Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 4, 2001

To: Gregory Enas	**From:** Randy Hedin
Company: Lilly Research Laboratories	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 317-276-1652	**Fax number:** (301) 443-9282
Phone number: 317-277-4418	**Phone number:** (301) 827-6392

Subject: Chemistry labeling comments

Total no. of pages including cover: 5

Comments: Attached is a revised draft carton label, a revised draft pen label, and general comments concerning the package labeling. Further, page 22 of the User Manual provides instructions for 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. You can access the OSHA website at OSHA.com for additional guidance. Please change the instructions for recapping appropriately.

Document to be mailed: ☐ YES ☑ NO

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Number of Pages Redacted 2

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Draft Labeling
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/s/

Randy Hedin
9/7/01 09:19:09 AM
CSO

Randy Hedin
9/13/01 09:06:55 AM
CSO

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

1 page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-318

INFORMATION REQUEST LETTER

Eli Lilly and Company
Attention: Gregory Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2546

Dear Dr. Enas:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Forteo (teriparatide) Injection.

We are reviewing the chemistry (microbiology) section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please describe the methods used to determine preservative effectiveness, including data demonstrating the efficacy of the preservative (meeting USP criteria) in the to be marketed formulation.

2. Provide an endotoxin specification for the finished product.

Also, the actual numbers of contaminated cartridges required to exceed media fill action limits may be less than those specified in the statistical table depending on the specific circumstances under which the contamination occurs. Additionally, we believe that it would be prudent to investigate any contaminated container.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson, R.Ph.
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
8/31/01 02:31:41 PM
CSO

Duu-gong Wu
8/31/01 03:32:14 PM
CHEMIST

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/s/

Joe Contrera
11/8/02 09:30:22 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-318

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

Dear Dr. Enas:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Forteo (teriparatide injection)
Review Priority Classification:	Standard (S)
Date of Application:	November 29, 2000
Date of Receipt:	November 30, 2000
Our Reference Number:	NDA 21-318

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 29, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 30, 2001, and the secondary user fee goal date will be November 30, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days

from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Executive CAC
Date of Meeting: November 5, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Robin Huff, Ph.D., HFD-570, Alternate Member
Josie Yang, Ph.D., HFD-550, Alternate Member
Karen Davis-Bruno, HFD-510, Team Leader
Gemma Kuijpers, HFD-510, Presenting Reviewer

Author of Draft: Gemma Kuijpers

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-318
Drug Name: Forteo™ (teriparatide, rhPTH1-34)
Sponsor: Eli Lilly Laboratories

BACKGROUND:
PTH (parathyroid hormone) is secreted by the parathyroid gland and is involved in the maintenance of Ca homeostasis. When it is administered in an intermittent manner by subcutaneous injection it has an anabolic effect on bone in humans and animals. The compound teriparatide (recombinant human PTH1-34, Forteo™) has been developed by Eli Lilly for the treatment of osteoporosis in postmenopausal women and men. The proposed dose is 20 mcg/day.

RAT CARCINOGENICITY STUDY:
In a previous study in male and female rats with s.c. doses of 5, 30, 75 mcg/kg/day, teriparatide caused a dose-dependent increase in the incidence of osteosarcomas and other bone tumors in all treatment groups. A follow-up s.c. carcinogenicity study with teriparatide was performed in female rats to evaluate the effects of dosing duration and age of animals at treatment onset. Animals were dosed from the age of 2 months or 6 months, for a duration of either 6 months or 24/20 months. Study doses were 5 and 30 mcg/kg/day, N/group was 60. Groups were labeled alphabetically (A through I) with suffix 1 indicating the 5 mcg/kg low dose, and suffix 2 the 30 mcg/kg high dose. Arm A was the negative (vehicle) control, and arm B the positive control (30 mcg/kg/day, 24mo). The most relevant study arms were those in which animals were dosed for 6 months with follow-up (H1 and H2, E1 and E2), or dosed continuously for 24-20 months (B, I1 and I2). Doses were expected to yield AUC multiples of 3x and 20x the human AUC at the 20 mcg/day clinical dose.

