CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021318Orig1s054

Trade Name:	FORTEO
Generic or Proper Name:	(teriparatide)
Sponsor:	Eli Lilly & Company
Approval Date:	November 16, 2020
Indication:	FORTEO is a parathyroid hormone analog, (PTH 1-34), indicated for: • Treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1) • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1) • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 021318/S-054

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: John L. Komacko
Advisor, Global Regulatory Affairs - US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Mr. Komacko:

Please refer to your supplemental new drug application (sNDA) dated and received January 16, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Forteo (teriparatide injection).

This Prior Approval supplemental new drug application provides for:

a. Removal of the Boxed Warning regarding osteosarcoma.
b. Modification of Section 2.3 (Dosage and Administration, Recommended Treatment Duration) to allow for longer duration of treatment in patients who remain at or return to having a high risk for fracture.
c. Addition of the risk of cutaneous calcification including calciphylaxis to the existing warning regarding hypercalcemia and hypercalcemic disorders
d. Revision of Section 6.3 (Adverse Reactions, Postmarketing Experience) to reflect the findings from the long-term osteosarcoma surveillance studies.
e. Revisions to the carton and container labeling.

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on October 26, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 021318/S-054**.” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

If you have any questions, call Meghna M. Jairath, Pharm.D., Senior Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, MD
Director
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021318Orig1s054

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FORTEO safely and effectively. See full prescribing information for FORTEO.

FORTEO (teriparatide injection), for subcutaneous use
Initial U.S. Approval: 1987

---------- RECENT MAJOR CHANGES ----------

Osteosarcoma Boxed Warning, Removed	11/2020
Dosage and Administration: Treatment Duration (2.3)	11/2020
Warnings and Precautions, Osteosarcoma (5.1)	11/2020
Warnings and Precautions, Hypercalcemia and Cutaneous Calcification (5.2)	11/2020

---------- INDICATIONS AND USAGE ----------

FORTEO is a parathyroid hormone analog, (PTH 1-34), indicated for:
- Treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1)
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1)
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage is 20 mcg subcutaneously once a day (2.1)
- Consider supplemental calcium and Vitamin D based on individual patient needs (2.1)
- Administer as a subcutaneous injection into the thigh or abdominal region (2.2)
- Administer initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (2.2)
- Use of FORTEO for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)

---------- CONTRAINDICATIONS ----------
- Patients with hypersensitivity to teriparatide or to any of its excipients (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Osteosarcoma: Avoid use in patients with increased risk of osteosarcoma including patients with open epiphyses, metabolic bone diseases including Paget's disease, bone metastases or history of skeletal malignancies, prior external beam or implant radiation therapy involving the skeleton, and hereditary disorders predisposing to osteosarcoma. (5.1)
- Hypercalcemia and Cutaneous Calcification: Avoid in patients known to have an underlying hypercalcemic disorder. Discontinue in patients developing worsening of previously stable cutaneous calcification. (5.2)
- Risk of Urolithiasis: Consider the risk/benefit in patients with active or recent urolithiasis because of risk of exacerbation (5.3)
- Orthostatic Hypotension: Transient orthostatic hypotension may occur with initial doses of FORTEO (5.4)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (>10%) include: arthralgia, pain, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

Digoxin: Transient hypercalcemia may predispose patients to digitalis toxicity (5.5, 7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Consider discontinuing when pregnancy is recognized (8.1)
- Lactation: Breastfeeding is not recommended (8.2)
- Pediatric Use: Safety and effectiveness not established. Avoid use due to increased baseline risk of osteosarcoma (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FORTEO is indicated:

- For the treatment of postmenopausal women with osteoporosis at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, FORTEO reduces the risk of vertebral and nonvertebral fractures.
- To increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.
- For the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is 20 mcg given subcutaneously once a day. Instruct patients to take supplemental calcium and vitamin D if daily dietary intake is inadequate.

2.2 Administration Instructions

- Administer FORTEO as a subcutaneous injection into the thigh or abdominal region. FORTEO is not approved for intravenous or intramuscular use.
- FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur *[see Warnings and Precautions (5.4)]*.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration (FORTEO is a clear and colorless liquid). Do not use if solid particles appear or if the solution is cloudy or colored.
- Patients and/or caregivers who administer FORTEO should receive appropriate training and instruction on the proper use of the FORTEO prefilled delivery device (pen) from a qualified health professional.

2.3 Recommended Treatment Duration

Use of FORTEO for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg.

4 CONTRAINDICATIONS

FORTEO is contraindicated in patients with hypersensitivity to teriparatide or to any of its excipients. Hypersensitivity reactions have included angioedema and anaphylaxis *[see Adverse Reactions (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Osteosarcoma

An increase in the incidence of osteosarcoma (a malignant bone tumor) was observed in male and female rats treated with teriparatide. Osteosarcoma has been reported in patients treated with FORTEO in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of FORTEO use *[see Dosage and Administration (2.3), Adverse Reactions (6.3), and Nonclinical Toxicology (13.1)]*.

Avoid FORTEO use in patients with (these patients are at increased baseline risk of osteosarcoma):

- Open epiphyses (pediatric and young adult patients) (FORTEO is not approved in pediatric patients) *[see Use in Specific Populations (8.4)]*.
- Metabolic bone diseases other than osteoporosis, including Paget's disease of the bone.

- Bone metastases or a history of skeletal malignancies.
- Prior external beam or implant radiation therapy involving the skeleton.
- Hereditary disorders predisposing to osteosarcoma.

5.2 Hypercalcemia and Cutaneous Calcification

Hypercalcemia

FORTEO has not been studied in patients with pre-existing hypercalcemia. FORTEO may cause hypercalcemia and may exacerbate hypercalcemia in patients with pre-existing hypercalcemia *[see Adverse Reactions (6.1, 6.3)]*. Avoid FORTEO in patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism.

Risk of Cutaneous Calcification Including Calciphylaxis

Serious reports of calciphylaxis and worsening of previously stable cutaneous calcification have been reported in the post-marketing setting in patients taking FORTEO. Risk factors for development of calciphylaxis include underlying auto-immune disease, kidney failure, and concomitant warfarin or systemic corticosteroid use. Discontinue FORTEO in patients who develop calciphylaxis or worsening of previously stable cutaneous calcification.

5.3 Risk of Urolithiasis

In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and patients treated with placebo. However, FORTEO has not been studied in patients with active urolithiasis. If FORTEO-treated patients have pre-existing hypercalciuria or suspected/known active urolithiasis, consider measuring urinary calcium excretion. Consider the risks and benefits of use in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

5.4 Orthostatic Hypotension

FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies of FORTEO in healthy volunteers, transient episodes of symptomatic orthostatic hypotension were observed in 5% of volunteers. Typically, these events began within 4 hours of dosing and resolved (without treatment) within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

5.5 Risk of Digoxin Toxicity

Hypercalcemia may predispose patients to digitalis toxicity because FORTEO transiently increases serum calcium. Consider the potential onset of signs and symptoms of digitalis toxicity when FORTEO is used in patients receiving digoxin *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Men with Primary or Hypogonadal Osteoporosis and Postmenopausal Women with Osteoporosis

The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years) *[see Clinical Studies (14.1, 14.2)]*. The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in the FORTEO group and 19% in the placebo group. Early discontinuation due to adverse events occurred in 7% in the FORTEO group and 6% in the placebo group.

Table 1 lists adverse events from these two trials that occurred in ≥2% of FORTEO-treated and more frequently than placebo-treated patients.

Table 1: Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality

	FORTEO N=691	Placebo N=691
Event Classification	**(%)**	**(%)**
Body as a Whole		
Pain	21.3	20.5
Headache	7.5	7.4
Asthenia	8.7	6.8
Neck pain	3.0	2.7
Cardiovascular		
Hypertension	7.1	6.8
Angina pectoris	2.5	1.6
Syncope	2.6	1.4
Digestive System		
Nausea	8.5	6.7
Constipation	5.4	4.5
Diarrhea	5.1	4.6
Dyspepsia	5.2	4.1
Vomiting	3.0	2.3
Gastrointestinal disorder	2.3	2.0
Tooth disorder	2.0	1.3
Musculoskeletal		
Arthralgia	10.1	8.4
Leg cramps	2.6	1.3
Nervous System		
Dizziness	8.0	5.4
Depression	4.1	2.7
Insomnia	4.3	3.6
Vertigo	3.8	2.7
Respiratory System		
Rhinitis	9.6	8.8
Cough increased	6.4	5.5
Pharyngitis	5.5	4.8
Dyspnea	3.6	2.6
Pneumonia	3.9	3.3
Skin and Appendages		
Rash	4.9	4.5
Sweating	2.2	1.7

Laboratory Findings

Serum Calcium — FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was 11% of women and 6% of men treated with FORTEO compared to 2% of women and 0% of the men treated with placebo. The percentage of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men.

Urinary Calcium — FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo *[see Clinical Pharmacology (12.2)]*.

Serum Uric Acid — FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO-treated patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo-treated patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

Renal Function — No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment.

Men and Women with Glucocorticoid-Induced Osteoporosis

The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥5mg per day prednisone or equivalent for a minimum of 3 months *[see Clinical Studies (14.3)]*. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to an oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

There was no increase in mortality in the FORTEO group compared to the active control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control).

Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively.

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other teriparatide products may be misleading.

In the clinical trial of postmenopausal women with osteoporosis *[see Clinical Studies (14.1)]*, antibodies that cross reacted with teriparatide were detected in 3% of women (15/541) who received FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

6.3 Postmarketing Experience

Adverse Reactions from Postmarketing Spontaneous Reports

The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period *[see Warnings and Precautions (5.2)]*.
- Hypercalcemia greater than 13 mg/dL has been reported with FORTEO use.

Adverse events reported since market introduction that were temporally related to FORTEO therapy include the following:

- Allergic Reactions: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria
- Investigations: Hyperuricemia
- Respiratory System: Acute dyspnea, chest pain
- Musculoskeletal: Muscle spasms of the leg or back
- Other: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema

Adverse Reactions from Observational Studies to Assess Incidence of Osteosarcoma
Two osteosarcoma surveillance safety studies (U.S. claims-based database studies) were designed to obtain data on the incidence rate of osteosarcoma among FORTEO-treated patients. In these two studies, three and zero osteosarcoma cases were identified among 379,283 and 153,316 FORTEO users, respectively. The study results suggest a similar risk for osteosarcoma between FORTEO users and their comparators. However, the interpretation of the study results calls for caution owing to the limitations of the data sources which do not allow for complete measurement and control for confounders.

