

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Drug Safety and Risk Management Advisory Committee

February 1, 2008
Hilton Washington DC/Silver Spring, Maryland Ballrooms,
8727 Colesville Rd., Silver Spring, MD.

Drug Safety and Risk Management Advisory Committee Members Present (voting)

Terry Davis, Ph.D., Sean Hennessy, Pharm.D, Ph.D., Judith Kramer, M.D., M.S., Timothy Lesar, Pharm.D., Sander Greenland, Dr.P.H. (via telecon)

Drug Safety and Risk Management Advisory Committee Consultants (voting):

Michael Lincoff, M.D., Robert Harrington, M.D., Emil Paganini, M.D., Henry Black, M.D., Gail Macik, M.D., Gary Brittenham, M.D., Charles Peterson, M.D., Harvey Klein, M.D., Cassandra Henderson, M.D., Charles Lockwood, M.D., Arthur Levin, M.P.H (Consumer Representative), JoEllen Deluca (Patient Representative)

Industry Representative (non-voting):

Bruce Burlington, M.D.

Drug Safety and Risk Management Advisory Committee Members Absent:

Susan Heckbert, M.D., Ph.D., Richard Platt, M.D., M.Sc.

FDA Participants:

Richard Pazdur, M.D., Dwaine Rieves, M.D., Kathy Robie Suh, M.D., Ph.D., Min Lu, M.D., Christy John, Ph.D.

Open Public Hearing Speakers:

Indu Lew, Susan Wysocki, Elena Rios, Ralph Rogers, Phillip Hadley, Jonathan Waters, Francis Hutchins

Executive Secretary

Teresa A. Watkins

I certify that I attended the February 1, 2008 meeting of the Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Teresa A. Watkins
Executive Secretary, DSaRM

_____/s/_____
Sean Hennessy, PharmD, Ph.D.
Acting Chair, DSaRM

Minutes

Drug Safety and Risk Management Advisory Committee Meeting February 1, 2008

A verbatim transcript will be available in approximately four to six weeks, sent to the Division and posted on the FDA website at:

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

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA. The meeting was called to order by Sean Hennessy, Pharm.D., Ph.D. (Acting Chair, DSaRM); the conflict of interest statement was read into the record by Teresa Watkins (Designated Federal Official). There were approximately 95 persons in attendance. There were 7 speakers for the Open Public Hearing Session

Attendance:

Drug Safety and Risk Management Advisory Committee Members Present (voting)

Terry Davis, Ph.D., Sean Hennessy, Pharm.D, Ph.D., Judith Kramer, M.D., M.S., Timothy Lesar, Pharm.D., Sander Greenland, Dr.P.H. (via telecon)

Drug Safety and Risk Management Advisory Committee Consultants (voting):

Michael Lincoff, M.D., Robert Harrington, M.D., Emil Paganini, M.D., Henry Black, M.D., Gail Macik, M.D., Gary Brittenham, M.D., Charles Peterson, M.D., Harvey Klein, M.D., Cassandra Henderson, M.D., Charles Lockwood, M.D., Arthur Levin, M.P.H (Consumer Representative), JoEllen Deluca (Patient Representative)

Industry Representative (non-voting):

Bruce Burlington, M.D.

Drug Safety and Risk Management Advisory Committee Members Absent:

Susan Heckbert, M.D., Ph.D., Richard Platt, M.D., M.Sc.

FDA Participants:

Richard Pazdur, M.D., Dwaine Rieves, M.D., Kathy Robie Suh, M.D., Ph.D., Min Lu, M.D., Christy John, Ph.D.

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Issue:

The committee discussed the efficacy and safety of new drug application (NDA) 22-054, INJECTAFER® (Ferric Carboxymaltose), Luitpold Pharmaceuticals, Incorporated, used for the treatment of iron deficiency anemia in postpartum patients or iron deficiency anemia in patients with heavy uterine bleeding

The agenda proceeded as follows:

Call to Order

Introduction of Committee

Sean Hennessy, Pharm.D, Ph.D.

Acting Chair, DSaRM

Conflict of Interest Statement

Teresa Watkins, Pharm.D., R.Ph.

Acting Designated Federal Officer,
DSaRM

Opening Remarks

Dwaine Rieves, M.D.

Acting Director, Division of Medical
Imaging and Hematology Products,
CDER/FDA

Overview of Iron Deficiency Anemia

Reema Batra, M.D.

Assistant Professor of Medicine
The George Washington University
School of Medicine Washington, DC

Sponsor Presentation

Luitpold Pharmaceuticals, Inc.

Introduction

Marc Tokars

Senior Director, Clinical Operations
Luitpold Pharmaceuticals

Medical Need

Patricia Ford, M.D.

Professor of Medicine,
University of Pennsylvania Medical
School

FCM Rationale, Overall Safety Summary and
Risk Management, Overall Cardiac Safety

Antoinette Mangione, MD, Pharm.D

Medical Director, Luitpold
Pharmaceuticals

Preclinical Safety

James Connor, Ph.D.

