

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-318

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: October 15, 2002

To: NDA 21-318, N-000

From: Yvonne Yang, Ph.D.
Chemist Reviewer, HFD-510

Subject: Overall Compliance Recommendation

An overall acceptable cGMP status has been granted by the Office of Compliance on Sept-25-02 (see attached EER report for details).

This NDA can be approved. Issue an Approval Letter.

Cc: NDA # 21-318, N-000
HFD-510/Division file
HFD-510/Y Yang
HFD-510/DG Wu
HFD-510/D Hedin

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MEMORANDUM

Date: Apr-17-02
To: NDA 21-318, Forteo™, Eli Lilly and Company
From: Yvonne Yang, Ph.D.
Chemist Reviewer, HFD-510
Subject: Final Chemistry Labeling Changes

Amendment dated Apr-11-02 provides for the final chemistry labeling changes after the Mar-28-02 teleconference between the firm and the Agency. The firm has complied with all of the Agency's request regarding chemistry labeling changes, and the final chemistry labeling is acceptable.

Cc: NDA # 21-318
HFD-510/Division file
HFD-510/Y Yang
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HFD-510/R Hedin

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Duu-gong Wu
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DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-318
REVIEW #: 1

DATE REVIEWED: Sept-19-2001
REVIEWER: Yvonne Yang

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 11-29-00 | 11-30-00 | 12-04-00 |
| Amendment | 03-09-01 | 03-16-01 | |
| Amendment | 03-15-01 | 03-16-01 | |
| Amendment | 08-30-01 | 08-31-01 | |
| Amendment | 09-10-01 | 09-12-01 | |
| Amendment | 09-18-01 | 08-20-01 | |

NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Indianapolis, Indiana 46285

DRUG PRODUCT NAME:

Proprietary: Forteo™
Non-Proprietary:
Established: Teriparatide Injection
Code Name/#: CAS-52232-67-4, LY333334 (Lilly)
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION:

DOSAGE FORM: Sterile solution for injection
STRENGTHS: 825 µg/cartridge (250 µg/ml)
ROUTE OF ADMINISTRATION: Subcutaneous injection
Rx/OTC: X RX OTC
SPECIAL PRODUCTS: X YES NO

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Recombinant human parathyroid hormone (1-34)
C₂₈₁H₂₉₁N₅₅O₅₁S₂ (MW = 4,117.8 Da)
See also Chemist's Review Notes

REMARKS:

Forteo™ is a product of teriparatide [human parathyroid hormone (1-34)], which has the identical sequence of the 34 N-terminal amino acids, the biologically active fragment, of the 84-amino acid human parathyroid hormone. Teriparatide is produced in
 E. coli in which the gene encoding for rhPTH(1-34) was introduced through recombinant DNA technology. During the production phase,

 rhPTH(1-34)-fusion protein is converted to rhPTH(1-34)
 and rhPTH(1-34) subsequently purified by

Forteo™ is supplied as a sterile solution intended for subcutaneous injection in a glass cartridge pre-assembled in a pen-injector device. Each cartridge contains 825 µg of teriparatide in 3.3 ml of solution that allows delivery of 80 µl (20 µg) of teriparatide per dose for up to 28 days. The pen-injector device is similar to that used in the Humalog drug product.

Amendment dated 3-09-01 provides for corrections and clarifications to the CMC section of the original application. Amendment dated 8-30-01 provides justification for (1) comparability of drug product in cartridges and pen-injectors, and (2) the volume in cartridge sufficient to cover the 28-day dosing period. Amendments dated 9-10-01 and 9-18-01 provide for (1) more corrections to the CMC section of the original application, and (2) responses for the agency's Information Request on 8-31-01. The applicant has provided a satisfactory response to all questions listed in the Draft List of Information Request.

Tradename consult is completed, and OPDRA does not recommend the use of the proprietary name, Forteo™. However, it was found acceptable by DMEDP. Microbiology consult is completed (review #1, 2-01-01), and the list of microbiology deficiencies has been forwarded to the applicant. The firm has satisfactorily responded to all the microbiology deficiencies (see amendment dated 3-15-01 and review #2 dated 8-22-01 for details). A consult request for the pen-injector has been forwarded to CDRH, and the reviewer has concluded that the device is substantially equivalent to legally marketed pen-injectors in terms of intended use, technological characteristics, and safety and effectiveness (see review by V. Nakayama dated Mar-23-01). The recommended changes in Proposed User Manual will be forwarded to the applicant together with the recommended changes for labeling.

The Division of Manufacturing and Product Quality (HFD-324) issued a Recommendation to Withhold Approval letter dated Aug-27-01.

