



NDA 21-318/S-012

Eli Lilly and Company
Attention: Jean A. Wright, D.V.M.
Regulatory Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Wright:

Please refer to your supplemental new drug application (sNDA) dated February 8, 2007, received February 12, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Forteo (teriparatide, rPTH[1-34]).

We acknowledge receipt of your submissions dated January 23 and 29, March 13, April 20, June 11 and 29, July 7, 9, 13, 15, 16, 17, and 21, 2009.

Your submission of January 23, 2009, constituted a complete response to our November 25, 2008, action letter.

This supplemental new drug application provides for the use of Forteo (teriparatide, rPTH[1-34]) for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-318/S-012.**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because Forteo (teriparatide, rPTH[1-34]) would be unsafe for use in the pediatric population and is not intended for patients with open epiphyses.

Section 505(o) and Section 505-1 of the FDCA authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)) and to require the submission of a Risk Evaluation and Mitigation Strategy (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)).

Since Forteo (teriparatide, rPTH[1-34]) was approved on November 26, 2002, we have become aware of postmarketing reports of cases of osteosarcoma in patients treated with Forteo (teriparatide, rPTH[1-34]). The new indication proposed in Supplement 12 for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture will expand the population of patients expected to use the drug, thus changing the risk-benefit profile of Forteo (teriparatide, rPTH[1-34]). We consider this information to be “new safety information” as defined in FDAAA.

After consideration of this new safety information, we have determined that postmarketing requirements are needed to assess the risk of osteosarcoma and that a REMS is necessary for the drug to ensure that the benefits of the drug outweigh the risks. These requirements are described more fully below.

POSTMARKETING REQUIREMENTS UNDER 505(o)

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of osteosarcoma.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. Teriparatide Post-Approval Osteosarcoma Surveillance Study (B3D-MC-GHBX). Study B3D-MC-GHBX is an ongoing, case-series study to identify cases of osteosarcoma among men and women 40 years of age and older and determine which cases, if any, have a history of teriparatide treatment. The study was initiated after Forteo (teriparatide, rPTH[1-34]) was first approved in 2002 and will continue with the following changes:
 - The revised objective of this study will be to identify approximately 1/3 of the incident cases of osteosarcoma annually, in men and women > 40 years of age in the United States, and determine if the patients were exposed to Forteo (teriparatide, rPTH[1-34]).
 - The duration of the study, which was originally a minimum of 10 years, will be increased to 15 years.

The timetable you submitted on July 16, 2009, states that you will conduct this study according to the following timetable:

| | |
|---------------------------|--------------------|
| Final Protocol Submission | September 23, 2009 |
| Study Completion Date: | December 15, 2018 |
| Final Report Submission: | September 1, 2019 |

2. Forteo User Registry Study (B3D-MC-GHBX[2])
Study B3D-MC-GHBX(2) is a prospective cohort study that will allow voluntary registration of adult Forteo (teriparatide, rPTH[1-34]) users in the United States during a 5 year enrollment period that will be initiated on approval of this supplement. On an annual basis, data collected from the registered patients will be linked with participating cancer registries to ascertain any new cases of osteosarcoma in Forteo-exposed patients. Outcomes will be ascertained through pathologically confirmed cases of osteosarcoma newly reported at any time after the registered patient began Forteo (teriparatide, rPTH[1-34]) treatment.

The timetable you submitted on July 16, 2009, states that you will conduct this study according to the following timetable:

| | |
|----------------------------|--------------------|
| Final Protocol Submission: | September 23, 2009 |
| Study Completion Date: | December 15, 2021 |
| Final Report Submission: | September 1, 2022 |

Submit the revised protocols to your IND, with a cross-reference letter to this NDA 21-318. Submit all final reports to your NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

You previously committed to conduct the above-described Teriparatide Post-Approval Osteosarcoma Surveillance Study under Postmarketing Commitment #1, NDA 21-318, approved on November 26, 2002. At this time, we are releasing this commitment because it has been converted to a postmarketing requirement.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Forteo to ensure the benefits of the drug outweigh the risks based on the new safety information described above.

Your proposed REMS, submitted on July 21, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

- a. Patients' understanding of the serious risks of Forteo (teriparatide, rPTH[1-34])
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
- d. An assessment of healthcare providers' awareness of:
 1. the maximum 2-year lifetime duration of therapy,
 2. appropriate patient population characteristics, and
 3. the potential risk for osteosarcoma
- e. An assessment of the number of Forteo (teriparatide, rPTH[1-34]) prescribers identified to receive the Dear HealthCare Provider (DHCP) Letter and the number of DHCP letters mailed
- f. An assessment of the percentage of targeted physicians who are presented with the Highlighted Information for Prescribers via Sales Specialists, the website, or medical information department

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. 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 updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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.

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

NDA 21-318 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 21-318
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21-318
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

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

CONTENT OF LABELING

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission “Product Correspondence – Final SPL for approved NDA 21-318/S-012.” In addition, within 14 days of the date of this letter, amend any pending supplement(s) for this NDA with content of labeling in SPL format to include the changes approved in this supplement.

Pursuant to 21 CFR 201.57(x)(18) and 201.80(f)(2), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling.

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

PROMOTIONAL MATERIALS

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 Celia Peacock, R.D., M.P.H., Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

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

/s/

George Benson

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