CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022560Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Reproductive and Urologic Products

NDAs:	20-560 – Fosamax/alendronate sodium tablets 20-835 – Actonel/ risedronate sodium tablets 21-455 – Boniva/ibandronate sodium tablets 21-575 – Fosamax/alendronate sodium oral solution 21-762 – Fosamax/alendronate sodium with cholecalciferol tablets 21-817 – Reclast/zoledronic acid injection, 5 mg 21-823 – Actonel with Calcium/risedronate sodium with calcium carbonate 21-858 – Boniva/ibandronate sodium injection 22-560 – Atelvia/risedronate sodium delayed release tablets
Product Class:	Bisphosphonate products approved for osteoporosis indications
SPONSORS:	Warner Chilcott Company, LLC (Actonel, Actonel with Calcium, Atelvia) Novartis Pharmaceutical Corp (Reclast) Merck, Sharp and Dohme, Corp (Fosamax, Fosamax plus D) Hoffman-LaRoche Inc (Boniva)
FROM:	Scott Monroe, M.D.
DATE:	October 8, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

There are four FDA-approved bisphosphonates for the treatment and/or prevention of osteoporosis indications: alendronate (Fosamax, Fosamax Plus D), risedronate (Actonel, Actonel W/Calcium), ibandronate (Boniva), and zoledronic acid (Reclast). The first approval of a bisphosphonate product for the prevention and/or treatment of postmenopausal osteoporosis occurred in 1995 (Fosamax, NDA 20-560). In June, 2008, the Division became aware of cases of atypical subtrochanteric and diaphyseal femoral fractures through peer-reviewed literature. At that time, initial review of all available data, including bisphosphonate manufacturers' clinical trials and postmarketing reports, as well as published literature, did not clearly demonstrate a relationship between the bisphosphonate use and atypical femoral

fractures. The review of the data was constrained by the lack of a uniform case definition for the atypical femoral fractures of concern.

In September, 2009, the American Society of Bone and Mineral Research (ASBMR) convened a Task Force to evaluate atypical subtrochanteric fractures seen with bisphosphonate use. The plan of the task force was to conduct a comprehensive scientific investigation and develop a case definition, recommend diagnostic techniques, and recommend orthopedic and medical management. The task force report was published on September 14, 2010.[1] The task force concluded that there is biologic plausibility and evidence suggesting a relationship between long-term bisphosphonate use and atypical subtrochanteric and femoral shaft fractures. However, these fractures can also occur in patients who have not been treated with bisphosphonates and their true incidence in both treated and untreated patients is unknown. Atypical subtrochanteric and femoral shaft fractures appear to be more common in patients who have been exposed to long-term bisphosphonates, usually for more than 3 years. The task force recommendations include 1) that specific diagnostic and procedural codes be created and that an international registry be established to facilitate studies of the clinical and genetic risk factors and optimal surgical and medical management of these fractures; 2) physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of bisphosphonates; and 3) research directions should include development of animal models, increased surveillance and additional epidemiological and clinical data to establish the true incidence of and risk factors for this condition and to inform orthopaedic and medical management.

Therefore, we consider the new safety analyses obtained from the ASBMR taskforce publication, which includes a comprehensive review of published and unpublished data, to be "new safety information" as defined in FDAAA.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of bisphosphonate products outweigh the risk of atypical fracture. In reaching this determination we considered the following:

A. It is estimated, based on the National Health and Nutrition Examination Survey III (NHANES III) data, that approximately 10 million patients in the U.S. have osteoporosis and another 33.6 million have low bone mass (osteopenia) of the hip. Osteoporosis is a systemic skeletal disease characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased risk of fracture. While it is not possible to precisely estimate the number of women with osteoporosis on bisphosphonates, bisphosphonates have the largest market share for treatment of osteoporosis. In 2009, it was estimated that approximately 5.19 million patients filled a prescription for bisphosphonates, of those 4.18 million were women over 55 years of age.

[1] Shane E (co-chair), Burr D (co-chair), et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a Task Force of the American Society for Bone Mineral Research. Epub September 14, 2010.