7 DRUG INTERACTIONS

7.1 Digoxin
Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. FORTEO may transiently increase serum calcium. Consider the potential onset of signs and symptoms of digitalis toxicity when FORTEO is used in patients receiving digoxin *[see Warnings and Precaution (5.5) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no available data on FORTEO use in pregnant women to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Consider discontinuing FORTEO when pregnancy is recognized.

In animal reproduction studies, teriparatide increased skeletal deviations and variations in mouse offspring at subcutaneous doses equivalent to more than 60 times the recommended 20 mcg human daily dose (based on body surface area, mcg/m^2), and produced mild growth retardation and reduced motor activity in rat offspring at subcutaneous doses equivalent to more than 120 times the human dose (see *Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. The background risk in the US general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data
Animal Data
In animal reproduction studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses equivalent to 8 to 267 times the human dose (based on body surface area, mcg/m^2). At subcutaneous doses ≥60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received teriparatide during organogenesis at subcutaneous doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study in pregnant rats dosed subcutaneously from organogenesis through lactation, mild growth retardation was observed in female offspring at doses ≥120 times the human dose. Mild growth retardation in male offspring and reduced motor activity in both male and female offspring were observed at maternal doses of 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

8.2 Lactation
Risk Summary
It is not known whether teriparatide is excreted in human milk, affects human milk production, or has effects on the breastfed infant. Avoid FORTEO use in women who are breastfeeding.

8.4 Pediatric Use
The safety and effectiveness of FORTEO have not been established in pediatric patients. Pediatric patients are at higher baseline risk of osteosarcoma because of open epiphyses *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use
Of the patients who received FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and older and 23% were 75 years of age and older. Of the patients who received FORTEO in the trial of 437 men with primary or hypogonadal osteoporosis, 39% were 65 years of age and over and 13% were 75 years of age and over. Of the 214 patients who received FORTEO in the glucocorticoid induced osteoporosis trial, 28% were 65 years of age and older and 9% were 75 years of age and older. No overall differences in safety or effectiveness of FORTEO have been observed between patients 65 years of age and older and younger adult patients.

8.6 Hepatic Impairment
No studies have been performed in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

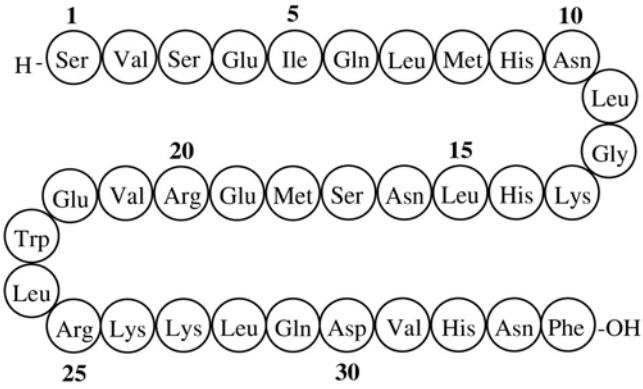
8.7 Renal Impairment
In 5 patients with severe renal impairment (CrCl<30 mL/minute), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. It is unknown whether FORTEO alters the underlying metabolic bone disease seen in chronic renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) (40 times the recommended dose) of the FORTEO prefilled delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. No fatalities associated with overdose have been reported. Additional signs, symptoms, and complications of FORTEO overdosage may include a delayed hypercalcemic effect, vomiting, dizziness, and headache.

Overdose Management — There is no specific antidote for a FORTEO overdosage. Treatment of suspected overdosage should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

11 DESCRIPTION
FORTEO (teriparatide injection) is a recombinant human parathyroid hormone analog (PTH 1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and molecular weight is 4117.8 daltons. Its amino acid sequence is shown below:



Teriparatide is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology.

FORTEO is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a single-patient-use delivery device (pen) for subcutaneous injection. Each delivery device (pen) is filled with 2.7 mL to deliver 2.4 mL. Each mL contains 250 mcg of teriparatide (as a free base), 0.41 mg of glacial acetic acid, 0.1 mg of sodium acetate (anhydrous), 45.4 mg of mannitol, 3 mg of Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the pH to 4.

Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous 84-amino acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

12.2 Pharmacodynamics

Pharmacodynamics in Men with Primary or Hypogonadal Osteoporosis and Postmenopausal Women with Osteoporosis

Effects on Mineral Metabolism — Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (e.g., increases serum calcium and decreases serum phosphorus).

Serum Calcium Concentrations — When teriparatide 20 mcg was administered once daily, the serum calcium concentration increased transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium concentration began to decline approximately 6 hours after dosing and returned to baseline by 16 to 24 hours after each dose.

In a clinical study of postmenopausal women with osteoporosis, the median peak serum calcium concentration measured 4 to 6 hours after dosing with FORTEO (20 mcg subcutaneous once daily) was 9.68 mg/dL at 12 months. The peak serum calcium remained below 11 mg/dL in >99% of women at each visit. Sustained hypercalcemia was not observed.

In this study, 11.1% of women treated with FORTEO had at least 1 serum calcium value above the upper limit of normal (ULN) (10.6 mg/dL) compared with 1.5% of women treated with placebo. The percentage of women treated with FORTEO whose serum calcium was above the ULN on consecutive 4- to 6-hour post-dose measurements was 3% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or FORTEO doses were reduced. The timing of these dose reductions was at the discretion of the investigator. FORTEO dose adjustments were made at varying intervals after the first observation of increased serum calcium (median 21 weeks). During these intervals, there was no evidence of progressive increases in serum calcium.

In a clinical study of men with either primary or hypogonadal osteoporosis, the effects on serum calcium were similar to those observed in postmenopausal women. The median peak serum calcium concentration measured 4 to 6 hours after dosing with FORTEO was 9.44 mg/dL at 12 months. The peak serum calcium remained below 11 mg/dL in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6% of men treated with FORTEO daily had at least 1 serum calcium value above the ULN (10.6 mg/dL) compared with none of the men treated with placebo. The percentage of men treated with FORTEO whose serum calcium was above the ULN on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Calcium supplementation was reduced in these men *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

In a clinical study of women previously treated for 18 to 39 months with raloxifene (n=26) or alendronate (n=33), mean serum calcium >12 hours after FORTEO treatment was increased by 0.36 to 0.56 mg/dL, after 1 to 6 months of FORTEO

treatment compared with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium >11 mg/dL, and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >11 mg/dL. The highest serum calcium reported was 12.5 mg/dL. None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum calcium were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Urinary Calcium Excretion — In a clinical study of postmenopausal women with osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily FORTEO increased urinary calcium excretion. The median urinary excretion of calcium was 190 mg/day at 6 months and 170 mg/day at 12 months. These levels were 30 mg/day and 12 mg/day higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>300 mg/day) was similar in the women treated with FORTEO or placebo.

In a clinical study of men with either primary or hypogonadal osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily FORTEO had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 220 mg/day at 1 month and 210 mg/day at 6 months. These levels were 20 mg/day higher and 8 mg/day lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (>300 mg/day) was similar in the men treated with FORTEO or placebo.

Phosphorus and Vitamin D — In single-dose studies, teriparatide produced transient phosphaturia and mild transient reductions in serum phosphorus concentration. However, hypophosphatemia (<2.4 mg/dL) was not observed in clinical trials with FORTEO.

In clinical trials of daily FORTEO, the median serum concentration of 1,25-dihydroxyvitamin D was increased at 12 months by 19% in women and 14% in men, compared with baseline. In the placebo group, this concentration decreased by 2% in women and increased by 5% in men. The median serum 25-hydroxyvitamin D concentration at 12 months was decreased by 19% in women and 10% in men compared with baseline. In the placebo group, this concentration was unchanged in women and increased by 1% in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum phosphorus were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Effects on Markers of Bone Turnover — Daily administration of FORTEO to men and postmenopausal women with osteoporosis in clinical studies stimulated bone formation, as shown by increases in the formation markers serum bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months. The maximum increases of BSAP were 45% above baseline in women and 23% in men. After discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption: urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling. Changes in BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic exposure to teriparatide in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of FORTEO on serum markers of bone turnover were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

12.3 Pharmacokinetics

Absorption — Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses (1-, 2-, and 4- times the recommended dosage, respectively). The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.

Distribution — Volume of distribution following intravenous injection is approximately 0.12 L/kg..

Elimination — Systemic clearance of teriparatide (approximately 62 L/hour in women and 94 L/hour in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. The half-life of teriparatide in serum was approximately 1 hour when administered by subcutaneous injection.

No metabolism or excretion studies have been performed with teriparatide. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

Specific Populations

Geriatric Patients — No age-related differences in teriparatide pharmacokinetics were detected (range 31 to 85 years).

Male and Female Patients — Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than women, the recommended dosage for men and women is the same.

Racial Groups — The influence of race has not been determined.

Patients with Renal Impairment — No pharmacokinetic differences were identified in 11 patients with creatinine clearance (CrCl) 30 to 72 mL/minute administered a single dose of teriparatide. In 5 patients with severe renal impairment (CrCl<30 mL/minute), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure.

Patients with Hepatic Impairment — No studies have been performed in patients with hepatic impairment. Non-specific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH(1-34) and PTH(1-84) into fragments that are cleared from the circulation mainly by the kidney.

Drug Interaction Studies

Digoxin — In a study of 15 healthy people administered digoxin daily to steady state, a single FORTEO dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect).

Hydrochlorothiazide — In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with 40 mcg of FORTEO (2 times the recommended dose) did not affect the serum calcium response to FORTEO. The 24-hour urine excretion of calcium was reduced by a clinically unimportant amount (15%). The effect of coadministration of a higher dose of hydrochlorothiazide with FORTEO on serum calcium levels has not been studied.

Furosemide — In a study of 9 healthy people and 17 patients with CrCl 13 to 72 mL/minute, coadministration of intravenous furosemide (20 to 100 mg) with FORTEO 40 mcg (2 times the recommended dose) resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%); however, these changes did not appear to be clinically important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 mcg/kg/day for 24 months from 2 months of age. These doses resulted in rat systemic exposures that were 3, 20, and 60 times higher than the systemic exposure observed in humans, respectively, following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.

The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous teriparatide doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, respectively, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of teriparatide exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day of teriparatide for 24 months or with 5 or 30 mcg/kg/day of teriparatide for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day of teriparatide for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day of teriparatide for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

No bone tumors were detected in a long-term monkey study *[see Nonclinical Toxicology (13.2)]*.

Mutagenesis
Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.

Impairment of Fertility
No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100, or 300 mcg/kg/day prior to mating and in females continuing through gestation Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m^2).

13.2 Animal Toxicology
In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 mcg/kg (2700 times the human dose based on surface area, mcg/m^2).

In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women
The safety and efficacy of once-daily FORTEO, median exposure of 19 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis. In this study 541 postmenopausal women were treated with 20 mcg FORTEO subcutaneously once daily.