CONCLUSIONS & RECOMMENDATIONS:

All deficiencies forwarded to the applicant in the Information Request letter faxed on 8-31-01 have been satisfactorily addressed. The only remaining unresolved issue is the withhold recommendation by the Office of Compliance. From a chemistry point of view, this submission is approvable pending a satisfactory cGMP inspection.

cc:

Org. NDA 21-318
HFD-510/Division File
HFD-510/Y Yang/date
HFD-510/DG Wu
HFD-510/R Hedin
R/D Init. by:

Yvonne Yang, Ph.D.
Review Chemist

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Yvonne Yang

9/21/01 08:15:37 AM

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Approvable pending a satisfactory cGMP inspection.

Duu-gong Wu

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MEMORANDUM

Date: September 6, 2001

To: NDA 21-318, Forteo™, Eli Lilly and Company

From: Yvonne Yang, Ph.D., Chemist Reviewer, HFD-510

Subject: Clarification for the consultation review by CDRH

This memo is to provide a clarification for the consultation review by CDRH. The CDRH review dated Mar-23-01 identified:

- (1) Review: second paragraph, lines 3-4
"The pen injector for FORTEO is designed to administer fixed doses of **80 mcg**; the pen injector for _____"

The 80 mcg (in bold) mentioned here should be 80 mL (μ l). The pen injector for FORTEO is designed to administer fixed doses of 80 mL to deliver 20 mcg of teriparatide.

- (2) Recommendation:
"Page 37 identifies the "2" setting as a 20 mcg dose, and that the pen is ready to inject. This is inconsistent with the dose, identified by a "2", being an **80 mcg** quantity, and other discussions that the 20 mcg quantity is a priming, not dose, quantity."

The 80 mcg and 20 mcg (in bold) mentioned here are incorrectly quoted. The applicant has consistently stated in the application that the priming dose is 20 mL (μ l), and the injection dose is 80 mL (μ l), not mcg.

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HFD-510/Division file
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Blvd
Rockville, Maryland 20850

CONSULTATION REVIEW

Date: March 23, 2001

To: CDER/Division of Metabolic and Endocrine Drug Products (HFD-510)

Thru: Branch Chief,
Patricia Cricenti

From: Scientific Reviewer/HFZ-480

Document No: NDA 21-318
Company Name: Lilly Research Laboratories
Device: Forteo™ Pen Injector

Indications for Use:
The self-injection of rhPTH(1-34) Injection.

I. Review:

This is a review of the device component of an NDA for FORTEO™ teriparatide injection (rDNA origin), a parathyroid hormone. The device is a disposable, manually operated, pen injector prefilled with a 28-day supply of FORTEO (3mL). The pen injector is labeled for use with single use, disposable, pen needles made by ———. This review does not cover the pen needle, which is not provided with the device, or the 3mL drug cartridge.

The pen injector is similar to a pen injector model that is used by the sponsor in their Humalog insulin pen injector product. The construction, technical, and mechanical features of the FORTEO pen injector are the same as the Humalog pen injector. The significant difference between the two devices is in the ability to set a dose. The pen injector for FORTEO is designed to administer fixed doses of 80mcg; the pen injector for ——— is dose-adjustable from 10-600mcg. In addition to the 80mcg dose setting, the pen injector has a 20mcg setting that is used to prime the device. This priming quantity is indicated by a "1" on the dose dial; a "2" is used on the dose dial to indicate the therapeutic dose of 80mcg. The pen injector was performance tested to the requirement of ISO 11608-1:(E) "Pen Injectors for Medical Use-Part 1: Requirements and Test Methods", August 1999.

The pen injector is not a sterile device and is not intended to be sterilized.

II. Recommendation:

The pen injector is substantially equivalent to legally marketed pen injector devices, which are Class II devices, classification panel 21 CFR 880.5860, product code 80 FMF. The review of the information and data provided in NDA 21-318, volume 6 did not identify any new questions about the safe and effective use of the pen injector for the administration of FORTEO, and demonstrated that the pen injector is substantially equivalent to legally

marketed pen injectors in terms of intended use, technological characteristics, and safety and effectiveness. However, we recommend that the following two items in the Proposed User Manual (vol. 6, section 4.A.III) be discussed with the sponsor for corrective action:

page 37 identifies the "2" setting as a 20mcg dose, and that the pen is ready to inject. This is inconsistent with the dose, identified by a "2", being an 80mcg quantity, and other discussions that the 20mcg quantity is a priming, not dose, quantity.

page 41 provides instructions for the recapping of the pen needle that is inconsistent with the OSHA standard for these procedures – "Operational Exposure to Bloodborne Pathogens; Needlestick and Other Sharps Injuries; Final Rule" 29 CFR Part 1910. The sponsor can access the OSHA website at OSHA.com for additional guidance.

If you have any questions, please call me at (301) 594-1287.

Von Nakayama

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Yvonne Yang
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