Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee
September 9, 2011

Topic:
The committee discussed the benefits and risks of long-term bisphosphonate use for the treatment and prevention of osteoporosis (thinning and weakening of bones that increases the chance of having a broken bone) in light of the emergence of the safety concerns of osteonecrosis of the jaw (jawbone death) and atypical femur fractures (unusual broken thigh bone) that may be associated with the long-term use of bisphosphonates. Bisphosphonates for the treatment and prevention of osteoporosis include: FOSAMAX (alendronate sodium) tablets and solution and FOSAMAX PLUS D (alendronate sodium/cholecalciferol) tablets, Merck & Co., Inc.; ACTONEL (risedronate sodium) tablets, ATELVIA (risedronate sodium) delayed release tablets, and ACTONEL WITH CALCIUM (Copackaged) (risedronate sodium with calcium carbonate) tablets, Warner Chilcott, LLC; BONIVA (ibandronate sodium) tablets and injection, Roche Therapeutics, Inc.; RECLAST (zoledronic acid) injection, Novartis Pharmaceuticals Corporation; and the generic equivalents for these products, if any.

The summary minutes for the September 9, 2011 joint Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee meeting were approved on September 16, 2011.

I certify that I attended the September 9, 2011 joint Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee meeting and that these minutes accurately reflect what transpired.

-signed-
Yvette Waples, Pharm.D.
(Designated Federal Officer)

-signed-
Sandra A. Carson, M.D.
(Acting Chair)

Summary Minutes of the Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee
September 9, 2011

The following is the final report of the joint Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee meeting held on September 9, 2011. A verbatim transcript will be available in approximately six weeks, sent to the Division of Reproductive and Urologic Drugs and the Office of Surveillance and Epidemiology and posted on the FDA website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm262537.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm250295.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Advisory Committee for Reproductive Health Drugs (ACRHD) and Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on September 9, 2011 at the Marriott Inn and Conference Center, University of Maryland University College (UMUC), Adelphi, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and sponsors. The meeting was called to order by Sandra Carson, M.D. (Acting Chair). The conflict of interest statement was read into the record by Yvette Waples, Pharm.D. (Acting Designated Federal Officer). There were approximately 300 people in attendance. There were eighteen (18) Open Public Hearing speakers.

Issues: The committee discussed the benefits and risks of long-term bisphosphonate use for the treatment and prevention of osteoporosis (thinning and weakening of bones that increases the chance of having a broken bone) in light of the emergence of the safety concerns of osteonecrosis of the jaw (jawbone death) and atypical femur fractures (unusual broken thigh bone) that may be associated with the long-term use of bisphosphonates. Bisphosphonates for the treatment and prevention of osteoporosis include: FOSAMAX (alendronate sodium) tablets and solution and FOSAMAX PLUS D (alendronate sodium/cholecalciferol) tablets, Merck & Co., Inc.; ACTONEL (risedronate sodium) tablets, ATELVIA (risedronate sodium) delayed release tablets, and ACTONEL WITH CALCIUM (Copackaged) (risedronate sodium with calcium carbonate) tablets, Warner Chilcott, LLC; BONIVA (ibandronate sodium) tablets and injection, Roche Therapeutics, Inc.; RECLAST (zoledronic acid) injection, Novartis Pharmaceuticals Corporation; and the generic equivalents for these products, if any.

Attendance:
ACRHD Members Present (Voting): Bart Clarke, M.D.; Kathleen Hoeger, M.D., M.P.H.; John Kittelson, Ph.D.; Michele Orza, Sc.D. (Consumer Representative)

ACRHD Members Present (Non-Voting): Robert Gut, M.D., Ph.D. (Industry Representative)

ACRHD Members Not Present: Paul Blumenthal, M.D., M.P.H.; Richard Bockman, M.D., Ph.D.; Melissa Gilliam, M.D., M.P.H.; Valerie Montgomery Rice, M.D.

DSaRM Members Present (Voting): William Cooper, M.D., M.P.H.; Brian Erstad, Pharm.D.; Sonia Hernandez-Diaz, M.D., Dr.PH.; David Madigan, Ph.D.; Elaine Morrato, Dr.PH.; Lewis Nelson, M.D.; Maria Suarez-Almazor, M.D., Ph.D.; Allen Vaida, Pharm.D., FASHP; Almut Winterstein, Ph.D.; T. Mark Woods, Pharm.D.

DSaRM Members Present Not Present: Sherine Gabriel, M.D.; Peter Kaboli, M.D.; Sidney Wolfe, M.D.

Temporary Members (Voting): Kenneth Burman, M.D.; Sandra Carson, M.D. (Acting Chair); Michael Collins, M.D.; William Duncan, M.D., Ph.D.; Julia Johnson, M.D.; Karla Miller, M.D.; Clifford Rosen, M.D.; Mary Ruppe, M.D.; Elizabeth Tucker (Patient Representative)

Guest Speaker (Non-Voting): Douglas C. Bauer, M.D.

Speaker (Non-Voting): Robert A. Adler, M.D.