FOLLOW-UP RAT STUDY RESULTS:
Arms B and I2 were clearly positive with 9/60 and 5/60 osteosarcomas,

respectively. Also, 1/60 to 2/60 osteomas or osteblastomas were observed in each of these two treatment arms. One (1/60) osteosarcoma was observed in arm A. Two osteosarcomas (2/60) each were seen in the 6-month treatment arms with 30 mcg/kg/day in older animals (E2) and younger animals (H2). One (1/60) osteosarcoma and one (1/60) osteoma were observed in the 6-month treatment arm with 5 mcg/kg/day in younger animals (H1). No bone tumors were detected in the 5 mcg/kg/day arms in which animals were started on treatment at the skeletally mature age of 6 months, for a duration of either 6 or 20 months. Large, reversible increases in bone mass were seen in all treatment arms.

EXECUTIVE CAC RECOMMENDATIONS AND CONCLUSIONS:

- The Committee agreed that the tumor findings were clearly related to dose and treatment-duration

- The Committee felt that the study was well designed and informative, and that the results appeared to be consistent with those of the previous study.

- Considering the results of the previous and the current study with 5 and 30 mcg/kg, the Committee felt that the maturity of the skeleton at the time of treatment onset was an important factor determining bone tumor incidence.

- The Committee noted that although the 5 mcg/kg dose in mature animals produced no osteosarcomas or other bone tumors, due to the relatively low statistical power of rodent bioassays especially for rare tumor types, this dose should not be considered a no-adverse-effect level.

- The Committee suggested that the results at 5 mcg/kg could be included in the product label with the animal dose represented by a human exposure multiple.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, HFD 510
/KDavis-Bruno, HFD-510
/GKuijpers, HFD-510
/RHedin, HFD-510
/ASeifried, HFD-024

Meeting Date: November 28, 2001 Time: 12:00 - 1:30 AM Location: Conf. Rm. "C"

NDA 21-318 Forteo [teriparatide injection (rDNA origin)]

Type of Meeting: Guidance

External participant: Eli Lilly and Company

Meeting Chair: Dr. Eric Colman

External participant lead: Dr. Sunita Zulani

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Office of Drug Evaluation II:

John Jenkins, M.D., Director

Division of Metabolic and Endocrine Drug Products:
David Orloff, M.D., Director
Eric Colman, M.D., Clinical Team Leader
Bruce Schneider, M.D., Clinical Reviewer
Bruce Stadel, M.D., Clinical Reviewer
Gemma Kuijpers, Ph.D., Pharmacology Reviewer
Randy Hedin, R.Ph., Senior Regulatory Management Officer

Division of Biometrics II:

Joy Mele, M.S., Reviewer
Todd Sahlroot, Ph.D., Team Leader

Office of New Drug Chemistry:
Yvonne Yang, Ph.D., Reviewer

Division of Pharmaceutical Evaluation II
Jim Wei, Ph.D., Reviewer
Sang Chung, Ph.D., Reviewer
Hae-Young Ahn, Ph.D., Team Leader

Division of Drug Marketing, Advertising and Communications
Margaret Kober, R.Ph., Reviewer
Karen Lechter, Ph.D., J.D., Reviewer

External participant Attendees and titles:

Gregory Enas, Ph.D., Director, US Regulatory Affairs
Paul Gesellchen, Ph.D., Regulatory Advisor, U.S. Regulatory Affairs
Hunter Heath, M.D., Medical Director (Endocrine), U.S. Medical Division
Bruce Mitlak, M.D. Medical Director, PTH Product Team
Ouhong Wang, Ph.D., Research Scientist, Statistics
Sunita Zalani, Ph.D., Regulatory Scientist, U.S. Regulatory Affairs
Daniel Masica, M.D., Senior Clinical Research Physician, Pharmacovigilance, Regulatory Affairs
John Vahle, Ph.D., D.V.M., Senior Research Scientist, Toxicology
Teri Crouse, J.D., DDMAC Liaison US Affiliate
Lynn Kippenhan, Global Product Team Leader, Forteo Product Team
Robert Marcus, M.D., Medical Advisor, U.S. Medical Division
Andrea Heslin-Smiley, U.S. Forteo Business Unit Leader, Forteo Business Unit

Meeting Objectives:

The meeting was requested by Lilly to discuss the October 2, 2001, Forteo approvable letter. Lilly requested feedback on the proposed risk management proposal, and post-approval osteosarcoma surveillance program. The NDA was submitted on November 29, 2000, and received on November 29, 2000, for the treatment of osteoporosis in postmenopausal women and in men. The NDA was discussed at an Advisory Committee meeting on July 27, 2001. The ten-month user fee goal date was October 2, 2001. We issued an approvable letter on October 2, 2001, and Lilly submitted a complete response to this letter on November 15, 2001, which was received on November 16, 2001. The six-month goal date for the complete response is May 16, 2002. The phase three pivotal trials were halted at approximately 18 months because osteosarcomas were seen in a rat study.