All women received 1000 mg of calcium and at least 400 IU of vitamin D per day. Baseline and endpoint spinal radiographs were evaluated using the semiquantitative scoring. Ninety percent of the women in the study had 1 or more radiographically diagnosed vertebral fractures at baseline. The primary efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height of previously undeformed vertebrae. Such fractures are not necessarily symptomatic.

Effect on Fracture Incidence
New Vertebral Fractures — FORTEO, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, reduced the risk of 1 or more new vertebral fractures from 14.3% of women in the placebo group to 5.0% in the FORTEO group (444 of the 541 patients treated with 20 mcg once daily of FORTEO were included in this analysis). This difference was statistically significant ($p<0.001$); the absolute reduction in risk was 9.3% and the relative reduction was 65%. FORTEO was effective in reducing the risk for vertebral fractures regardless of age, baseline rate of bone turnover, or baseline BMD (*see* Table 2).

Table 2: Effect of FORTEO on Risk of Vertebral Fractures in Postmenopausal Women with Osteoporosis

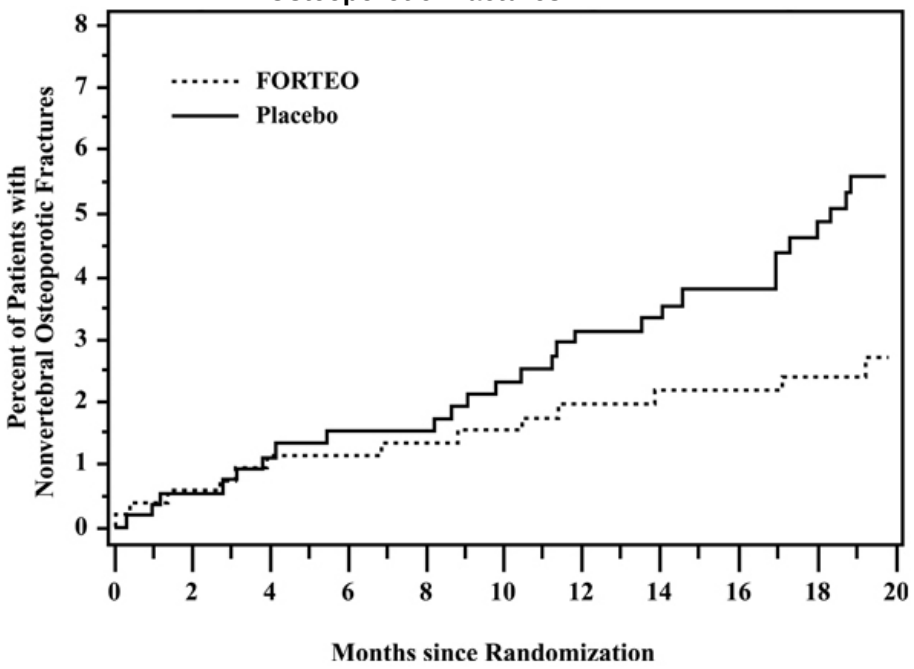
Percent of Women With Fracture				
	FORTEO (N=444)	**Placebo (N=448)**	**Absolute Risk Reduction (%, 95% CI)**	**Relative Risk Reduction (%, 95% CI)**
New fracture (≥1)	5.0[a]	14.3	9.3 (5.5-13.1)	65 (45-78)
1 fracture	3.8	9.4		
2 fractures	0.9	2.9		
≥3 fractures	0.2	2.0		

[a] p≤0.001 compared with placebo.

New Nonvertebral Osteoporotic Fractures — FORTEO significantly reduced the risk of any nonvertebral fracture from 5.5% in the placebo group to 2.6% in the FORTEO group (p<0.05). The absolute reduction in risk was 2.9% and the relative reduction was 53%. The incidence of new nonvertebral fractures in the FORTEO group compared with the placebo group was ankle/foot (0.2%, 0.7%), hip (0.2%, 0.7%), humerus (0.4%, 0.4%), pelvis (0%, 0.6%), ribs (0.6%, 0.9%), wrist (0.4%, 1.3%), and other sites (1.1%, 1.5%), respectively.

The cumulative percentage of postmenopausal women with osteoporosis who sustained new nonvertebral fractures was lower in women treated with FORTEO than in women treated with placebo (*see* Figure 1).

Figure 1: Cumulative Percentage of Postmenopausal Women with Osteoporosis Sustaining New Nonvertebral Osteoporotic Fractures



Effect on Bone Mineral Density (BMD)

FORTEO increased lumbar spine BMD in postmenopausal women with osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Postmenopausal women with osteoporosis who were treated with FORTEO had statistically significant increases in BMD from baseline to endpoint at the lumbar spine, femoral neck, total hip, and total body (*see* Table 3).

Table 3: Mean Percent Change in BMD from Baseline to Endpoint[a] in Postmenopausal Women with Osteoporosis, Treated with FORTEO or Placebo for a Median of 19 Months

	FORTEO N=541	**Placebo N=544**

Lumbar spine BMD	9.7[b]	1.1
Femoral neck BMD	2.8[c]	-0.7
Total hip BMD	2.6[c]	-1.0
Trochanter BMD	3.5[c]	-0.2
Intertrochanter BMD	2.6[c]	-1.3
Ward's triangle BMD	4.2[c]	-0.8
Total body BMD	0.6[c]	-0.5
Distal 1/3 radius BMD	-2.1	-1.3
Ultradistal radius BMD	-0.1	-1.6

[a] Intent-to-treat analysis, last observation carried forward.

[b] p<0.001 compared with placebo.

[c] p<0.05 compared with placebo.

FORTEO treatment increased lumbar spine BMD from baseline in 96% of postmenopausal women treated. Seventy-two percent of patients treated with FORTEO achieved at least a 5% increase in spine BMD, and 44% gained 10% or more.

Both treatment groups lost height during the trial. The mean decreases were 3.61 and 2.81 mm in the placebo and FORTEO groups, respectively.

Bone Histology

The effects of FORTEO on bone histology were evaluated in iliac crest biopsies of 35 postmenopausal women treated for 12 to 24 months with calcium and vitamin D and FORTEO. Normal mineralization was observed with no evidence of cellular toxicity. The new bone formed with FORTEO was of normal quality (as evidenced by the absence of woven bone and marrow fibrosis).

14.2 Treatment to Increase Bone Mass in Men with Primary or Hypogonadal Osteoporosis

The safety and efficacy of once-daily FORTEO, median exposure of 10 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis. In this study, 151 men received 20 mcg of FORTEO given subcutaneously once daily. All men received 1000 mg of calcium and at least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine BMD.

FORTEO increased lumbar spine BMD in men with primary or hypogonadal osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. FORTEO was effective in increasing lumbar spine BMD regardless of age, baseline rate of bone turnover, and baseline BMD. The effects of FORTEO at additional skeletal sites are shown in Table 4.

FORTEO treatment for a median of 10 months increased lumbar spine BMD from baseline in 94% of men treated. Fifty-three percent of patients treated with FORTEO achieved at least a 5% increase in spine BMD, and 14% gained 10% or more.

Table 4: Mean Percent Change in BMD from Baseline to Endpoint[a] in Men with Primary or Hypogonadal Osteoporosis, Treated with FORTEO or Placebo for a Median of 10 Months

	FORTEO N=151	**Placebo N=147**
Lumbar spine BMD	5.9[b]	0.5
Femoral neck BMD	1.5[c]	0.3
Total hip BMD	1.2	0.5
Trochanter BMD	1.3	1.1
Intertrochanter BMD	1.2	0.6
Ward's triangle BMD	2.8	1.1
Total body BMD	0.4	-0.4
Distal 1/3 radius BMD	-0.5	-0.2
Ultradistal radius BMD	-0.5	-0.3

[a] Intent-to-treat analysis, last observation carried forward.
[b] p<0.001 compared with placebo.
[c] p<0.05 compared with placebo.

14.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis

The efficacy of FORTEO for treating glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥5 mg/day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months. In the trial 214 patients were treated with FORTEO 20 mcg given subcutaneously once daily. In the FORTEO group, the baseline median glucocorticoid dose was 7.5 mg/day and the baseline median duration of glucocorticoid use was 1.5 years. The mean (SD) baseline lumbar spine BMD was 0.85 ± 0.13 g/cm^2 and lumbar spine BMD T-score was –2.5 ± 1 (number of standard deviations below the mean BMD value for healthy adults). A total of 30% of patients had prevalent vertebral fracture(s) and 43% had prior non-vertebral fracture(s). The patients had chronic rheumatologic, respiratory or other diseases that required sustained glucocorticoid therapy. All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

Because of differences in mechanism of action (anabolic vs. anti-resorptive) and lack of clarity regarding differences in BMD as an adequate predictor of fracture efficacy, data on the active comparator are not presented.

Effect on Bone Mineral Density (BMD)

In patients with glucocorticoid-induced osteoporosis, FORTEO increased lumbar spine BMD compared with baseline at 3 months through 18 months of treatment. In patients treated with FORTEO, the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck (p <0.001 all sites). The relative treatment effects of FORTEO were consistent in subgroups defined by gender, age, geographic region, body mass index, underlying disease, prevalent vertebral fracture, baseline glucocorticoid dose, prior bisphosphonate use, and glucocorticoid discontinuation during trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FORTEO (teriparatide injection) is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size:

- 620 mcg/2.48 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 0002-8400-01 (MS8400).

16.2 Storage and Handling

- Store FORTEO under refrigeration at 2° to 8°C (36° to 46°F) at all times except when administering the product.
- Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
- When using FORTEO, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
- Do not freeze. Do not use FORTEO if it has been frozen.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and the User Manual) before starting FORTEO and each time the prescription is renewed. Failure to follow the instructions may result in inaccurate dosing.

Osteosarcoma

Patients should be made aware that in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor). Although cases of osteosarcoma have been reported in patients using FORTEO no increased risk of osteosarcoma was observed in adult humans treated with FORTEO *[see Warnings and Precautions (5.1)]*.

Hypercalcemia

Instruct patients taking FORTEO to contact a health care provider if they develop persistent symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness) *[see Warnings and Precautions (5.2)]*.

Orthostatic Hypotension

When initiating FORTEO treatment, instruct patients to be prepared to immediately sit or lie down during or after administration in case they feel lightheaded or have palpitations after the injection. Instruct patients to sit or lie down until

the symptoms resolve. If symptoms persist or worsen, instruct patients to consult a healthcare provider before continuing treatment *[see Warnings and Precautions (5.4)]*.

Other Osteoporosis Treatment Modalities
Patients should be informed regarding the roles of supplemental calcium and/or vitamin D.

