CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-318

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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 ≥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 ≥ 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™ Post-Approval Surveillance Study: Case Series" was submitted to IND [redacted] 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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/s/

David Orloff
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We acknowledge receipt of your submissions dated October 3, 12, and 30, November 15, December 6(2), 10, and 13, 2001, and January 22, 23, and 31, February 4, March 14 and 20, and April 11, 23(2), 25, and 29, and May 2, 6, 9, and 14, 2002. Your submission of November 15, 2001 constituted a complete response to our October 2, 2001 action letter.

This new drug application provides for the use of Forteo [teriparatide (rDNA origin)] 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 it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

> During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved.

In addition, we anticipate submission of the final study report for a follow-up rat carcinogenicity study entitled, "A Special Chronic Study in Female Fischer 344 Rats Given LY333334 by Subcutaneous Injection for up to 2 years, Studies R00100 and R00200."

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

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/s/

David Orloff
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We acknowledge receipt of your submissions dated December 14, 2000, and January 10, February 26(2) and 28, March 9, 12, 14, 15, 22, 28, 29, and 30, April 10, May 1, 2, 4, 15, 16, 23, 24, 25, 30, and 31, June 4(2), 5, 6(2), 8, 11(3), 12(2), 15(2), 18, 19, 20(2), and 25, July 2, 11, 16(2), 19, 20, 23, and 24, August 13, 17, 23, and 24, and September 10, 18(2), 19, and 26(2), 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved for the *treatment* of osteoporosis in a restricted population of post-menopausal women or *to increase bone mineral density* (BMD) in a restricted population of men with osteoporosis, targeted because of a high risk for fracture, it will be necessary for you to address the following:

1. Labeling

   Submit draft labeling (including a Medication Guide as described under 21 CFR Part 208) that appropriately represents benefits and risks (e.g., with a Boxed Warning regarding the osteosarcoma finding in rats) and includes specific selection criteria for patients at high risk for fracture (e.g., history of osteoporotic fracture, multiple risk factors for fracture, failure or intolerance of previous therapy in such patients).

2. Risk management

   A. Submit a plan for limiting use of Forteo to the target populations described in the draft labeling (See #1) in whom expected benefits outweigh potential risks. The plan may possibly include a patient registry, a system that documents patient assent to treatment and acknowledgement of receipt of information regarding risks and benefits, a program of physician education, and a plan for limited initial marketing.

B. Submit a plan for post-marketing surveillance for the potential occurrence of osteosarcoma in humans treated with Forteo.

Also, during recent inspection of the Lilly Corporate Center, White River Park, manufacturing facility for the subject product of your NDA, a number of deficiencies were noted and conveyed to you by the investigator. Satisfactory inspection of that facility will be required before this application may be approved. Also, our investigators could not inspect your manufacturing facility at Rue de Colonel, Lilly, B.P. 10, in Fegersheim, France, on May 10, 2001, as FDA requested, because the facilities were not ready for inspection. A satisfactory inspection of that facility will also be required before this application may be approved.

We also anticipate submission of the final report of your ongoing repeat rat carcinogenicity study to assess the impact of age at initiation of therapy and duration of therapy with teriparatide on osteosarcoma risk in that animal model, once the study has been completed.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

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David G. Orloff, M.D.
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/s/

David Orloff
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