Discussion Points:

- Lilly submitted the following four questions in a background document dated on October 30, 2001. Our answers (in *italics*) follow the questions.

  1. Lilly has provided a revised label which addresses labeling elements outlined in Section 1 of the approvable letter dated 2 October 2001, including the Boxed Warning regarding the osteosarcoma finding in rats and specific selection criteria for patients at high risk of fracture. This revised label also addresses the labeling comments provided by the Agency on 20 September 2001. Per the approvable letter, Lilly agrees to submit a **Medication Guide** as a part of the complete response. Does the Agency agree that these elements

adequately address the labeling requirements outlined in the approvable letter? If not, please provide guidance. Please comment specifically on the proposed Black Box and indication language.

Specific comments will be addressed during a future labeling meeting. We have the following general comments regarding the Black Box warning and Indications and Usage sections of the labeling.

Black Box:

- *Specific information about the dose-related increase in incidence of tumors should be included in the black box warning. At a minimum the lowest multiple of exposure (3 fold) between rats and humans at which osteosarcomas were seen should be stated.*

- *Information regarding Paget's Disease and unexplained elevations in alkaline phosphatase should be retained.*

Indications and Usage:

- *The first sentence under each indication should include, "at high risk for fracture," or similar language. This is important to differentiate Forteo from other drugs approved for the treatment of postmenopausal osteoporosis and from alendronate which is approved to increase bone mineral density in men with osteoporosis. In order to clarify why Forteo is indicated only for patients at high-risk for osteoporotic fracture, we believe it is important to mention the theoretical risk of osteosarcoma in this section of the labeling.*

Lilly agreed to submit a proposal for new wording of the black box, and indications and usage section of the package insert.

Serum calcium is an additional label issue that will require discussion by the clinicians before the general meeting between Lilly and the Division to discuss labeling.

[redacted]

[redacted]

- Phased product uptake

- Limited initial marketing
- Stakeholder education (physician, patient, and pharmacist)
- Program evaluation

The Division agreed with the general approach outlined by Lilly. However, the Division will need to review the actual material planned for stakeholder education before we can comment on the appropriateness of this aspect of the risk management program.

Lilly reiterated its commitment to provide periodic updates to the Division on a quarterly basis and on an annual basis as part of the Forteo NDA Annual Report. The Division stated it would have to discuss with Lilly the specific reporting requirements, which might be specified in an action letter.

3. Lilly has also provided a post-approval osteosarcoma surveillance program, which includes active case finding and data collection; an external safety review board; long-term follow-up of clinical trial patients (Study GHBJ); and descriptive epidemiology using the SEER database (Section 4). Lilly has had multiple interactions with the Agency regarding this program, and Agency feedback has been incorporated. Lilly believes this program meets the requirement for a post-marketing surveillance plan as stated in Section 2.B. of the approvable letter. Does the Agency agree? If not, please provide guidance.

The proposal is reasonable. The Division asked if Lilly would lower the age limit for the post-approval osteosarcoma surveillance to 35 or 40 years. The

Division also requested Lilly to consider a change in wording regarding the duration of the case-series study. The wording should be modified to provide clarity that the study might not conclude at 5 years. Lilly indicated that extensive pharmacovigilance surveillance is already in place and will go on for the life of the product. The Division and Lilly agreed that these issues should be discussed further.

The Division stated that postmarketing surveillance should be a formal commitment, and formal progress reports will need to be submitted to the Division. Lilly should submit a protocol for a post-approval surveillance program as part of the commitment. Lilly asked the Division to hold all sponsors of PTH and PTH-like molecules to the same standards and commitments, and the Division replied that it tries to maintain a level playing field.

4. This briefing document provides Lilly's response to FDA comments on labeling and Lilly's proposal for risk management program. Completion of Lilly's response to the approvable letter will be submitted in November 2001. This response will have addressed all remaining requests outlined in the approvable latter. Because Lilly will have met all conditions of the approvable letter, how can Lilly and the Agency work together to achieve approval of Forteo in the first quarter of 2002?