Use of the Prefilled Delivery Device (Pen)
Instruct patients and caregivers who administer FORTEO on how to properly use the delivery device *(refer to User Manual)*, to properly dispose of needles, and not to share their prefilled delivery device with other patients. Instruct patients and caregivers who administer FORTEO that the contents of the delivery device should not be transferred to a syringe.

Inform patients that each FORTEO delivery device can be used for up to 28 days. After the 28-day use period, instruct patients to discard the FORTEO delivery device, even if it still contains some unused solution. Instruct patients not to use FORTEO after the expiration date printed on the delivery device and packaging.

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www.forteo.com

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MEDICATION GUIDE
FORTEO® (for-TAY-o)
teriparatide injection
for subcutaneous use

Read this Medication Guide before you start using FORTEO and each time you get a refill. There may be new information. Also, read the User Manual that comes with the FORTEO delivery device (pen) for information on how to use the device to inject your medicine the right way. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about FORTEO?

Possible bone cancer. During drug testing, the medicine in FORTEO caused some rats to develop a bone cancer called osteosarcoma. Studies in people have not shown that FORTEO increases your chance of getting osteosarcoma. There is little information about the chance of getting osteosarcoma in patients using FORTEO beyond 2 years.

What is FORTEO?

FORTEO is a prescription medicine used to:

- treat postmenopausal women who have osteoporosis who are at high risk for having broken bones (fractures) or who cannot use other osteoporosis treatments. FORTEO can lessen the chance of broken bones (fractures) in the spine and other bones in postmenopausal women with osteoporosis.
- increase the bone mass in men with primary or hypogonadal osteoporosis who are at high risk for having broken bones (fractures) or who cannot use other osteoporosis treatments.
- treat both men and women with osteoporosis due to use of glucocorticoid medicines, such as prednisone, for several months, who are at high risk for having broken bones (fractures) or who cannot use other osteoporosis treatments.

It is not known if FORTEO is safe and effective in children.

FORTEO should not be used in children and young adults whose bones are still growing.

Who should not use FORTEO?

Do not use FORTEO if you:

- are allergic to any of the ingredients in FORTEO. See the end of this Medication Guide for a complete list of the ingredients in FORTEO.

Symptoms of a serious allergic reaction of FORTEO may include swelling of the face, lips, tongue or throat that may cause difficulty in breathing or swallowing. Call your healthcare provider right away or get emergency medical help if you get any of these symptoms.

What should I tell my healthcare provider before using FORTEO?

Before you use FORTEO, tell your healthcare provider about all of your medical conditions, including if you:

- have a certain bone disease called Paget's disease or other bone disease.
- have bone cancer or have had a history of bone cancer.
- are a young adult whose bones are still growing.
- have had radiation therapy.
- are affected with a condition that runs in your family that can increase your chance of getting cancer in your bones.
- have or have had too much calcium in your blood (hypercalcemia).
- have or have had a skin condition with painful sores or wounds caused by too much calcium.
- have or have had kidney stones.
- take medicines that contain digoxin.
- are pregnant or plan to become pregnant. It is not known if FORTEO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if FORTEO passes into your breastmilk. You should not breastfeed while taking FORTEO.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use FORTEO?

- Read the detailed Instructions for Use (User Manual) included with your FORTEO delivery device.
- Use FORTEO exactly as your healthcare provider tells you to. Your healthcare provider will tell you how much FORTEO to use and when to use it.
- Before you try to inject FORTEO yourself, a healthcare provider should teach you how to use the FORTEO delivery device to give your injection the right way.
- Inject FORTEO 1 time each day in your thigh or abdomen (lower stomach area). Do not inject into a vein or a muscle. Talk to a healthcare provider about how to rotate injection sites.
- The FORTEO delivery device has enough medicine for 28 days. It is set to give a 20-microgram dose of medicine each day. Do not inject all the medicine in the FORTEO delivery device at any one time.
- Do not transfer the medicine from the FORTEO delivery device to a syringe. This can result in taking the wrong dose of FORTEO. If you do not have pen needles to use with your FORTEO delivery device, talk with your healthcare provider.

- FORTEO should look clear and colorless. Do not use FORTEO if it has particles in it, or if it is cloudy or colored.
- Inject FORTEO right away after you take the delivery device out of the refrigerator.
- After each use, safely remove the needle, recap the delivery device, and put it back in the refrigerator right away.
- When you inject the first few doses of FORTEO, make sure you are in a place where you can sit or lie down right away in case you feel dizzy or have an abnormal heartbeat after the injection.
- Do not take more than 1 injection in the same day.
- Do not share your FORTEO delivery device with other people.
- If you take more FORTEO than prescribed, call your healthcare provider. If you take too much FORTEO, you may have nausea, vomiting, weakness, or dizziness.
- You should not use FORTEO for more than 2 years over your lifetime unless your healthcare provider finds that you need longer treatment because you have a high chance of breaking your bones.

If your healthcare provider recommends calcium and vitamin D supplements, you can take them at the same time you take FORTEO.

What are the possible side effects of FORTEO?

FORTEO may cause serious side effects including:

- See "**What is the most important information I should know about FORTEO?**"
- **Bone cancer (osteosarcoma):** Tell your healthcare provider right away if you have pain in your bones, pain in any areas of your body that does not go away, or any new or unusual lumps or swelling under your skin that is tender to touch.
- **Increased calcium in your blood.** Tell your healthcare provider if you have nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs there is too much calcium in your blood.
- **Worsening of your kidney stones.** If you have or have had kidney stones your healthcare provider may check the calcium levels in your urine while you use FORTEO to see if there is worsening of this condition.
- **Decrease in blood pressure when you change positions.** Some people may feel dizzy, get a fast heartbeat, or feel light-headed right after the first few doses of FORTEO. This usually happens within 4 hours of taking FORTEO and goes away within a few hours. For the first few doses, give your injections of FORTEO in a place where you can sit or lie down right away if you get these symptoms. If your symptoms get worse or do not go away, contact your healthcare provider before you continue using FORTEO.

The most common side effects of FORTEO include:

- pain
- nausea
- joint aches

These are not all the possible side effects of FORTEO. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FORTEO?

- Store FORTEO in the refrigerator between 36°F to 46°F (2°C to 8°C) until ready to use. Use FORTEO right away after you remove it from the refrigerator.
- Do not freeze FORTEO. Do not use FORTEO if it has been frozen.
- Throw away the FORTEO delivery device after 28 days even if it has medicine in it (see the User Manual).
- Do not use FORTEO after the expiration date printed on the delivery device and packaging.
- Recap FORTEO when not in use to protect it from physical damage and light.

Keep FORTEO and all medicines out of the reach of children.

General information about the safe and effective use of FORTEO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FORTEO for a condition for which it was not prescribed. Do not give FORTEO to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about FORTEO that is written for health professionals.

What are the ingredients in FORTEO?

Active ingredient: teriparatide

Inactive ingredients: glacial acetic acid, sodium acetate (anhydrous), mannitol, metacresol, and water for injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

For more information, go to www.FORTEO.com or call Lilly at 1-866-436-7836.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

A3.0-FOR-NL0002-MG-202011

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 11/2020

FPO

Read User Manual BEFORE Injecting

Preset dose: 20 mcg teriparatide once daily subcutaneously. Throw pen away 28 days after first use.

Do NOT transfer contents to a syringe. Each prefilled delivery device is filled with 2.7 mL to deliver 2.4 mL.

Keep in refrigerator at 2° to 8°C (36° to 46°F). Do NOT freeze.

GTIN: 00300028400012

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA
Product of Austria

Each mL contains 250 mcg teriparatide, 0.41 mg glacial acetic acid, 0.10 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg metacresol, and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust pH.

Sterile.

NOT a child-resistant container.

Toll free: 1-866-4FORTEO (1-866-436-7836)

3 00028 40001 2

Lilly

NL034FSAM00

FORTEO®
teriparatide injection

MS8400

For Single-Patient-Use Only

20 mcg per dose (given once daily subcutaneously)
620 mcg/2.48 mL (250 mcg/mL)

Lilly

To open, lift here and pull.

FORTEO®

Lilly

Do NOT transfer contents to a syringe
ATTENTION PHARMACIST: Medication Guide and device User Manual for patient inside carton

NDC 0002-**8400**-01
MS8400

FORTEO®
teriparatide injection

For Single-Patient-Use Only

20 mcg per dose (given once daily subcutaneously)

Each single-patient-use prefilled pen will deliver 28 subcutaneous doses.
620 mcg/2.48 mL (250 mcg/mL)

REFRIGERATE / **DO NOT FREEZE**
For subcutaneous use / **Rx only**

Needles not included
Becton, Dickinson and Company pen needles are recommended for use with this device

www.forteo.com

Lilly

Lot
Exp Date
Serial Number

FORTEO®
teriparatide injection

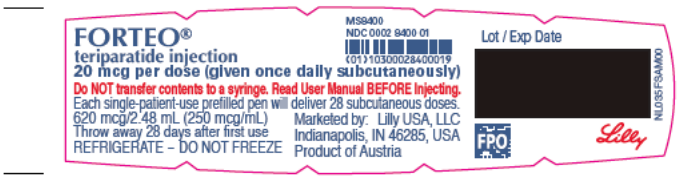
MS8400

For Single-Patient-Use Only

20 mcg per dose (given once daily subcutaneously)
620 mcg/2.48 mL (250 mcg/mL)

Lilly

(b) (4)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NDC 0002 9400 01
(01)10300028400019
FORTEO®
teriparatide injection
20 mcg per dose (given once daily subcutaneously)
Do NOT transfer contents to a syringe. Read User Manual BEFORE Injecting.
Each single-patient-use prefilled pen will deliver 28 subcutaneous doses.
620 mcg/2.48 mL (250 mcg/mL)
Throw away 28 days after first use
REFRIGERATE – DO NOT FREEZE
Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA
Product of Austria
Lot / Exp Date
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Lilly
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA E KEHOE
11/16/2020 03:36:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021318Orig1s054

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental NDA
Application Number(s)	NDA 021318 supplement 54
Priority or Standard	Standard
Submit Date(s)	January 16, 2020
Received Date(s)	January 16, 2020
PDUFA Goal Date	November 16, 2020
Division/Office	Division of General Endocrinology/OCHEN
Review Completion Date	11/13/2020
Established/Proper Name	teriparatide
(Proposed) Trade Name	Forteo
Applicant	Eli Lilly
Dosage Form(s)	injectable
Applicant Proposed Dosing Regimen(s)	20 mcg daily subcutaneous (SC) injection
Applicant Proposed Indication(s)/Population(s)	No change to proposed indications
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of postmenopausal women with osteoporosis at high risk for fracture Treatment to increase bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	102447009 Postmenopausal osteoporosis (disorder) 276661002 Primary osteoporosis (disorder) 390833005 Osteoporosis caused by corticosteroid (disorder)
Recommended Dosing Regimen	20 mcg daily subcutaneous (SC) injection

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Reviewers of Multi-Disciplinary Review and Evaluation

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OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPV=Division of Pharmacovigilance
DEPI=Division of Epidemiology
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Forteo (teriparatide) is a parathyroid hormone analog that is composed of the first 34 amino acids of human parathyroid hormone and is manufactured by recombinant DNA technology.[1] Teriparatide is indicated for the treatment of the following conditions:

- Post-menopausal women with osteoporosis at high risk for fracture
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- Men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

In the clinical trials conducted for the Forteo marketing application, high risk for fracture was defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who had failed or were intolerant to other available osteoporosis therapy. The approved dose of teriparatide for all indications is 20 mcg subcutaneously once daily.

