Food and Drug Administration
Center for Drug Evaluation and Research
National Labor College, 10000 New Hampshire Avenue, Silver Spring, Maryland

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on October 16, 2007.

On October 16, 2007 the committee discussed regulatory considerations for extending the use of phosphate binders from the dialysis population (where they are approved) to the pre-dialysis population (where no products are approved). The committee heard presentations on this topic from Shire Development, Genzyme Corporation, and Fresenius Medical Care.

These summary minutes for the October 16, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on Tuesday, October 23, 2007.

I certify that I attended the October 16, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Miller, M.P.H., R.N.	Robert A. Harrington, M.D.	Date
Designated Federal Official	(Acting) Chair	

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 October 16, 2007 at the National Labor College, 10000 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the sponsors (Fresenius, Genzyme and Shire). The meeting was called to order by Robert A. Harrington, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy A. Miller, M.P.H. (Designated Federal Official). There were approximately 100 persons in attendance. There was one speaker for the Open Public Hearing sessions.

Issue: The committee discussed regulatory considerations for extending the use of phosphate binders from the dialysis population (where they are approved) to the pre-dialysis population (where no products are approved). The committee heard presentations on this topic from Shire Development, Genzyme Corporation, and Fresenius Medical Care.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
Steven D. Findlay, M.P.H.; John M. Flack, M.D., M.P.H.,; Robert A. Harrington, M.D., F.A.C.C.; Lynn L. Warner Stevenson, M.D.; Abraham Michael Lincoff, M.D., F.A.C.C.; Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.; John R. Teerlink, M.D.

Special Government Employee Consultants (Voting):
Henry R. Black, M.D.; Jeffrey Kopp, M.D.; Michael Proschan, Ph.D.; Malazia Scott; Susan Shurin, M.D.; Nelson B. Watts, M.D., F.A.C.P.; Kathryn L. Weise, M.D., M.A.

Non-voting Participants:
John Neylan, M.D. (Industry Representative)

Cardiovascular and Renal Drugs Advisory Committee Members Not Present:
Frederick J. Kaskel, M.D., Ph.D.

FDA Participants (Non-Voting):
Robert Temple, M.D.
Norman Stockbridge, Ph.D., M.D.

Designated Federal Official:
Cathy A. Groupe Miller, M.P.H., R.N.

Open Public Hearing Speaker:
Kathe LeBeau

The agenda was as follows:

Call to Order and Introductions	**Robert A. Harrington, M.D., F.A.C.C.** (Acting) Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy Groupe, M.P.H., R.N.** Designated Federal Official Cardiovascular and Renal Drugs Advisory Committee
Introduction and Background	**Norman Stockbridge, M.D., Ph.D.** Director, Division of Cardiovascular and Renal Products FDA Center for Drug Evaluation and Research

Open Public Hearing

Sponsor Presentations:

Introduction of Invited Speakers	**Raymond Pratt, M.D.** Research and Development Scientific Lead Renal Business Unit Shire Incorporated
Overview Fresenius/Genzyme/Shire	**Pamela M. Williamson, R.A.C.** Senior Vice President, Regulatory Affairs and Collaboration Corporate Quality Genzyme Corporation

FDA Guest Speaker Presentation:

Chronic Kidney Disease-Related Mineral and Bone Disorders: Public Health Problem	**Kerry Willis, Ph.D.** Senior Vice President, Scientific Activities National Kidney Foundation

Break

Sponsor Presentations Continued:

Pathophysiology of Hyperphosphatemia	**Keith Hruska, M.D.** Professor of Pediatrics, Medicine and Cell Biology Unit Leader Pathobiology Director Division of Pediatric Nephrology Washington University School of Medicine
Clinical Consequences of Chronic Kidney Disease Bone and Mineral Disease	**Peter McCullough, M.D., M.P.H.** Chief, Division of Nutrition and Preventive Medicine William Beaumont Hospital
Benefits and Risks of Phosphate Binder Therapy In Pre-Dialysis Patients	**David Bushinsky, M.D.** Professor of Medicine, Nephrology Unit and of Pharmacology and Physiology Associate Chair of Medicine University of Rochester School of Medicine and Dentistry
Fresenius/Genzyme/Shire Conclusion	**Jose Diaz-Buxo, M.D.** Medical Director, Products and Hospital Group Senior Vice President, Home Therapies Development Fresenius Medical Care

Lunch

Questions to Presenters for Fresenius Medical Care, Genzyme Corporation and Shire Incorporated

Break

Question to the Committee

Adjournment

Questions to the Committee:

1. One possible theory for approving phosphate binders for use in pre-dialysis patients is the following:

   Serum phosphate is a valid surrogate for clinical benefit *in pre-dialysis patients*.