   This is a class 2 resubmission, and the user fee goal date is May 16, 2002. The Division stated it would review the complete response as quickly as possible; however, Lilly still has manufacturing and inspection issues that need to be resolved.

- The Division inquired about the status of the ongoing rat study. Lilly indicated that the ongoing rat study will be completed in April of 2002, and an interim report will be provided to the Agency in July of 2002. The Division stated that if Forteo is approved in this review cycle, additional revisions of the label will be considered when the second rat study is complete.

Decisions (agreements) reached:

- None

Unresolved or issues requiring further discussion:

- None

Action Items:

- Lilly will submit a proposal for revised label language regarding the black box

and indications and usage sections of the label.

- Lilly and the Division will meet via telecon to discuss the serum calcium issues prior to the joint labeling meeting.

- Lilly should submit a draft protocol for a post-approval surveillance program.

Signature, minutes preparer:

Concurrence Chair:

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/s/

Randy Hedin
1/10/02 03:47:18 PM

Eric Colman
1/10/02 03:55:57 PM

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Meeting Date: July 11, 2001 Time: 3:00 - 4:00 PM Location: 14B-45

NDA 21-318 Forteo [teriparatide injection (rDNA origin)]

Type of Meeting: Teleconference

External participant: Eli Lilly and Company

Meeting Chair: Dr. Eric Colman

External participant lead: Dr. Sunita Zulani

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles, Division of Metabolic and Endocrine Drug Products:

David Orloff, M.D., Director
Eric Colman, M.D., Clinical Team Leader
Bruce Schneider, M.D., Clinical Reviewer
Bruce Stadel, M.D., Clinical Reviewer
Randy Hedin, R.Ph. Senior Regulatory Management Officer

External participant Attendees and titles:

Gregory Enas, Ph.D., Director, US Regulatory Affairs
Paul Gesellchen, Ph.D., Regulatory Advisor, U.S. Regulatory Affairs
Bruce Mitlak, M.D., Medical Director, PTH Product Team
Ouhong Wang, Ph.D., Research Scientist, Statistics
Sunita Zalani, Ph.D., Regulatory Scientist, U.S. Regulatory Affairs
Daniel Masica, M.D., Senior Clinical Research Physician, Pharmacovigilance, Regulatory Affairs
Ken Hornbuckle, Ph.D., D.V.M., Manager, Pharmacovigilance, Regulatory Affairs
John Vahle, Ph.D., D.V.M., Senior Research Scientist, Toxicology

Meeting Objectives:

The NDA was submitted on November 29, 2000, and received on November 29, 2000, for the treatment of osteoporosis in postmenopausal women and in men. The NDA will be discussed at an Advisory Committee meeting on July 27, 2001. The ten-month user fee goal date is September 30, 2001, and the twelve-month goal date is November 30, 2001. The phase three pivotal trials were halted at approximately 18 months because osteosarcomas were seen in a rat study. This teleconference was requested by the firm to discuss osteosarcoma surveillance if the drug is approved.

Discussion Points:

- The participants agreed that if teriparatide is approved a post-approval osteosarcoma surveillance program should be set up.

- The Division and the firm discussed the surveillance program, and agreed that the program should include, but not be limited to, the following elements.

    1. Quarterly reports summarizing demographic and geographic information regarding patients treated with teriparatide.

    2. An osteosarcoma case-control study. The objective of the case-control study will be to evaluate any quantifiable risk of newly diagnosed osteosarcoma that is associated with the use of teriparatide. Potential resources for the study include the National Cancer institute SEER system and possibly the Swedish Cancer Registry.

    3. The program should be set up before the drug is launched.

    4. If the male osteoporosis indication is approved, men should be included in the program.

- The firm stated they would draft a proposed osteosarcoma post-approval surveillance study, and submit it to the Division for review. The firm further stated they would work with the Division on coming to an agreement on an appropriate study.

- The above program will be discussed at the Advisory Committee meeting scheduled for July 27, 2001.

Decisions (agreements) reached:

- None

Unresolved or issues requiring further discussion:

- The makeup of the final osteosarcoma surveillance program.

Action Items:

- The firm will submit a draft osteosarcoma post-approval surveillance program for review and comment.