FDA Participants (Non-Voting): Julie Beitz, M.D.; Judy Staffa, Ph.D., R.Ph.; George Benson, M.D.; Theresa Kehoe, M.D.; Marcea Whitaker, M.D.; Fatmatta Kuyateh, M.D., M.S.

Designated Federal Officer: Yvette Waples, Pharm.D.

Open Public Hearing Speakers: Cynthia Pearson (Executive Director, National Women's Health Network); Diana Klebanow, Ph.D. (Femur Fracture Victims' Group); Kerry L. Bryan; Liyun Lai; Elizabeth Shane, M.D. (The American Society for Bone and Mineral Research); Betsy Levin; Andrea Cook; Diane Zuckerman, Ph.D. (President, National Research Center for Women's & Families, Cancer Prevention and Treatment Fund); Jerri Iehl; Sammy Almashat, M.D., M.P.H. (Staff Researcher, Public Citizen Health Research Group); Robert D. Bunning, M.D., FACP, FACR (Medical Director of Orthopedic and Musculoskeletal Programs, National Rehabilitation Hospital); Jennifer P. Schneider, M.D., Ph.D.; Jeanne Mathews (Assistant Vice President, Public Relations and Marketing); Karen Wright; Laura Tosi, M.D. (American Association of Orthopaedic Surgeons); Carol Unanski; Orrel Judith Lanter; Robert R. Recker, M.D., M.A.C.P., F.A.C.E. (President, National Osteoporosis Foundation and Director, Osteoporosis Research Center Creighton University)

The agenda proceeded as follows:

Call to Order and Opening Remarks *Introduction of Committee*	***Sandra A. Carson, M.D.*** *Acting Chair, Advisory Committee for Reproductive Health Drugs (ACRHD)*
Conflict of Interest Statement	***Yvette Waples, Pharm.D.*** *Acting Designated Federal Officer* *ACRHD*

Opening Remarks	***George Benson, M.D.*** *Deputy Director, Division of Reproductive and Urologic Drugs (DRUP)*
Speaker Presentation	
Osteoporosis Treatment: Clinical Decisions Today	***Robert A. Adler, M.D. (Speaker)*** *Professor, Division of Endocrinology* *Virginia Commonwealth University* *McGuire VA Medical Center*
FDA Presentations	
Bisphosphonates: The Regulatory History	***Theresa Kehoe, M.D.*** *Clinical Team Leader, DRUP*
Bisphosphonate Long Term Use Risk Benefit Analysis: Safety	***Fatmatta Kuyateh, M.D.*** *Lead Medical Officer* *Division of Epidemiology (DEPI)*
Bisphosphonate Long Term Use Risk Benefit Analysis: Efficacy	***Marcea Whitaker, M.D.*** *Medical Officer, DRUP*
Clarifying Questions to the Presenters	
BREAK	
Guest Speaker Presentation *Fracture Risk After Discontinuation of Bisphosphonates*	***Douglas C. Bauer, M.D. (Guest Speaker)*** *Professor, Department of Medicine* *University of California, San Francisco*
Clarifying Questions to the Presenters	
Sponsor Presentations	
Merck: *Summary of Merck Responses to FDA Questions (FOSAMAX® and FOSAMAX® PLUS D)*	***Arthur Santora. II., M.D., Ph.D.*** *Executive Director* *Clinical Research, Diabetes and Endocrinology* *Merck Research Laboratories* *Merck & Co., Inc.*
Warner Chilcott: *Risedronate Sodium Actonel®, Actonel® with Calcium & Atelvia®* *NDA #s 020835, 021823 & 022560*	***Matthew W. Lamb, Pharm.D.*** *Senior Director, Regulatory Affairs* *Warner Chilcott (US), LLC*
	Paul D. Miller, M.D. *Distinguished Clinical Professor of Medicine* *University of Colorado Health Sciences*

	Center *Medical Director* *Colorado Center for Bone Research*
Hoffmann- La Roche: *BONIVA® (ibandronate sodium)*	***Joseph Kohles, Ph.D.*** *International Medical Leader for Boniva* *Hoffmann-La Roche, Inc.*
Novartis: *Reclast® (zoledronic acid) Injection: Presentation to the Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee*	***Christina Bucci-Rechtweg, M.D.*** *Global Program Medical Director* *Novartis Pharmaceuticals Corporation*
Clarifying Questions to the Presenters	
LUNCH	
Open Public Hearing	
Bisphosphonate Long Term Use Risk Benefit Analysis Wrap Up	***Theresa Kehoe, M.D.*** *Clinical Team Leader, DRUP*
Clarifying Questions to the Presenters	
Questions to the ACRHD & DSaRM and ACRHD & DSaRM Discussion	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Please discuss the strength of the available evidence that suggests that the safety concerns outlined below are associated with long-term (greater than 3 to 5 years) use of bisphosphonates.
   - atypical subtrochanteric and femoral fractures
   - osteonecrosis of the jaw
   - esophageal cancer