Teriparatide has pharmacodynamic effects consistent with endogenous parathyroid hormone. It elevates serum calcium and decreases serum phosphorous and increases new bone formation by preferential stimulation of osteoblastic over osteoclastic activity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The central efficacy issue with this application is whether data support use of teriparatide beyond the current 24 month limit. The pivotal efficacy and safety trials conducted for the initial Forteo marketing application had planned for 36 months of drug exposure. However, the Applicant terminated the trials early when an osteosarcoma signal became evident in non-clinical rat studies. That resulted in median duration of exposure ranging from 10 months (in males with primary or hypogonadal osteoporosis) to f 19 months (PMO). (b) (4) (b) (4) .

Study GHCA in post-menopausal women with osteoporosis at high risk for fracture compared the effect of 24 months of teriparatide 20 mcg daily with teriparatide 20 mcg daily for 12 months followed by 12 months of no active treatment (i.e., T-N group), and teriparatide 20 mcg daily for 12 months followed by raloxifene 60 gm daily for 12 months (i.e. T-R group). Results showed that teriparatide 20 mcg daily for 24 months increased lumbar spine, total hip and femoral neck BMD compared to baseline (percent change of 10.7%, 2.5% AND 3.5% for lumbar spine, total hip and femoral neck, respectively) without plateauing prior to 24 months.

[1] Clinical Review of NDA 21318 dated November 26, 2002 accessed https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-318_Forteo.cfm.

In study GHCA, previous anti-resorptive therapy appeared to blunt, but not negate, the BMD response to teriparatide. Study GHBU, an open-label trial in women with PMO, evaluated the effect of previous anti-resorptive therapy (raloxifene 60 mg daily or alendronate 10 mg daily) on BMD response to teriparatide 20 mcg daily. In that study, previous treatment with alendronate blunted the response to teriparatide – particularly during the first six months of treatment.

Study GHBZ in adults with glucocorticoid induced osteoporosis at high risk for fracture compared the effect of teriparatide 20 mcg daily to alendronate 10 mg daily on BMD at 18 months and again at 36 months. The 18-month data served as the pivotal efficacy data supporting approval of Forteo for the GIOP indication in 2009. The 36-month data were reviewed for this application. Compared to baseline, teriparatide increase LS BMD statistically significantly more than alendronate (mean percent change of 11% versus 5.3%, respectively) at 36 months. Change from baseline to 36 months in hip and femoral neck BMD was also greater for teriparatide-treated patients than for those receiving alendronate. When examining the change from month 18 to month 36, lumbar spine BMD increased in both the teriparatide and alendronate groups (2.41% and 1.44%, respectively). The sample size of the second 18 month treatment period was smaller than the first 18 months, so the study lacked sufficient power to detect a statistically significant difference at 36 months compared to month 18. The incidence of vertebral fractures was lower over the 36-month treatment period in the teriparatide group than in the alendronate group. The findings from study GHBZ support that teriparatide treatment has clinically meaningful efficacy over a 36 month treatment period in patients with GIOP at high risk for fracture.

(b) (4)

. Data were limited by small sample sizes (total of 52 subjects in two different studies) and differences in treatment regimen and enrollment criteria. Additional controlled data in a larger and more uniform population with a consistent dose regimen are needed (b) (4)

1.3. Benefit-Risk Assessment

The sponsor has demonstrated clinically meaningful benefit of up to 36 months of teriparatide 20 mcg daily for patients with GIOP who remain at high risk for fracture. A small 3-year study of teriparatide 25 mcg daily in combination with hormone replacement therapy in women with PMO at high risk for fracture provided additional supportive efficacy data. Although the applicant did not investigate longer treatment periods of teriparatide 20 mcg daily in patients with other etiologies of osteoporosis (i.e., post-menopausal or male hypogonadism), the beneficial 24-month BMD response in women with PMO suggest that the effect would not differ according to etiology.

The most significant safety concern that had limited longer treatment duration with teriparatide was the theoretical risk of osteosarcoma. There has been no clinical signal of osteosarcoma from any of the following sources:

- Clinical trial data involving 1952 patients exposed to teriparatide
- Required post-marketing observational studies

- Post-marketing safety surveillance in which the number of spontaneous reports of confirmed osteosarcoma in a population of 2.47 million teriparatide-treated patients did not, according to literature cited by the Applicant, exceed the predicted background incidence

Although extent of exposure is limited, there are no new safety signals apparent from data in patients exposed to teriparatide for longer than 24 months and up to 42 months. Five years of follow-up following teriparatide discontinuation in study GHBJ showed no increased risk of osteosarcoma or other delayed adverse effects. In that study, lumbar spine BMD decreased in both men and women after teriparatide discontinuation, but total hip BMD remained stable over thirty months following discontinuation. In post-menopausal women, prior treatment with teriparatide appeared to protect against subsequent fracture during thirty months of follow-up after teriparatide withdrawal. Addition of osteoporosis drug treatment following discontinuation of teriparatide mitigated the reduction in BMD.

Benefit-Risk Integrated Assessment

For the reasons stated above, the risk-benefit balance is favorable in support of teriparatide use for more than two years in selected patients who remain at, or return to, high risk for fracture. Available data from clinical trials and 18 years of post-marketing experience no longer support a black box warning for osteosarcoma. The newly identified signal of calciphylaxis is biologically plausible and should be included in labeling but does not change the overall benefit-risk assessment of teriparatide.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoporosis is a bone disease characterized by loss of bone mass, leading to an increased risk for fractures. Primary osteoporosis (e.g., postmenopausal osteoporosis and male osteoporosis) are due to typical age-related loss of bone. Secondary osteoporosis (e.g., glucocorticoid induced osteoporosis) results from the presence of other conditions or the use of therapies that predispose to bone loss.	Osteoporosis increases the risk of fracture in postmenopausal women, men with primary or hypogonadal osteoporosis and men and women with glucocorticoid-induced osteoporosis. The risk of fracture increases with age and a history of a prior osteoporosis-related fracture.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current pharmacologic treatment options for osteoporosis are anti-resorptive agents (i.e., medications that inhibit bone loss) and anabolic agents (i.e., medications that stimulate bone formation. The anti-resorptive agents include bisphosphonates, RANK ligand inhibitors (denosumab), estrogen agonists/antagonists, and calcitonin. Anabolic agents are parathyroid hormone related peptide analogs (teriparatide and abaloparatide) and a sclerostin inhibitor (romosozumab). • Bisphosphonates are the most widely prescribed medications for osteoporosis. Rare but serious side effects with bisphosphonates are osteonecrosis of the jaw and atypical femoral fractures. • Denosumab is a RANK-ligand inhibitor that is also associated with osteonecrosis of the jaw and atypical femoral fractures, as well as an increased risk of fracture upon discontinuation. • Teriparatide and abaloparatide are parathyroid hormone analogues. Their use is limited to two years because of the potential risk of osteosarcoma, which was noted in animal studies. • Romosozumab is a sclerostin inhibitor that has the following risks: major adverse cardiac events, injection site reactions, hypersensitivity reactions, hypocalcemia, osteonecrosis of the jaw and atypical femoral fractures. Duration of use is limited to twelve monthly injections.	Multiple therapies are available for the treatment of osteoporosis in postmenopausal women, men with primary or hypogonadal osteoporosis and men and women with glucocorticoid-induced osteoporosis. Therapies that are indicated only in patients with osteoporosis who are at high risk of fracture or who are intolerant to other available osteoporosis therapy are teriparatide, abaloparatide, denosumab and romosozumab. Only denosumab contains no limit on duration of use, but there are risks associated with denosumab that may preclude long-term treatment in some patients.
Benefit	• Study GHCA in post-menopausal women with osteoporosis at high risk for fracture showed that 24 months of teriparatide 20 mcg daily increased lumbar spine, total hip and femoral neck BMD compared to baseline, and the response did not plateau prior to 24 months. • Study GHBZ in adults with glucocorticoid associated osteoporosis at high risk for fracture demonstrated continued efficacy of teriparatide with respect to increasing BMD out to 36 months. Fracture incidence over the 36-month treatment period was lower in patients assigned to teriparatide than those receiving alendronate.	Teriparatide 20 mcg daily has demonstrated efficacy with respect to increased BMD up to 24 months in patients with PMO at high risk of fracture and increasing BMD and reducing fracture incidence up to 36 months in patients with GIOP at high risk for fracture.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• There is no clinical evidence of an increased risk of osteosarcoma during 24 months of teriparatide treatment. The extent of exposure to more than 24 months of teriparatide is limited but has not shown a change in the safety profile of teriparatide.	The available evidence no longer supports a black box warning for risk of osteosarcoma. In the absence of identifiable risk and in light of efficacy demonstrated beyond two years, patients who are at high risk for fracture and who have no alternative treatment available should have the option to use teriparatide for more than 2 years.

1.4. Patient Experience Data

Table 1: Patient Experience Data Relevant to this Application

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Osteoporosis is a skeletal disorder characterized by low bone mass and structural deterioration of bone, which leads to fragility and increased fracture risk. It results from an imbalance between resorption of bone by osteoclasts and formation of new bone by osteoblasts during bone remodeling. A clinical diagnosis of osteoporosis can be made in the presence of the following:

- Fragility fracture (i.e. those occurring spontaneously or from minor trauma), OR

- T-score ≤-2.5 standard deviations (SDs) at any site based upon bone mineral density measurement by dual-energy x-ray absorptiometry (DXA).[2]

A BMD T-score is the difference between a patient's BMD and that of a young adult reference population.