Signature, minutes preparer:_____

Concurrence Chair:_____

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/s/

Randy Hedin
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Eric Colman
11/9/01 07:58:55 AM

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Meeting Date: April 26, 2001 Time: 11:00 - 11:55 AM Location: 14B-45

NDA 21-318 Forteo [teriparatide injection (rDNA origin)]

Type of Meeting: Teleconference

External participant: Eli Lilly and Company

Meeting Chair: Dr. Eric Colman

External participant lead: Dr. Sunita Zulani

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles, Division of Metabolic and Endocrine Drug Products:

David Orloff, M.D., Director
Eric Colman, M.D., Clinical Team Leader
Bruce Schneider, M.D., Clinical Reviewer
Bruce Stadel, M.D., Clinical Reviewer
Gemma Kuijpers, Ph.D., Pharmacology Reviewer
Karen Davis-Bruno, Ph.D., Pharmacology Team Leader
Randy Hedin, R.Ph. Senior Regulatory Management Officer

External participant Attendees and titles:

Gregory Enas, Ph.D., Director, US Regulatory Affairs
Gregory Gaich, M.D., Senior Clinical Research Physician, PTH Product Team
Paul Gesellchen, Ph.D., Regulatory Advisor, U.S. Regulatory Affairs
Hunter Heath, M.D., Medical Director (Endocrine), U.S. Medical Division
Bruce Mitlak, M.D. Medical Director, PTH Product Team
Ouhong Wang, Ph.D., Research Scientist, Statistics
Sunita Zalani, Ph.D., Regulatory Scientist, U.S. Regulatory Affairs
Daniel Masica, M.D., Senior Clinical Research Physician, Pharmacovigilance, Regulatory Affairs
Ken Hornbuckle, Ph.D., D.V.M., Manager, Pharmacovigilance, Regulatory Affairs
John Vahle, Ph.D., D.V.M., Senior Research Scientist, Toxicology

Meeting Objectives:

The NDA was submitted on November 29, 2000, and received on November 29, 2000, for the treatment of osteoporosis in postmenopausal women and in men. The NDA will be discussed at an Advisory Committee meeting on July 27, 2001. The ten-month user fee goal date is September 30, 2001, and the twelve-month goal date is November 30,

2001. The phase three pivotal trials were halted at approximately 18 months because osteosarcomas were seen in a rat study. This teleconference was requested by Dr. Stadel to discuss how we will deal with the osteosarcoma issue if teriparatide is marketed.

Discussion Points:

- The Divison stated that this meeting is to discuss the teriparatide osteosarcoma issue, and no decisions or commitments will be made. The purpose of the meeting is to open a dialog with the sponsor on this issue. In addition, the Division is interested in the sponsor's ideas on how to screen for Paget's Disease patients who are at increased risk of osteosarcoma. Further, we would like to discuss how the firm would respond if osteosarcomas are reported in patients treated with teriparatide.

  The firm stated that it plans to do a post-approval surveillance study. The firm does not believe that osteosarcoma will be an issue in older humans. The intended human treatment population will be older men and women who will be treated for a short duration of time. The following issues were left open for discussion:

  1. What actions can be taken to help ensure that the drug will not be administered to Paget's Disease patients. What is the firm's position on the potential for screening with alkaline phosphatase?

  2. How will the firm monitor the occurrence of osteosarcoma in the treated population?

  3. Specifically, does the firm consider it feasible to monitor the occurrence of osteosarcoma using a cancer registry?

  The Division and the firm discussed the limitations of spontaneous reporting for monitoring the occurrence of osteosarcoma, the potential for active monitoring of newly-diagnosed osteosarcoma cases identified through the SEER system, the potential for use of European cancer registries, and the possible need for a case-control study, depending on the results of monitoring.

  The Division asked the firm to address the above three points, and to submit a proposal for postmarketing surveillance.

- The above issues may be discussed at the Advisory Committee, scheduled for July 27, 2001, and may be labeling issues if teriparatide is approved.

Decisions (agreements) reached:

- None

Unresolved or issues requiring further discussion:

- All

Action Items:

- The firm was asked to provide, before the Advisory Committee meeting, a proposal on how the above issues will be handled.

- The firm agreed to provide information on alkaline phosphatase monitoring, and whether the firm considers it feasible for physicians to screen for Paget's Disease Patients prior to administering the drug, if approved.