   - For what clinical outcomes is serum phosphate plausibly part of the pathogenesis?
   - Considering only the variability related to the natural history of the disease, for which clinical outcomes has serum phosphate been shown to be predictive of risk?
   - For which clinical outcomes have interventions targeting serum phosphate in the pre-dialysis setting been shown to alter risk in the manner predicted by the change in phosphate?
   - **<u>Vote</u>: Is serum phosphate a validated surrogate for clinical outcomes among pre-dialysis patients?**

     YES: 0 NO: 14

     The committee commented that lowering serum phosphate by drugs had not been shown to lead to improvement in outcome.
   - If you voted *yes* above, please say whether you believe the clinical benefits to be manifest before patients require dialysis and why you believe this.

(See transcripts for detailed discussion)

2. A second theory for approving phosphate binders for use in pre-dialysis patients is the following:

   Serum phosphate is a valid surrogate for clinical benefit *in dialysis patients*, and earlier intervention is beneficial.

   Let us first consider whether serum phosphate is a valid surrogate in dialysis patients:
   - In the previous question, you described where you thought serum phosphate was in the pathophysiological chain to particular clinical end points. Please add anything you think relevant to distinguish pre-dialysis and dialysis settings.
   - For which clinical outcomes have interventions targeting serum phosphate in the dialysis setting been shown to alter risk in the manner predicted by the change in phosphate?
   - **<u>Vote:</u> Is serum phosphate a validated surrogate for clinical outcomes among dialysis patients?**

     YES: 3 NO: 11

   - If you voted *no* above, please say whether you believe specific clinical benefits are, nevertheless, attributable to treatment of elevated serum phosphate in dialysis patients, and if so, what the benefits are and why you believe this.

Most of the committee was reluctant to ascribe specific clinical benefits to the treatment of elevated serum phosphate. Nevertheless, some felt that alone or in combination with various other interventions, there was less bone disease (secondary hyperparathyroidism) in patients who receive

this therapy. The committee believed that lowering phosphate is 'part' of a therapeutic strategy that is beneficial to patients.

(See transcripts for detailed discussion)

3. If you believe that there is adequate evidence linking changes in serum phosphate to clinical outcomes in dialysis patients, then the issue is when one should initiate such treatment.
    - Please evaluate the following as risks of early treatment with phosphate binders. Please indicate if you believe these risks to be product-specific.
        - Minor gastrointestinal adverse events
        - Major gastrointestinal adverse events
        - Drug interactions
        - Interference with absorption of nutrients
        - Heavy metal accumulation
        - Development of intolerance to phosphate binder products
        - Others?
    - Please describe the incremental benefits of use of phosphate binders in pre-dialysis patients over use in dialysis patients.
    - Please evaluate the incremental benefits of pre-dialysis use compared with the risks.

Most of the committee did not feel there were adequate data provided to make product-specific distinctions regarding risk. Many had concerns about the lack of information regarding drug interactions.

The committee could not identify an incremental clinical benefit associated with treatment of hyperphosphatemia in the pre-dialysis setting.

(See transcripts for detailed discussion)

4. <u>Vote:</u> Should the indications for phosphate binders extend to use in pre-dialysis patients with marked hyperphostemia? Please make any appropriate product-specific qualifications.

YES: 8 NO: 4 ABSTAIN: 1

There was discussion and clarification around several of the "yes" votes. Three Committee members noted that they voted "yes" specifically so that clinicians would have an option available for treatment of markedly elevated levels of phosphate. All members felt that the body of evidence around phosphate binders in the pre-dialysis population was limited and inadequate to promote wide use in the pre-dialysis population with modest elevations in serum phosphate.

(See transcripts for detailed discussion)

5. If you voted *no* above, please outline what data would provide adequate support to establish a claim for use of phosphate binders in pre-dialysis patients.

The Committee unanimously noted that further studies were needed in both the dialysis and pre-dialysis populations to characterize the clinical benefits and risks associated with phosphate binders. The Committee appreciated the challenges of studying these populations but stated that innovative approaches to trial designs should allow insight into the use of these agents in the pre-dialysis population. Randomized clinical trials with clinical outcome endpoints were recommended by the majority of the Committee.

The committee adjourned at approximately 5:00 pm

(See transcript for detailed discussion)