2.2. Analysis of Current Treatment Options

Osteoporosis treatment consists of lifestyle changes (adequate vitamin D and calcium intake, weight-bearing exercise and smoking cessation) and pharmacologic therapy. There are two pharmacologic classes of drugs used to treat osteoporosis:

- anti-resorptive agents which increase bone mineral density by reducing the rate of bone remodeling
- anabolic agents which stimulate new bone formation.[3]

Table 2 summarizes the currently approved pharmacologic therapies for postmenopausal osteoporosis (PMO), osteoporosis in men (MO) and glucocorticoid-induced osteoporosis (GIOP). In most cases, unless there is a contraindication, oral bisphosphonates are first-tine therapy because of their efficacy, ease of administration and long-term safety data.

For patients who cannot tolerate a bisphosphonate, treatment options are the anabolic agents (teriparatide, abaloparatide or romosozumab) or denosumab. The duration of use of both teriparatide and abaloparatide is limited to two years because of the potential risk of osteosarcoma based on a higher incidence of osteosarcoma observed in pre-license, non-clinical rat studies. Romosozumab treatment duration is limited to 12 monthly doses.

Standard practice for patients who have completed two years of teriparatide treatment is to continue therapy with an anti-resorptive agent to preserve BMD gains.

[2] Rosen HN. (2020, April 13) *Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women.* Uptodate. https://www.uptodate.com

[3] Seeman E and TJ Martin. Antiresorptive and anabolic agents in the prevention and reversal of bone fragility. Nature Review Rheumatology 15, 225-236 (2019).

Table 2. FDA-Approved Pharmacologic Treatment Options for Osteoporosis[4]

Drug Class	Product Name	Year of Approval	Approved Indications	Dosing/ Administration	Important Safety and Tolerability Issues
Antiresorptive agents					
Bisphosphonates	Fosamax (alendronate)	1995	Post-menopausal osteoporosis (PMO), male osteoporosis (MO), glucocorticoid induced osteoporosis (GIOP)	70 mg PO weekly (tablet or solution) or 10 mg PO daily (tablet)	Hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femoral fractures (AFF), Not recommended or contraindicated in patients with severe renal impairment Upper gastrointestinal adverse events with oral formulations
	Fosamax Plus D (alendronate/ cholecalciferol)	2005	PMO, MO, GIOP	70 mg alendronate/2800 or 5600 IU cholecalciferol, 1 tablet weekly	
	Binosto (alendronate)	2012	PMO, MO	70 mg PO weekly (effervescent tablet for oral solution)	
	Actonel (risedronate)	2000	PMO, MO, GIOP	Tablets: 5 mg PO daily 35 mg PO weekly 150 mg PO monthly	
	Atelvia (risedronate)	2010	PMO	35 mg PO weekly (delayed release tablet)	
	Boniva (ibandronate)	2003	PMO	150 mg PO Monthly (tablet)	
	Boniva (ibandronate)	2006	PMO	3 mg IV q3 months	Hypocalcemia, ONJ, AFF,
	Reclast (zoledronic acid)	2007	PMO, MO, GIOP	5 mg IV yearly	Hypocalcemia, renal toxicity, acute phase reactions, ONJ, AFF
RANK-L antagonist	Prolia (denosumab)	2010	PMO, MO, GIOP at high risk for fracture	60 mg SC q6 months	Hypersensitivity, hypocalcemia, ONJ, AFF, multiple vertebral fractures following discontinuation, serious infections, dermatologic reactions
Estrogen agonist/antagonist	Evista (raloxifene)	1997	PMO	60 mg PO daily (tablet)	Venous thromboembolism, death due to stroke

Anabolic therapy					
PTH analog/ PTHrP analog	Forteo (teriparatide)	2002	PMO, MO, GIOP at high risk for fracture	20 mcg SC daily	Osteosarcoma risk (animal data) limiting use duration to 2 years, hypercalcemia
	Tymlos (abaloparatide)	2017	PMO at high risk for fracture	80 mcg SC daily	Osteosarcoma risk (animal data) limiting use duration to 2 years, hypercalcemia
	Bonsity (teriparatide)	2019	PMO, MO, GIOP at high risk for fracture	20 mcg SC daily	Osteosarcoma risk (animal data) limiting use duration to 2 years, hypercalcemia
Sclerostin inhibitor	Evenity (romosozumab)	2019	PMO at high risk for fracture	210 mg SC monthly	Major adverse cardiac events, hypersensitivity, hypocalcemia, ONJ, AFF

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The FDA first approved Forteo (teriparatide) in 2002 for the treatment of post-menopausal women with osteoporosis at high risk for fracture, and to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture. Forteo received a new indication of treatment of adults with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture in 2009.

3.2. Summary of Pre-submission/Submission Regulatory Activity

In the drug development program, non-clinical studies, teriparatide showed a higher incidence of osteosarcoma in rats (but not in monkeys) at a higher systemic exposure than in humans; and the risk appeared to be dose- and treatment duration-dependent. Since the bone metabolism in rats differs from that in humans, the relevance of the animal finding to humans is uncertain. There were no human cases of osteosarcoma identified in the premarketing clinical trials

Still, because of these findings in rats, product labeling included a boxed warning for the potential risk for osteosarcoma and a recommendation to limit lifetime use of Forteo to two years or less since clinical safety and efficacy beyond that time had not been demonstrated. In addition, the Agency required that the sponsor examine the clinical risk of osteosarcoma with teriparatide use in post-marketing.

Since approval, Lilly has completed five post-marketing observational studies to fulfill this requirement:

(1) a case-series study in Europe, (study GHBX [1])
(2) a case-series study in the US, (study GHBX [b])

[4] Multi-disciplinary review of NDA 211939 finalized in DARRTS on October 2, 2019.

(3) a prospective patient registry in the U.S. (study GHBX 2.1)
(4) two claims based retrospective cohort studies in Medicare D and IQVIA Longitudinal Prescription Database (GHBX 2.2 and 2.3)

The Division of Epidemiology II (DEPI II) reviewed the results of these post-marketing studies in a memorandum dated May 3, 2019, and concluded and recommended the following:

- The two case series studies (GHBX[1] and GHBX[b]) did not identify a safety concern for osteosarcoma.
- The results of the case series studies should be added to the Adverse Reaction Section of labeling.
- The patient registry [GHBX 2.1], which enrolled 71,417 teriparatide users, identified no incident and do not suggest a risk for osteosarcoma. The registry is unlikely to meet its target sample size (of 1.7 million patient years) so the sponsor should be released from the registry requirement.

DBRUP and DEPI II presented the findings from the post-marketing studies to the FDA Medical Policy and Program Review Council (MPPRC) on April 10, 2019. The MPRCC agreed that a boxed warning regarding risk of osteosarcoma was no longer necessary based on available data.

A type C meeting between Lilly and FDA occurred on July 26, 2019, to discuss changes to Forteo® labeling based on the GHBX program results. FDA advised the following:

- Discontinuation of study GHBX (2.1) is acceptable
- Lilly may submit a labeling supplement to remove the GHBX (2.1) registry information from labeling.
- removal of the boxed warning regarding risk of osteosarcoma is appropriate based on the additional post-marketing data
- (b) (4) .
- FDA would consider modifying the 2-year limitation of use if adequate data showed continued benefit beyond two years in the desired population. The Applicant should submit the following information to support the modification:
    - BMD data with both retreatment and chronic therapy with teriparatide
    - BMD response after discontinuation of teriparatide.
    - BMD, fracture and safety data from study GHBJ, the follow-on observational study for subjects enrolled in phase 3 study GHAC which was conducted for the initial marketing application.

Lilly submitted a prior approval labeling supplement request to remove references to the Forteo® Patient registry on November 25, 2019 (sequence 372/supporting document 1670/Supplement 53). That submission also contained the final GHBX (2.1) study report.

The current prior approval safety labeling supplement calls for the following major changes to the Forteo® US prescribing information (USPI):

1. Removal of the Boxed Warning regarding Osteosarcoma.
2. Modify the 2-year limitation of use to allow for longer duration of treatment in patients at high risk for fracture.
3. Modify the Warning regarding Osteosarcoma (b) (4)

4. Revise *Section 6.2 Post-marketing experience* to reflect the current status of the long-term osteosarcoma surveillance studies.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No new clinical trial data has been submitted in this supplemental NDA. Therefore, the Office of Scientific Investigations was not consulted.

4.2. Product Quality

No new product quality data was submitted in this supplemental NDA.

The Applicant submitted a claim for a categorical exclusion from the requirements to submit an Environmental Assessment for this supplemental NDA based on the exclusion allowed by 21 CFR 25.31 (b, c). This supplemental NDA, upon approval, will not increase the dose of teriparatide but may result in increases in both the number of patients that are dosed and the duration of use. An increase in the number of patients or the duration of use would not be expected to have adverse effects on the environment because environmental exposure to teriparatide will be below concentrations of concern. As a peptide, teriparatide is metabolized in humans such that it is excreted predominantly as a mixture of smaller peptides and amino acids. The end degradation products of teriparatide, amino acids, are the same as those of any other protein and occur naturally. The applicant's claim for categorical exclusion is acceptable.

5. Nonclinical Pharmacology/Toxicology

No new or additional Pharmacology/Toxicology data are submitted in this supplemental NDA.

6. Clinical Pharmacology

No new or additional Clinical Pharmacology data are submitted in this supplemental NDA.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Clinical studies that the Applicant submitted in support of the proposed labeling changes are summarized in Table 3 and Table 4.

Table 3. Studies submitted in support of removal of boxed warning regarding osteosarcoma

Trial Identity	Trial Design	Duration of study	No. of patients
B3D-MC-GHBX(b)	Retrospective US post-approval osteosarcoma surveillance study using cancer registry data to identify cases of osteosarcoma in US patients ≥40 years of age and determine, through interview of patients or a proxy, if any patients with osteosarcoma had a history of Forteo treatment before diagnosis of osteosarcoma.	**13 years**	1173 patients interviewed
B3D-MC-GHBX(1)	Initiated in Europe in 2004. 10-year surveillance study identified newly diagnosed cases of osteosarcoma among men and women aged >40 years in 5 Nordic countries evaluated the potential association between Forteo and osteosarcoma in adults using medical participating in the Osteosarcoma Scandinavian Registry and to ascertain whether these patients had a history of Forteo treatment before diagnosis of osteosarcoma.	**10 years**	112 osteosarcoma medical records were reviewed
B3D-MC-GHBX(2.1)	Voluntary registry of adult Forteo users (18 years and older) in the United States annually linking data obtained with 42 participating cancer registries to ascertain any new cases of osteosarcoma in Forteo-exposed patients.	**10 years**	75,247 enrollees in the Forteo Patient registry were linked
B3D-MC-GHBX(2.2)	Compared the incidence of osteosarcoma among Forteo users and non-Forteo users in the U.S. by linking Medicare Part D and state cancer registry data.	**4 years**	153,316 patients in the Forteo cohort; 613,247 patients in the comparator cohort
B3D-MC-GHBX(2.3[b])	Compared the incidence of osteosarcoma among Forteo users compared to an osteoporosis non-Forteo user cohort and a general population cohort by linking data from 29 state cancer registries (covering 65% of the U.S. population) to the U.S. Rx pharmacy claims database.	**4 years**	• 335,192 patients in the Forteo cohort matched to 637,388 patients in the osteoporosis comparator cohort • 379,283 patients in the Forteo cohort matched to 1.4 million patients in the general population cohort.