   Committee Discussion*: The committee agreed that there is emerging evidence that suggests that atypical subtrochanteric and femoral fractures and osteonecrosis of the jaw are associated with dose and duration of use of bisphosphonates. In addition, there is some concern of a possible association with esophageal cancer, although the evidence is less compelling. The committee noted that more definitive and longer term studies with larger sample sizes are necessary in order to evaluate background risks, dose and duration of use of bisphosphanates, and predetermining factors. The committee also recommended that research in basic science as well as translational science be performed in order to better understand the mechanism of action and bone physiology. Additionally, epidemiological data evaluating risk in patients on bisphosphonates for >3 years should be separated from those data in patients on bisphosphonates for >5 years. Lastly, a recommendation was*

made for better radiological evidence of the fractures and osteonecrosis. Please see the transcript for details of the Committee discussion.

2. **DISCUSSION:** Please discuss whether the data presented support the effectiveness of long-term (greater than 3 to 5 years) use of bisphosphonates.

   Does this apply to all patients undergoing treatment for osteoporosis or to a subset of patients, such as patients with a T-score of <-2.5 and/or a prior history of fracture?

   ***Committee Discussion**: Some committee members noted that the data presented does not address the efficacy of bisphosphonate use greater than three years thus more data is needed in order to evaluate the effectiveness of long-term use of bisphosphonates. On the other hand, some other members commented that efficacy was seen in patients with a T-score of <-2.5 and no prior history of fracture. In addition, it was recommended that subgroup analysis would be helpful in determining what subset of patients would benefit from long-term use of bisphosphonates and that each drug be evaluated individually and not as a class. Please see the transcript for details of the Committee discussion.*

3. **DISCUSSION:** Please discuss the overall risks and benefits of continuous long-term use (greater than 3 to 5 years) of bisphosphonates.

   ***Committee Discussion**: The committee raised the following concerns relating to the evaluation of the overall risks and benefits of continuous long-term use of bisphosphonates: limited data on risk, unclear as to what the alternatives to bisphosphonates are after three years of use, and what role body mass index (BMI) plays in bisphosphonate use, etc. There was a general consensus that the benefit to risk ratio can not be defined without more information. Please see the transcript for details of the Committee discussion.*

4. **DISCUSSION:** Please discuss whether restricting the duration of use or implementing a drug holiday would be beneficial for patients requiring long term bisphosphonate treatment for osteoporosis.

   Does this apply to all patients undergoing treatment for osteoporosis or to a subset of patients, such as patients with a T-score of <-2.5 and/or a prior history of fracture?

   ***Committee Discussion**: The committee noted that there is no data to truly support that restricting the duration of use was beneficial for patients requiring long-term bisphosphonate treatment for osteoporosis. Additionally, the committee was not confident that implementing a drug holiday or discontinuing bisphosphonate use after a period time would be beneficial. Therefore, the committee concurred that more data is needed and recommend the inclusion of biomarkers and alternative treatments for osteoporosis in the collection of data. Please see the transcript for details of the Committee discussion.*

5. **VOTE:** Bisphosphonate labeling for prevention or treatment of osteoporosis currently carries the following "Important Limitation of Use":

   The safety and effectiveness of [drug] for the treatment of osteoporosis are based on clinical data of [xx] years duration. The optimal duration of use has not been determined. All

patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

Do you recommend that the label should further clarify the duration of use for bisphosphonates? ***[Voting Question]*** *Yes, No, or Abstain*

- If yes, please outline your recommendation.

YES: 17 NO: 6 ABSTAIN: 0

Committee Discussion*: The majority of the committee recommended that the label should further clarify the duration of use for bisphosphonates. Those members who voted "Yes" commented that the frequency of re-evaluation is important as the risk versus benefit ration may change over time, and thus re-evaluation should be clearly defined and not left as "on a periodic basis". Also, some committee members recommended that the rare serious adverse events should be included in this section of the label. The committee members who voted "No" noted that the labeling does not need further clarification at this time and that it should only include information that is known since there is a lack of data on the benefit versus risk of limiting the duration of use of bisphosphonates. Please see the transcript for details of the Committee discussion.*

6. **DISCUSSION:** Please discuss for which outcomes further evidence should be obtained, how best that might be accomplished and in what priority order they should be investigated:
   - atypical subtrochanteric and femoral fractures
   - osteonecrosis of the jaw
   - esophageal cancer
   - osteoporotic fracture reduction efficacy with long-term (greater than 3-5 years) continuous bisphosphonate use
   - the effect of a drug holiday on bisphosphonate safety and effectiveness

   Committee Discussion*: The committee agreed that further evidence should be obtained on all the disorders listed. There was no consensus on the priority order; however, the majority of the committee agreed that osteoporotic fracture reduction efficacy with long-term continuous bisphosphonate use and atypical subtrochaneric and femoral fractures should be high on the list and esophageal cancer should be ranked last. As for priority ranking #3, the committee was divided between osteonecrosis of the jaw and the effect of a drug holiday on bisphosphonate safety and effectiveness. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 4:30 p.m.