Distinguished Professor and Vice Chair
Department of Neurosurgery
Pennsylvania State University

Cardiac SAE Case Review

Leslie Cooper, M.D.
Professor of Medicine,
Mayo Clinic College of Medicine

Non-Cardiac Safety and Mortality

David Van Wyck, M.D.
Professor of Medicine and Surgery,
University of Arizona College of
Medicine

Mortality Epidemiology

Elizabeth Andrews, Ph.D., M.P.H.
RTI International

Clinical Perspective

Lawrence T. Goodnough, M.D.
Professor of Pathology and Medicine,
Stanford University School of Medicine

Break

Luitpold's overview of Risk Management Program

Antoinette Mangione, MD, Pharm.D
Medical Director, Luitpold
Pharmaceuticals

FDA Presentation

FDA Overview of Parenteral Iron products

Kathy Robie Suh, M.D., Ph.D
Team Leader, Division of Medical
Imaging and Hematology Products,
CDER/FDA

FDA Medical Review

Min Lu, M.D.
Medical Officer, Division of Medical
Imaging and Hematology Products,
CDER/FDA

FDA Clinical Pharmacology Review

Christy John, Ph.D.
Clinical Pharmacologist, Office of
Clinical Pharmacology, CDER/FDA

Luitpold's Risk Management Plan and
Post Marketing Safety Surveillance
Program

Elizabeth Andrews, Ph.D., M.P.H.
RTI International

Questions to Presenters

Lunch Break

Open Public Hearing

Discussion

Break

Questions to the DSaRM committee

1. (Vote) Injectafer is proposed for use in the treatment of iron deficiency anemia among postpartum patients (PP) and patients with heavy uterine bleeding (HUB), including patients who might otherwise receive treatment with oral iron. Oral iron was the control treatment within most randomized clinical studies, although some studies compared Injectafer to Venofer or a placebo. Of concern were numerical imbalances in adverse events, including mortality, as follows:

Mortality		
Group	Injectafer	Control
All randomized, multicenter studies	5/1206 (0.4%)	1/994* (0.1%)
Randomized, multicenter, oral-iron controlled studies	4/1057 (0.4%)	0/834 (0%)

*oral iron, Venofer or placebo

Correlates to the mortality data include a slightly higher rate of serious cardiac events among patients receiving Injectafer than oral iron (0.9% vs. 0.4% in oral-iron controlled studies) and the relatively common occurrence of grade 3 hypophosphatemia (8 to 70% vs. 0 in oral-iron controlled, PP and HUB studies).

Do the clinical data indicate that Injectafer is associated with a mortality disadvantage compared to oral iron? Please discuss your response.

YES = 12

NO = 2

ABSTAIN = 2

TOTAL = 16

(Due to technical difficulties, the member participating via phone did not vote on this question)

2. Injectafer is proposed for use in the treatment of iron deficiency anemia in PP women or women who are anemic secondary to HUB. Injectafer has been shown to replenish iron and improve hemoglobin concentrations in these patients. Some women with anemia secondary to the PP condition or HUB can be successfully treated with oral iron. Clinical studies were not designed to assess the safety and efficacy of Injectafer specifically among women who had an unsatisfactory response to oral iron or were intolerant of oral iron. In addition, FDA has identified safety concerns of increased mortality and hypophosphatemia, as noted in question 1.

a. (Vote) Do the available efficacy and safety data support a favorable benefit-risk assessment for Injectafer in the treatment of iron deficiency anemia in PP women or women with HUB, without qualifiers or restrictions in this proposed usage?

YES = 2

NO = 14

ABSTAIN = 1

TOTAL = 17

b. (Vote) If you voted "no" in 2a, do the available efficacy and safety data support a favorable benefit-risk assessment for Injectafer in the treatment of iron deficiency anemia in PP women or women with HUB who have had an unsatisfactory response to oral iron or were intolerant of oral iron? As noted above, this population was not studied and safety issues identified in question 1 have not been examined in this population in a randomized trial in which Injectafer was compared to other parenteral iron compounds.

YES = 10

NO = 5

ABSTAIN = 2

TOTAL = 17

3. (Discussion) If you recommend marketing approval, please discuss designs for studies that FDA should request the manufacturer conduct post-marketing.

There were several suggestions including but not limited to restrictive prescribing (i.e., not for use in chronic kidney disease patients), large randomized clinical trials that involve chronic kidney disease patients and other high risk groups (i.e., postpartum patients with pre-eclampsia), trials which utilize active comparison to other available intravenous iron products in women who are unresponsive to or intolerant of oral iron, trials in women which utilize active comparison with the standard of care (oral iron and/or blood transfusions), and trials which further explore serious adverse events (i.e., infection including sepsis and cardiac adverse events). Please refer to the transcript for a complete description.

4. (Discussion) If you do not recommend marketing approval, discuss the important features of additional clinical studies to characterize safety and establish net clinical benefit for Injectafer.

There were several suggestions including but not limited to trials utilizing currently available intravenous iron products as the active comparators in broader populations than those Luitpold is currently studying, trials versus iron sucrose in chronic kidney disease patients, studies to address non-transferrin bound iron fraction, relative-risk studies utilizing currently available intravenous iron products as the active comparators, and trials to assess the risk of using Injectafer in women who are not iron deficient. Future studies must do a better job of creating balanced allocation. Please refer to the transcript for a complete description

4:30 p.m. Adjourn
