DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021858

SAFETY LABELING CHANGE AND REMS NOTIFICATION

Hoffman-La Roche, Inc
Attention: Margaret Jack
Program Director
340 Kingsland St Bldg 719/4
Nutley, NJ 07110-1199

Dear Ms. Jack:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Boniva, (ibandronate sodium) Injection 3mg/3mL.

Sections 505(o)(4) and 505-1 of the FDCA authorize FDA to require holders of approved drug and biological product applications to make safety related labeling changes, and to develop and comply with risk evaluation and mitigation strategies (REMS) based upon new safety information that becomes available after approval of the drug or biological product.

Since Boniva was approved on January 6, 2006, we have become aware of a possible increased risk of atypical subtrochanteric and diaphyseal femoral fractures in patients taking bisphosphonates, including Boniva, for the treatment and/or prevention of osteoporosis. Recent publications, including the 2010 Report of a Task Force of the American Society for Bone and Mineral Research, suggest that the risk of atypical fractures and diaphyseal femoral fractures increases with increased duration of bisphosphonate exposure. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

SAFETY LABELING CHANGE

In accordance with section 505(o)(4) of the FDCA, we are notifying you that, based on the new safety information described above, we believe that the information regarding possible increased risk of atypical fractures and diaphyseal femoral fractures should be included in the labeling for bisphosphonates approved for the treatment and/or prevention of osteoporosis as follows:

1. Add the following language (underlined) to the **INDICATIONS AND USAGE** section**,** Treatment and/or Prevention of Postmenopausal Osteoporosis section of the package insert:

The safety and effectiveness of Boniva for the treatment of osteoporosis are based on clinical data of one year 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.

2. Revise the **PRECAUTIONS** section of the package insert to add the following paragraphs (underlined) following the Musculoskeletal Pain discussion:

   Atypical Subtrochanteric and Diaphyseal Femoral Fractures:

   Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

   Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

   Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

3. Medication Guide

   In addition to the labeling changes described above, you should convert your patient package insert to a Medication Guide for Boniva, as shown in the Medication Guide attached (See ENCLOSURES). Your Medication Guide must include information about the serious risk of atypical subtrochanteric and diaphyseal femoral fractures and will be considered part of the proposed REMS described below.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements

described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT**" or "**SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED**."

If you do not submit electronically, please send 5 copies of the submission.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Boniva to ensure the benefits of the drug outweigh the risks of atypical subtrochanteric and diaphyseal femoral fractures in patients using bisphosphonates for the treatment and/or prevention of osteoporosis.

Your proposed REMS must include the following:

> **Medication Guide**: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Boniva poses 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 Boniva. FDA has determined that Boniva is a product for which patient labeling could help prevent serious adverse effects and/or that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Boniva.
>
> Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Boniva.
>
> **Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

In accordance with section 505-1, within 30 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to DRUG (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS for NDA 021858/S-###**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 021858**." If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
REMS Appendix A
REMS Appendix B
Medication Guide

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
10/13/2010