



NDA 21-318

Eli Lilly and Company  
Attention: Gregory Enas, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Enas:

Please refer to your new drug application (NDA) dated November 29, 2000, received November 30, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Forteo [teriparatide (rDNA origin)] Injection.

We acknowledge receipt of your submissions dated September 19, October 3, 10, 21, and 30, and November 12, 13, and 21(2), 2002. Your submission of September 19, 2002 constituted a complete response to our May 16, 2002, action letter.

This new drug application provides for the use of Forteo (teriparatide) Injection for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture, and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

Sufficient stability data has been submitted to support a 24-month expiration date.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert, medication guide, user manual, pen label, and pen carton submitted November 21, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-318." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated May 6, 2002:

The commitment is to establish a post-approval surveillance program to evaluate whether there is an association between treatment with Forteo and the occurrence of osteosarcoma. This will be based primarily on a case-series study with the objective of identifying approximately 40% of the incident cases of osteosarcoma annually, in men and women  $\geq 40$  years of age in the United States. A survey of these cases will be conducted to obtain data on the frequency of a history of Forteo treatment, and on gender, age, and other descriptive characteristics. If warranted, based on the results of case-series surveillance and discussions between you and FDA, the case-series study will be developed into a case-control study, to compare the frequency of a history of Forteo treatment between the osteosarcoma cases and appropriate controls, with control for any factors that are found to be confounding.

Data collection for the post-approval surveillance program will begin within 90 days after the first marketed use of Forteo. Progress reports will be submitted to FDA at six months, one year, and annually thereafter, with an emphasis on evaluating the effectiveness of surveillance in meeting the objective of obtaining data for approximately 40% of the incident cases of osteosarcoma in men and women  $\geq 40$  years of age in the United States, as described above.

You also committed to maintain the post-approval surveillance program, as described above, for ten years. Unless, discussions between you and FDA concerning new scientific developments occur that warrant, by mutual agreement, early termination of the study. In summary:

Protocol Submission:	The protocol entitled, "Forteo <sup>TM</sup> Post-Approval Surveillance Study: Case Series" was submitted to IND (b)-----on March 8, 2002.
Study Start:	Within 90 days after the first marketed use of Forteo.
Final Report Submission:	Eleven years from the date of this letter

Submit protocol amendments to your IND, and all study reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and the number of patients entered into the study. All submissions, including supplements, relating to this postmarketing study commitment must be prominently labeled **"Postmarketing Study Protocol Amendment," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."**

In addition, in your October 30, 2001, and May 6, 2002 submissions you agreed to a phased introduction to the marketplace of Forteo Injection with restricted initial marketing by a limited sales force. You also agreed to no direct-to-consumer advertising, and restrictions on physician receipt of samples. Further, you agreed to a physician education program to emphasize that Forteo is indicated to treat only patients at high risk for osteoporotic fractures.

Also, in your April 23, 2002, and May 6, 2002 submissions you agreed to include prescription data on Forteo Injection use by geographic regions of the USA in the quarterly periodic safety update reports for the first three years, and then submit the reports annually, as required under 21CFR 314.80(c)(2). You also agreed to an extended follow-up of patients in Study B3D-MC-GHBJ entitled, "Extended Follow-up of Patients in LY333334 Trials" for 5 years beyond the end of the original clinical trial, and submit a final report in the third quarter of 2004.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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David Orloff  
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