Table 4. Data Submitted to Support the modification of the two-year limitation of use

BMD response after teriparatide discontinuation					
	Design	Endpoint	duration		Population
B3D-MC-GHBJ -	Multicenter, multinational, observational study to assess safety and effect of teriparatide after treatment discontinuation. Subjects who completed up to 24 months of treatment with teriparatide 20 mcg/day, 40 mcg/day or placebo in a long-term (>3 month) clinical trial of teriparatide were followed for safety for up to 5 years following discontinuation of study drug.	Primary: Incidence of serious adverse events over five years of follow-up after discontinuation of teriparatide/placebo Secondary: change in spine/hip BMD between time of entry into study GHBJ and completion of teriparatide/placebo (approx. 6-8 month)	Followed up to five years	1943	Subjects who had participated in one of the following long-term (>3 month) clinical trials of teriparatide conducted for the initial marketing application: B3D-MC-GHAC, B3D-MC-GHAF, B3D-MC-GHAH, B3D-MC-GHAJ, B3D-MC-GHAL, B3D-MC-GHAU, and B3D-MC-GHAV
BMD effect after 2 years of continuous use					
B3D-EW-GHCA (EUROFORS)	Multi-center, prospective, open-label Phase 3-4 trial with two sub-studies. Substudy 1: parallel, controlled, randomized to: • teriparatide for 24 months • teriparatide for 12 months followed by raloxifene x 12 months or • teriparatide for 12 months followed by no active treatment for 12 months. Substudy 2: uncontrolled, all patients received teriparatide x 24 months	Change from baseline to 24 months in lumbar spine BMD	24 months	868	Post-menopausal women with severe osteoporosis
B3D-US-GHBZ	Global, multicenter, randomized, double-blind, double-dummy, active comparator-controlled study with three study periods: Screening x 1.5 months Double-blind primary phase x 18 months – subjects randomized 1:1 to teriparatide 20 mcg qd + placebo or alendronate 10 mg +placebo Continuation phase x 18 months—subjects continued treatment from the previous phase.	Change from baseline to 18 months in LS BMD	36 months	428	Adult men and women >21 years with osteoporosis associated with sustained glucocorticoid therapy

Lindsey, et. al. (1997)[5]	3-year randomized, controlled trial of the effect of teriparatide in post-menopausal women with osteoporosis taking hormone replacement therapy. Women were randomized 1:1 to teriparatide 20 mcg qd +estrogen or placebo + estrogen for 3 years	Change in LS and total hip BMD	36 months	23	Post-menopausal women with osteoporosis taking HRT

Efficacy of Re-Treatment with Teriparatide					
Cosman, et. al. (2009)[6]	Women who were enrolled in a previous study comparing daily teriparatide with alendronate to cyclic teriparatide with alendronate to alendronate alone, and who remained at high risk of fracture, received teriparatide 25 mcg daily x 15 months.	Change in LS and hip BMD	15 months	32	Post-menopausal women with osteoporosis
Finkelstein, et. al. (2009)[7]	Three phase randomized, unblinded study: • Phase 1 (30 months): subjects randomized to receive alendronate 10 mg qd (group 1), teriparatide 37 mcg qd (group 2) or both (group 3) x 30 months. Teriparatide administered from months 6-30. • Phase 2 (months 30-42): subjects in groups 1 and 3 continued alendronate x 12 months. Subject in group 2 discontinued teriparatide x 12 months. • Phase 3 (months 42-54): subjects in groups 1, 2 and 3 received teriparatide 37 mcg qd.	Change in BMD and markers of bone turnover between phase 1 and 3 in subjects receiving teriparatide alone	12 months	72 (phase 3 of study)	Men and post-menopausal women aged 46-85 years with osteoporosis
Mana et. al. (2017)[8]	Observational case study of BMD response to a second cycle of teriparatide.	Change in BMD and osteocalcin	Re-treatment ranged from 18-24 months	3	Post-menopausal women with osteoporosis

[5] Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, Dempster D, Cosman F. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet.* 1997;350(9077):550-555.
[6] Cosman F., Nieves JW, et. al. Retreatment with Teriparatide One Year after the first Teriparatide Course in patients on Continued long-term alendronate. J Bone Miner Res 2009;24:1110–1115.
[7] Finkelstein JS, Wyland JJ, Leder BZ, Burnett-Bowie SM, Lee H, Jüppner H, Neer RM. Effects of Teriparatide Retreatment in Osteoporotic Men and Women. *J Clin Endocrinol Metab.* 2009;94(7):2495–2501.
[8] Mana DL, Zanchetta MB, Zanchetta JR. Retreatment with teriparatide: our experience in three patients with severe secondary osteoporosis. *Osteoporos Int.* 2017;28(4):1491–1494.

7.2. Review Strategy

This document will address the data that were submitted in support of each of the proposed labeling changes. The five post-marketing observational studies that the sponsor conducted to assess for osteosarcoma risk were reviewed in detail by the Division of Pharmacovigilance I and will not be individually re-reviewed in this document.

Data submitted in support of modifying the two-year limitation include clinical study reports and published literature. Clinical study reports will be reviewed in detail while literature articles will be summarized. Only those sections of the unireview template relevant to this application will be completed. Of note, study GHBZ served as the pivotal efficacy trial for the glucocorticoid induced osteoporosis indication for which Forteo was approved in July 2009, and was previously reviewed.[9, 10]

8. Review of Relevant Individual Trials Used to Support Efficacy

8.1. Issue #1: Efficacy up to 24 months

8.1.1. GHCA: Comparison of a 2-Year therapy of teriparatide alone and its sequential use for one year, with or without raloxifene HCl, in the treatment of severe postmenopausal osteoporosis

8.1.1.1. Study Design

Overview and Objective
The sponsor submitted results of study GHCA to fulfill FDA's request for information about whether the increase in BMD during teriparatide treatment plateaus prior to patients completing 2 years of treatment.

The primary objective was to compare the effect of the following three treatment regimens on BMD in post-menopausal women with osteoporosis:

- teriparatide 20 mcg daily for 24 months
- teriparatide 20 mcg daily for 12 months followed by 12 months of no active treatment
- teriparatide 20 mcg daily for 12 months followed by raloxifene 60 mg daily for 12 months.

Trial Design
GHCA was a 2-year, multi-center, prospective, open-label phase ¾ trial consisting of two sub-studies. Sub-study 1 was parallel, controlled, randomized, with three treatment arms. Sub-study 2 was uncontrolled, with all patients receiving teriparatide.

Women ≥55 years of age who were at least 2 years postmenopausal, had a BMD T-score ≤−2.5 at the lumbar spine, total hip, or femoral neck, and at least one documented vertebral or nonvertebral fragility fracture in the 3 years before study entry were enrolled. Additional

[9] Benson, George, MD. NDA 21318 Supplement 12, Deputy Directory Summary Review of Regulatory Action, filed in DARRTS July 22, 2009.
[10] Gassman, Audrey, MD. NDA 21318 Supplement 2, Clinical Review, filed in DARRTS November 24, 2008.

eligibility criteria were normal baseline levels of serum parathyroid hormone (PTH), total alkaline phosphatase (ALP), and total calcium, and absence of severe chronically disabling conditions other than osteoporosis.

At enrollment, all patients were classified into one of three groups according to their previous use of anti-resorptive (AR) therapy at study entry:

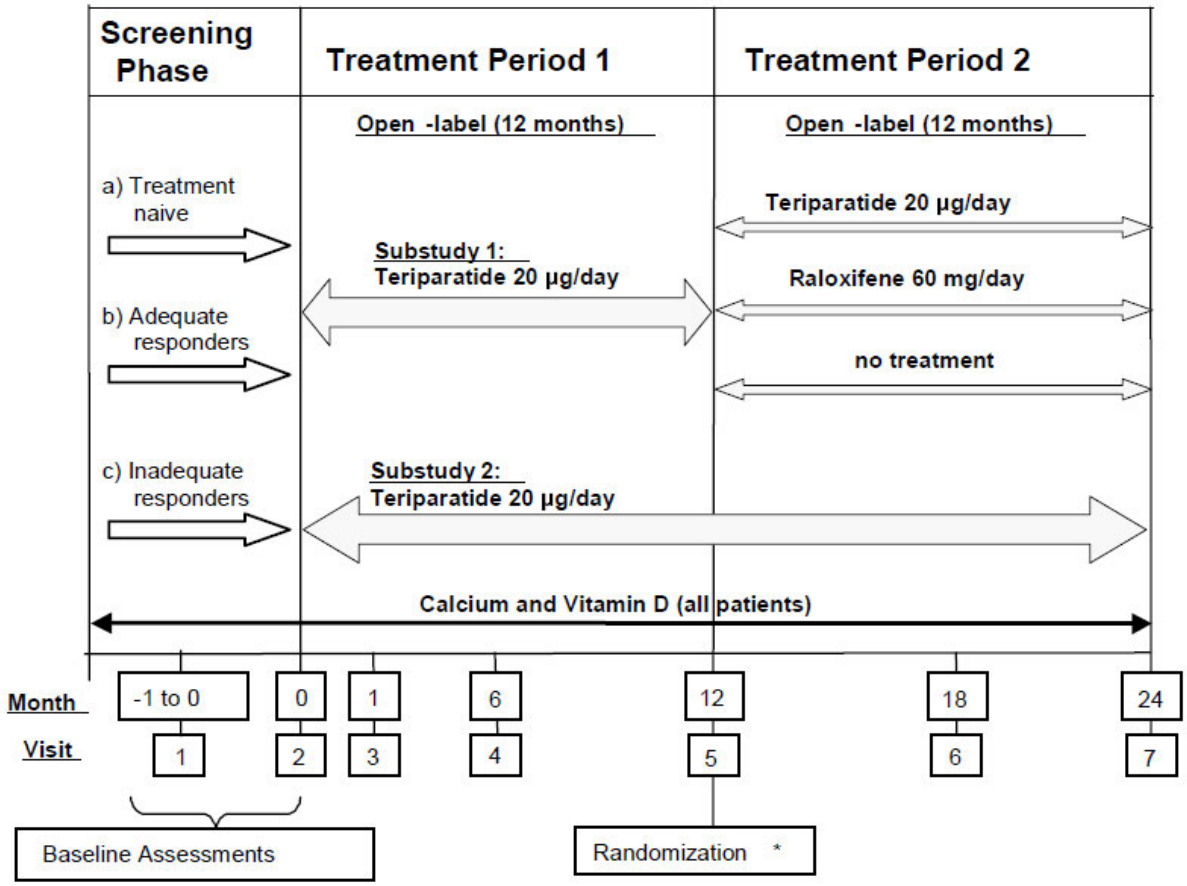
- treatment naïve
- AR pre-treated
- AR pretreated with inadequate response.

