: (Patients on hemodialysis) Based on the available data, primarily derived from the Normal Hematocrit study, should the ESA product labels be changed to state that the target hemoglobin should not exceed ~ 11 g/dL for patients on hemodialysis, the level associated with better survival in the Normal Hematocrit study? Any such hemoglobin target necessarily assumes achieved excursions into the ~ 12 g/dL range.

   YES: 5 ***NO: 14*** ***Abstain: 0***

   If no, provide a target hemoglobin and the basis for this suggestion. Describe the role that the Normal Hematocrit study contributed to your recommendation.

   Although the committee did not reach a consensus in recommending a specific target hemoglobin, many members recommended a specific target between 10-12 g/dL or a range bounded by those values. In addition, the committee suggested following:
   a) the label should be written in simpler language b) remove the words "SHOULD NOT EXCEED" from the label, and c) any important future studies should include pediatric populations.
   (Please refer to the transcript for details of the discussion.)

2. VOTE: (Patients not on dialysis) Based on the available data, primarily derived from the CHOIR study, should the ESA product labels be changed to state that the target hemoglobin should not exceed ~ 11 g/dL for patients who are not on dialysis, the level associated with fewer adverse cardiovascular events in the CHOIR study? Any such hemoglobin target necessarily assumes achieved excursions into the ~ 12 g/dL range.
   YES: 5 ***NO: 14*** ***Abstain: 0***

   If no, provide a target hemoglobin and the basis for this suggestion. Describe the role that the CHOIR study contributed to your recommendation.

   Although the committee did not reach a consensus in recommending a specific target hemoglobin, many members provided a variety of recommendations of hemoglobin ranges: 10-11 g/dL; 10.5-11.5 g/dL; 10-11 g/dL and 10-12 g/dL
   (Please refer to the transcript for details of the discussion.)

3. VOTE: Considering the Normal Hematocrit and CHOIR designs and results and the lack of randomized, controlled clinical study data to support the safety of specific hemoglobin targets lower than 11 g/dL or > 11 g/dL < 13 g/dL, discuss design considerations for subsequent studies that may provide additional dose

optimization information. Specifically, should randomized clinical studies examine an array of hemoglobin targets? If yes, what are the reasonable targets to study?

FDA requested that the committee to defer this question due to time constraints.

4. VOTE: Are the ESA dosages used to achieve the hemoglobin levels in the lower target groups in Normal Hematocrit and CHOIR sufficient to form the basis for ESA dosage recommendations? Any such recommendation necessarily recognizes the difference in dosage between subcutaneous administration to patients not on dialysis and intravenous administration to patients on dialysis.

YES: 14 ***NO: 3*** ***Abstain: 2***

If no, describe clinical study data or other considerations that should form the basis for the recommended ranges of ESA dosages and discuss whether the Normal Hematocrit and CHOIR studies be factored into that determination. If yes, suggest how the product labels should be revised.

5. DISCUSS: Please suggest ways to identify "ESA hypo-responders." For example, is failure to respond to a maximum ESA dose the most important consideration? Are sufficient data currently available to suggest how best to identify and dose these patients? If so, provide recommendations for how best to define and dose this population and your basis for such recommendations.

One or more committee members suggested the following to assist with identifying the ESA hypo-responders:
a) Conduct randomized controlled trials to look for potential ways to identify hypo-responders;
b) Establish a definition of "hypo-responder" to assist in recognizing toxicity vs. hypo-responsiveness;
c) Address a description of hypo-responsiveness in the label with the available observational data as soon as possible;
d) Recognize the clinical symptoms to identify hypo-responders in the hospitalized populations (i.e. iron deficiency, infection, inflammation) to assist with dose adjustments; and
e) Assess pharmacokinetics studies in Chronic Kidney Disease populations to see if there is a correlation with hypo-responders

Future trials

6. DISCUSS: Discuss dosing algorithm hypotheses that could be tested in clinical studies. Considerations may relate to criteria for terminating a dose or reducing a dose by specific amounts/proportions in patients whose hemoglobin response exceeds the target or who experience an excessive rate of rise, or conversely who do not show an appropriate hemoglobin response or rate of rise. What should be the primary efficacy outcomes?

One or more committee members addressed the following for both questions #3 and #6:
- ***a) The committee encouraged the agency to work with CMS to lighten the substantial constraints to reimbursement. The committee felt that the treatments are being tailored toward the reimbursement patterns. If clinicians were not forced into certain patterns, the treatment could occur in a rational way to achieve the optimal level;***
- ***b) There is great need for formal prospective clinical analysis of the risks/benefits of hemoglobin targets of 10, 11 and 12 g/dL, quality of life, and pediatric populations***
- ***c) The need to consider causes for insufficient responses to ESAs (i.e. iron, folic acid, carnitine, acidosis, nutritional status);***
- ***d) Routine surveillance in the care of patients for identification of hypo-responders; and***

e) Address new developments in pharmacokinetics and dosage formulations (i.e. extended subcutaneous, depo-form, infusion pumps, or sustained released form)

(Please refer to the transcript for detail discussions)

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