B. Postmenopausal osteoporosis is a serious disease that is characterized by low bone mass and structural deterioration of bone tissue. Osteoporosis leads to bone fragility and an increased risk of common types of fractures. While some fractures may heal with full recovery, other fractures particularly in the elderly population may be associated with chronic pain, loss of height, disability (physical limitations and stooped posture that can affect breathing and digestion), and death. Hip fracture can result in a 10 – 20% excess mortality within one year. The aim of bisphosphonate therapy is to restore or maintain bone mass and to prevent fractures. Bisphosphonates are a widely used treatment to reduce bone fractures.

C. Based on the phase 3 clinical trials, the bisphosphonate products listed above were demonstrated to be effective and safe in reducing the incidence of fractures and/or improvement of bone mineral density in postmenopausal women studied. These phase 3 clinical trials range in duration from three to five years.

D. Clinical trial data for bisphosphonate products which are used for treatment of postmenopausal osteoporosis support effectiveness for reduction of bone fractures for three to five years. At this time, the optimal duration of bisphosphonate treatment is unknown, although some patients continue bisphosphonate treatment for more than 5 years after initiation of treatment.

E. Reports of unusual subtrochanteric fractures emerged in the literature in 2005 and the Division of Reproductive and Urologic Products has been actively investigating this safety issue since 2008. During the literature review, it became clear that subtrochanteric fractures generally occur in two populations – younger patients with high energy trauma and elderly patients with minor trauma. Clinical and adverse event data were requested from all sponsors of bisphosphonate products to further evaluate the issue. The submissions described that subtrochanteric fractures accounted for approximately 1 – 6% of hip and femur fractures recorded in clinical trials. When evaluated in terms of postmarketing adverse event reports, subtrochanteric fractures accounted for approximately 2 – 29% of hip and femur fractures reported. Therefore, it is clear that subtrochanteric fractures occur in the osteoporotic population, but the data from the clinical trials and postmarketing reports do not allow adequate evaluation for the presence of the atypical features of the subtrochanteric fractures that are reported in the literature.

   The American Society of Bone and Mineral Research (ASBMR) provided a draft definition of atypical subtrochanteric fractures in January 2010. Based on this definition, an investigation of AERS reports was conducted. Overall, 1623 crude AERS reports of "fracture" associated with bisphosphonate use (alendronate, etidronate, ibandronate, pamidronate, risedronate, tiludronate, zoledronate) were found. After narrowing the search using specific terms, 211 unduplicated cases were identified, 126 cases involving treatment and prevention of osteoporosis.

   The recently published report by ASBMR's Subtrochanteric Femoral Fracture Task Force makes clear that a causal association between bisphosphate use and atypical fractures has not been firmly established and the actual incidence of atypical subtrochanteric and

diaphyseal femoral fractures in the postmenopausal osteoporosis population remains uncertain. To date, large epidemiologic evaluations are constrained by the lack of adequate radiographic evaluation of the fractures. Data from the Task Force report that suggest an association between bisphosphonate use and atypical fractures include a comprehensive review of 310 case reports of atypical fracture that revealed that 94% of patients had taken bisphosphonates, most for more than 5 years; as well as data from a large U.S. health maintenance organization that estimates that the incidence of atypical fractures increased progressively from 2/100,000 cases per year with 2 years of bisphosphonate use to 78/100,000 cases per year for 8 years of bisphosphonate use. These findings raise concern regarding the optimal duration of use of bisphosphonates medications in the prevention and treatment of osteoporosis.

F. None of the bisphosphonate products are new molecular entities. The first bisphosphonate approved for the treatment of postmenopausal osteoporosis was Fosamax (alendronate sodium) in 1995. Subsequently, Actonel (risedronate sodium), Boniva (ibandronate sodium), and Reclast (zoledronic acid) have been approved in 2000, 2003, and 2006 respectively. Most of these drugs are now available in multiple dosing regimens that range from daily to monthly for oral preparations and every three months to once yearly for intravenous preparations.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for bisphosphonate products. FDA has determined that bisphosphonate products pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of bisphosphonate products. FDA has determined that bisphosphonate products are products for which patient labeling could help prevent serious adverse effects and have serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use, a bisphosphonate product.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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/s/

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10/08/2010

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