



NDA 021817/S-009

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Monique Small, PharmD  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Small:

Please refer to your Supplemental New Drug Application (sNDA) S-009 (labeling and proposed risk evaluation and mitigation strategy [REMS]), dated November 11, 2010, received November 12, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Reclast (zoledronic acid) Injection 5 mg in a 100mL ready-to-infuse solution.

We acknowledge receipt of your amendments dated January 11 and 12, 2011.

We also refer to our letter dated October 13, 2010, notifying you, under Section 505(o)(4) and 505-1 of the FDCA, of new safety information that we believe should be included in the labeling for bisphosphonates and that a REMS is necessary. This information pertains to the risk of atypical subtrochanteric and diaphyseal femoral fractures with the bisphosphonate drug class.

This supplemental new drug application provides for revisions to the labeling for Reclast. The agreed upon changes to the language included in our October 13, 2010, letter are as follows (additions are noted by underline and deletions are noted by ~~striketrough~~):

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, the following text was added:
  - a. Recent Major Changes:
    - Indications and Usage (1.6) 01/2011
    - Warnings and Precautions (5.5) 01/2011
  - b. Indications and Usage :

The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.
  - c. Warnings and Precautions:

- Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture

2. In the **INDICATIONS AND USAGE** section, the following text was added:

#### 1.6 Important Limitations of Use

The safety and effectiveness of Reclast for the treatment of osteoporosis are based on clinical data of three 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.

3. In the **WARNINGS AND PRECAUTIONS** section, the following text was added:

#### 5.5 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 trauma 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 (b) (4) bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients (b) (4) 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.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days from the date of this letter, amend all pending supplemental applications for this NDA, including pending CBE supplements, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes with the revisions indicated above approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the carton and immediate container labels attached as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 021817/S-009.**” Approval of this submission by FDA is not required before the labeling is used.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

This supplemental new drug application provides for a proposed REMS. Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated October 13, 2010.

Since Reclast was approved on April 16, 2007, we have become aware of the risk of atypical subtrochanteric and diaphyseal femoral fractures with the bisphosphonate drug class. We

consider this information to be “new safety information” as defined in section 505-1(b) of FDCA.

Your proposed REMS, submitted on January 11, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, an evaluation of patients’ understanding of the serious risks of Reclast.

We remind you that assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you will also need to submit a REMS, REMS supporting document, and any required appended documents for that authorized generic, to this NDA. In other words, you must submit a complete proposed REMS that relates only to the authorized generic product. Review and approval of the REMS is required before you may market your product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 021817 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 021817  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 021817  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

**PROMOTIONAL MATERIALS**

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

**LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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:

Content of Labeling  
Carton and Container Labeling  
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AUDREY L GASSMAN  
01/25/2011