Signature, minutes preparer:_____

Concurrence Chair:_____

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/s/

Eric Colman
7/24/01 07:30:25 AM

Randy Hedin
7/23/01 03:34:01 PM

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Executive CAC
March 20, 2001

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Frank Sistare, Ph.D., HFD-910, Alternate Member
Jim Farrelly, Ph.D., HFD-530, Alternate Member
Karen Davis-Bruno, Ph.D., Team Leader
Gemma Kuijpers, Ph.D., Presenting Reviewer

Author of Draft: Gemma Kuijpers

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21,318
Drug Name: Forteo
Sponsor: Eli Lilly

LY333334 (Forteo^{R}) is the recombinant (1-34)-amino-acid fragment of human parathyroid hormone (rhPTH(1-34). When administered by daily s.c. injections, this compound causes an increase in osteoblastic bone formation resulting in increased bone mass and bone strength. The compound is under review for marketing for the indication of treatment [redacted]
One 2-year carcinogenicity study in the rat was carried out using doses of **0, 5, 30, 75 ug/kg/day**.

RAT CARCINOGENICITY STUDY:
The main result of the study was a dose-related statistically significant ($p<0.05$) increase in incidence of osteoblastoma and osteosarcoma at various bone sites in males and females in all dose groups. No bone tumors were seen in the control groups. The human exposure multiple in the dose groups varied from 1.6x to 42x. There was also a statistically significant positive dose-response relationship in the incidence of thyroid C-cell adenoma in males.

Executive CAC Recommendations and Conclusions:

- The Committee confirmed the validity of the study and the dose selection.
- The Committee concluded that the study is positive for carcinogenic findings, and that treatment of F344 rats with Forteo is associated with an increased incidence of osteosarcomas at exposure levels equivalent to intended human exposure.
- The Committee was concerned about the increased incidences in the treated groups of a number of combined neoplasms:
  - lung alveolar/bronchiolar neoplasms
  - thyroid gland C-cell adenoma and C-cell carcinoma (males)
  - skin epithelial cell neoplasms and keratoacanthoma (males and females)
  - clitoral gland (adenoma and carcinoma) in females
- The Committee recommended that additional statistical analyses of these combined tumor data be performed by CDER's Biostatistics Reviewer. Subsequent statistical analysis revealed that there was a statistically significant positive dose-response relationship in the incidence of combined thyroid C-cell adenoma and C-cell carcinoma in males, but not in the incidence of any other tumor combinations.
- The Committee recommended to the Division to request histopathologic evaluation of clitoral gland tissue from all treated animals by the Sponsor. Subsequent examination of the protocol, however, showed that clitoral gland tissue was not preserved unless a gross lesion was present. Therefore, the recommended evaluation could not be performed.
- The Committee recommended that the Division obtain historical control incidences from the testing laboratory in order to better evaluate any positive findings.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-510
/KDavisBruno, HFD-510
/GKuijpers, HFD-510
/RHedin, HFD-510
/ASeifried, HFD-024

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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.

/s/

Joseph DeGeorge
7/5/01 03:01:58 PM

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This report contains public information that has not been reviewed by the agency or the Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts will be available in about 10 days. External requests should be submitted to the Freedom of Information office.

The 76th Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee was held on July 26 and 27, 2001 at the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Versailles Rooms I, II and III.

On July 27, 2001, the meeting was 8:00 called to order by Mark E. Molitch, M.D., Acting Chair to consider **NDA 21-318, Fortéo™ (teriparatide injection, rDNA origin) Eli Lilly and Company.** There were approximately 150 people in the audience.

The committee had been provided with a briefing document from the sponsor and the FDA four weeks before the meeting. The meeting was attended by Members Allan Sampson, Ph.D., Marie Gelato, M.D., Ph.D., Deborah Grady, M.D., M.P.H., William Tamborlane, M.D., Lynne Levitsky, M.D., Thomas Aoki, M.D. , and Consultants Robert Kreisberg, M.D., Mark Molitch, M.D., Jody Pelosi, Ph.D., Consumer Representative, Eric Holmboe, MD for risk management and guest Henry G. Bone III, M.D.

Following the reading of the Meeting Statement by Kathleen Reedy, Executive Secretary, David G. Orloff, M.D., Director of the Division of Metabolic and Endocrine Drug Products extended a welcome and introduction to the topic for the day.

The Eli Lilly and Company Presentation was as follows:
Introduction: Jennifer L. Stotka, MD, Executive Director,
US Regulatory Affairs, Eli Lilly and Company
History, Mechanism of Action and Clinical Need: Robert Lindsay, MD, PhD
Professor of Clinical Medicine, Columbia University
Chief of Internal Medicine, Helen Hayes Hospital
Nonclinical Overview: John L. Vahle, DVM, PhD, Senior Research Pathologist,
Toxicology, Eli Lilly and Company
Clinical Efficacy: Bruce H. Mitlak, MD, Medical Director, Fortéo Product Team
Eli Lilly and Company
Clinical Safety: Gregory A. Gaich, MD , Senior Research Clinical Physician,
Fortéo Product Team, Eli Lilly and Company
Summary and Conclusions: Bruce H. Mitlak, MD

The FDA Presentation consisted of:
Preclinical Studies: Gemma Kuijpers, Ph.D.
Efficacy: Bruce S. Schneider, M.D.
Safety: Bruce V. Stadel, M.D., M.P.H.
all of the Division of Metabolic and Endocrine Drug Products

Speakers at the Open Public Hearing were:

1. Ronald H. White, M.S.T., Assistant Executive Director, Education, Research, and Community Affairs, National Osteoporosis Foundation
2. Deborah Zeldow, Senior Director, Strategies and Programs, Alliance for Aging Research
3. Peter Lurie, M.D., Assistant Director, Public Citizen Health Research Group

Following the Charge to the Committee by David G. Orloff, M.D. the participants engaged in discussion and addressed the following questions posed by the agency.

EFFICACY

1. Based on the information presented by the sponsor in the NDA, are the data adequate to establish that teriparatide 20 ug/day is an effective dose
   a. for the treatment of postmenopausal osteoporosis to reduce fracture risk?
      Yes – 10 No – 0
   b. to increase BMD in men with osteoporosis? **Yes – 8 No - 2**
   If the answer to either of the above is no, what additional data would be required?

SAFETY

2. Based on the information presented by the sponsor in the NDA, are the data adequate to define the safety profile of teriparatide
   a. for the treatment of postmenopausal osteoporosis? **Yes – 0 No - 10**
   b. for use to increase BMD in men with osteoporosis? **Yes – 0 No - 10**
   Consider in particular with regard to duration of use.
   If the answer to either of the above is no, what additional data would be required?

APPROVABILITY

3. Based on the data presented by the sponsor in the NDA, do you recommend approval of teriparatide
   a. for the treatment of postmenopausal osteoporosis? **Yes – 10 No - 0**
   b. to increase BMD in men with osteoporosis? **Yes – 5 No - 5**
   Consider in particular with regard to duration of use and appropriateness of teriparatide as first-line or second-line therapy for both indications.
   First Line in post-menopausal osteoporosis: 4
   Second Line: 5 (I abstention)
   If the answer to either of the above is no, what additional data would be required?

4. If the answer to either question in #3 is yes, given the theoretical risk for the development of osteosarcoma in humans treated with teriparatide:
   a. Should duration of treatment with teriparatide be limited? If yes, please comment on the recommended duration of use. **Two year limitation – unanimous**
   b. Should use of teriparatide be recommended only for certain subgroups of patients? If yes, please comment on the recommended target population(s).
   Women; as second line except in cases of failure of other therapies, high fracture rates/risk; eliminate subgroups i.e. Paget's, adolescents.

c. Should teriparatide be limited to use as second line therapy? If yes, please comment on what criteria should be established to define second-line therapy.
Yes – 5 (First line in women, second line in men – 2)
Calcium monitoring, registry of users, monitor tumor registry, (SEER)

d. Please comment on how the osteosarcoma findings in rodents should be addressed in labeling (e.g., Bolded Warning, Black Boxed Warning).
Bold print – 2 **Black Box – 6**
Patient education; nurse/educator education

POSTMARKETING/RISK MANAGEMENT

5. If the answer to either question in #3 is yes, please provide recommendations regarding strategies for postmarketing surveillance for the possible development of osteosarcoma in teriparatide-treated patients.
Case finding study to determine exposure
Case ascertainment (to determine denominator and numerator)
Rare occurrence, case collective
Registry: determine patient exposure, tumor registry, national death index
Registry: rebate card for money to increase compliance
Get advice.

6. If the answer to either question in #3 is yes, what, if any, postmarketing studies do you recommend?
Future studies with mature rats and increase number of exposures
Quality of life data with patients
Head to head with other treatments
Combination studies
Diagnose and classify disease to determine therapy, i.e. anabolic or anti-resorptive.

The meeting was adjourned at 3:30 pm.

Kathleen Reedy, RDH, MS, Health Scientist Administrator
Executive Secretary, Endocrinologic and Metabolic Drugs Advisory Committee

FDA Links Searches Check Lists Tracking Link Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

NDA Number:	021318	**Trade Name:**	FORTEO (TERIPARATIDE) 3ML CARTRIDGE
Supplement Number:	000	**Generic Name:**	TERIPARATIDE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	TREATMENT OF [redacted]
Original NDA Action Date:	10/2/01		

Indication # 1 FORTEO is indicated 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.

Comments (if any): A waiver of pediatric studies for the indication of treatment of osteoporosis is granted. See clinical team leader's memo. 5/2/02

Ranges for This Indication

Lower Range	Upper Range	Status	Date
Tanner1	Tanner5	Waived	

Comments: A waiver of pediatric studies for the indication of treatment of osteoporosis is granted. See clinical team leader's memo. 5/2/02

This page was last edited on 5/2/02

/S/ 5/2/02

Signature Date

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21318/000
Org Code : 510
Priority : 3S

Stamp Date : 30-NOV-2000
PDUFA Date : 20-NOV-2002
Action Goal :
District Goal: 21-SEP-2002

Sponsor: LILLY
, ,

Brand Name : FORTEO (TERIPARATIDE) 3ML CARTRIDGE
Estab. Name:
Generic Name: TERIPARATIDE
Dosage Form: (INJECTION)
Strength 250 MCG/ML

FDA Contacts:			
D. HEDIN	Project Manager	(HFD-510)	301-827-6392
Y. YANG	Review Chemist	(HFD-820)	301-827-6371
D. WU	Team Leader	(HFD-510)	301-827-6375

Overall Recommendation: ACCEPTABLE on 25-SEP-2002by J. D AMBROGIO(HFD-324) 301-827-0062

WITHHOLD on 15-MAY-2002by P. LEFLER(HFD-324) 301-827-0062

Establishment : CFN : 1819470 FEI : 1819470
ELI LILLY AND CO
LILLY CORP CTR/WHITE RIVER PKY/EAST DR
INDIANAPOLIS, IN 46200
DMF No: AADA:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Profile : CBI OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-SEP-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610945 FEI : 3002807475
LILLY FRANCE SA
RUE DE COLONEL LILLY B.P. 10
FEGERSHEIM, , FR
DMF No: AADA:

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-MAY-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : ——— FEI : ———

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DMF No: ---- AADA:

Responsibilities: ----

Profile	: CBI	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-APR-01		
Decision	: ACCEPTABLE		
Reason	: DISTRICT RECOMMENDATION		

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21318/000**
Priority: **1S**
Org Code: **510**
Stamp: **30-NOV-2000** Regulatory Due: **30-SEP-2001**
Action Goal:
District Goal: **01-AUG-2001**
Applicant: **LILLY**
Brand Name: **FORTEO (TERIPARATIDE) 3ML CARTRIDGE**
Established Name:
Generic Name: **TERIPARATIDE**
Dosage Form: **INJ (INJECTION)**
Strength: **250 MCG/ML**

FDA Contacts:

D. HEDIN	**(HFD-510)**	**301-827-6392**	**, Project Manager**
Y. YANG	**(HFD-820)**	**301-827-6371**	**, Review Chemist**
D. WU	**(HFD-510)**	**301-827-6375**	**, Team Leader**

Overall Recommendation:

Establishment: **1819470**
ELI LILLY AND CO
LILLY CORP CTR/WHITE RIVER PK
INDIANAPOLIS, IN 46200
DMF No:
AADA No:

Profile: **CBI**
OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-AUG-2001**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRIC**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Establishment: **9610945**
LILLY FRANCE SA
RUE DE COLONEL LILLY B.P. 10
FEGERSHEIM, , FR
DMF No:
AADA No:

Profile: **SVS**
OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date **30-JAN-2001**
Responsibilities: **FINISHED DOSAGE LABELER**
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CBI**
OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Milestone Date **10-APR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

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NDA 21-318
Forteo (tereparatide) Injection
Lilly Research Laboratories

This section is not applicable at this time.

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NDA 21-318
Forteo (tereparatide) Injection
Lilly Research Laboratories

This section is not applicable at this time.

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Number of Pages Redacted 23

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