The protocol defined inadequate response as

(1) sustained at least one new vertebral or nonvertebral fragility fracture occurring at least 12 months after the documented start of anti-resorptive therapy;
(2) had a lumbar spine, total hip, or femoral neck BMD T-score of −3.0 or less occurring at least 24 months after the documented start of anti-resorptive therapy; and/or
(3) decline of ≥3.5% in BMD between a BMD scan obtained in the 12 months prior to initiation of antiresorptive treatment and the other obtained 24 months after the date of the first prescription for antiresorptive treatment.

All enrolled patients initially received teriparatide 20 mcg daily for one year. After the first year, patients were then divided into one of the two sub-studies according to their previous experience with AR therapy. Inadequate responders comprised sub-study 2 and those patients continued teriparatide 20 mcg daily for twelve additional months. Treatment naïve and adequate responders enrolled into sub-study 1 and were randomized in a 3:1:1 ratio to receive teriparatide 20 mcg daily, raloxifene 60 mg daily or no treatment, respectively, for twelve additional months. Study design is depicted in Figure 1.

Figure 1. GHCA Study Design



Source: NDA 021318 SD 1694, GHCA study report, Figure GHCA.9.1, p. 65.
*randomization applies to sub-study 1 only

Lumbar spine and hip BMD were assessed by DXA at baseline and after 6, 12, 18, and 24 months of teriparatide treatment.

Study Endpoints

The primary endpoint was the change from baseline in lumbar spine BMD measured by areal DXA at 24 months. DXA assessments were performed centrally.

The primary comparison was between the teriparatide-teriparatide arm versus the teriparatide-no active treatment arm in sub-study one. The co-primary comparison was the between-group difference of the teriparatide-raloxifene arm versus the teriparatide-no active treatment arm.

Statistical Analysis Plan

Sub-study 1

For the primary analysis of BMD, a mixed model repeated measures (MMRM) methodology was applied to analyze the between treatment group differences. The model included fixed effects for treatment-by-visit interaction and random effects for patient nested within treatment.
A last-observation carried forward (LOCF) approach was used for the BMD efficacy analyses. There were no imputations for missing data.

There was no adjustment for multiplicity included in the statistical analysis plan.

The efficacy analyses were based on the full analysis population which included all patients randomized and who had at least one dose of study medication and one follow-up visit after randomization.

The sample size was calculated to provide ≥80% power based on a 2-sided alpha of 0.05 for the co-primary comparisons of change in BMD for teriparatide-teriparatide (T-T, Arm 1) and teriparatide-no active treatment (T-N, Arm 3) groups, and teriparatide-raloxifene (T-R, Arm 2) and teriparatide-no active treatment (Arm 3) groups. The power calculation assumed a mean LS BMD difference of 0.03 g/cm2 between Arms 2 and 3, and 0.06 g/cm2 between Arms 1 and 3.

Sub-study 2

The primary analysis adjusted for covariates of treatment-by-visit interaction and random effects for patient nested within treatment.

The efficacy assessment was based on the full analysis population.

For each sub-study and each treatment arm, the time course of BMD over the entire trial was also described using descriptive statistics for the observed values at each visit and at the study endpoint based on the LOCF approach

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that the study was conducted in accordance with GCP.

Financial Disclosure

Not applicable for this non-covered study.

Patient Disposition

A total of 868 patients enrolled into the study. A total of 658 (75%) completed the two-year study: One-hundred and sixty-two patients (19%) discontinued during the first year during which all patients received teriparatide. The primary reason for early discontinuation in year one was patient decision (7% of all patients) and adverse event (6%). The discontinuation rate in year 2 ranged from 4% to 10% of subjects (see Table 5). Patient decision and adverse event were the most common reasons cited.

Table 5. Patient Disposition Year 2 of Study GHCA

	T-T N (%)	T-R N (%)	T-N N (%)	T N (%)
Randomized	305	100	102	199
Completed	285 (93)	90 (90)	92 (90)	191 (96)
Discontinued	20 (7)	10 (10)	10 (10)	8 (4)
Adverse event	6 (2)	7 (7)	1 (1)	4 (2)
Patient decision	9 (3)	1 (1)	5 (5)	17 (2)

Source: NDA 021318 SD 1694, GHCA study report, Table GHCA.10.2, p. 91.

Protocol Violations/Deviations

The incidence of protocol deviations in sub-study 1/year 2 was greatest in the teriparatide treatment group and was driven largely by poor compliance (see Table 6). A similar rate was observed in sub-study 2/year 2.

Table 6. Protocol violations in Year 2 of Study GHCA

	Sub-study 1			Sub-study 2
	T-T N=305	T-R N=100	T-N N=102	T N=234
At least 1 violation	31 (10)	5 (5)	5 (5)	22 (9)
Compliance <70%	12 (4)	3 (3)	0 (0)	9 (4)
Prohibited concomitant medications	10 (3)	2 (2)	5 (5)	7 (3)
No fragility fractures	4 (1)	1 (1)	0	3 (1)
Visit more than 3 months overdue	4 (1.3)	0	0	0
Abnormal/clinically significant lab values	1 (0)	0	0	1 (0)

Source: NDA 021318 SD 1694, GHCA study report, Table GHCA.10.3 and 10.4, p. 92 and p. 93.

Table of Demographic Characteristics

All enrolled patients were Caucasian females. Demographic characteristics, shown in Table 7, were similar between studies and across treatment groups in sub-study 1.

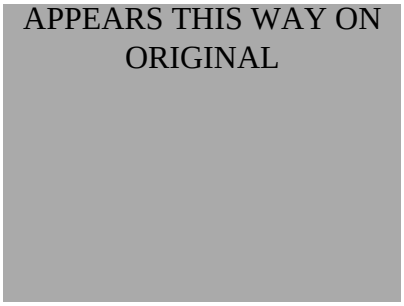


Table 7. Baseline Demographic characteristics Sub-study 1 and Sub-study 2, GHCA

	Sub-study 1			Sub-study 2
	T-T (N=304)	T-R (N=97)	T-N (N=102)	T (N=234)
Mean age (years)	69	69	69	70
Median BMI (kg/m2)	25	25	25	25
Median time since menopause (months)	264	264	244	288
Lumbar spine				
Mean (SD) BMD	0.74 (0.11)	0.75 (0.12)	0.74 (0.11)	0.72 (0.12)
Mean T-score	-3.2	-3.2	-3.1	-3.4
Total hip				
Mean (SD) BMD	0.7	0.7	0.7	0.7
Mean T-score	-2.2	-2.1	-2.1	-2.3
Femoral neck				
Mean (SD) BMD	0.6	0.6	0.6	0.6

Source: NDA 021318 SD 1694, GHCA study report, Table GHCA.14.1.5.1, p. 194.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Compliance for teriparatide and raloxifene treatment was assessed and calculated as the percentage of medication actually taken compared with the medication prescribed. Non-compliance was slightly higher in the teriparatide group in sub-study 1 compared to the raloxifene group (6.4% versus 3.6%, respectively). In sub-study 2, 2.1% of subjects were non-compliant.

Reviewer comment: Given teriparatide's subcutaneous route of administration, lower compliance is expected as compared to an orally administered product.

Efficacy Results – Primary Endpoint
This review focuses on the primary comparison of interest –teriparatide-teriparatide versus teriparatide-no active treatment.

In sub-study 1, the change from study baseline to month 24 in lumbar spine BMD was greatest in the teriparatide-teriparatide group and statistically significantly greater than teriparatide-no active treatment groups (see Table 8).

In sub-study 2, LS BMD also increased at month 24 compared to baseline though the degree of increase was not as large as in the population that did not include AR non-responders. P-value is not shown because this was not comparison was not pre-specified in the statistical analysis plan (see Table 8).

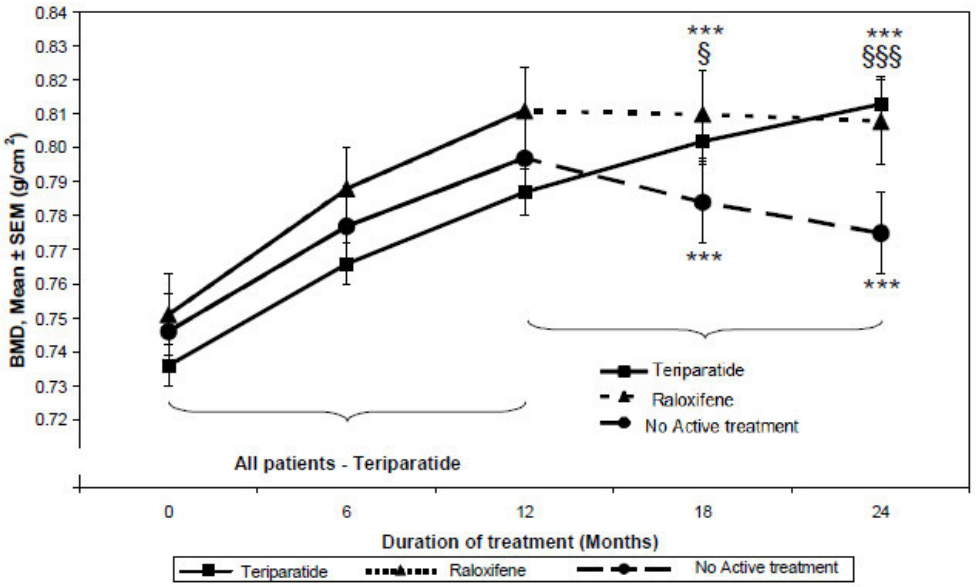
Table 8. Least squares (LS) Mean change from baseline at 24 months in Lumbar Spine Bone Mineral Density (g/cm2) – MMRM analysis, Full Analysis population, GHCA

	Sub-study 1			Sub-study 2 (AR non-responders)
	T-T(N=304)	T-R (N=97)	T-N (N=102)	T (N=234)
LS mean change	0.079	0.058	0.028	0.067
SE	0.003	0.005	0.005	0.005
95% CI	0.07 – 0.08	0.05-0.07	0.03-0.04	0.06 – 0.08
% change[+]	10.7	7.9	3.8	9.2
p-value	<0.001*			

Source: NDA 021318 SD 1694, GHCA study report, Table GHCA.11.12, p. 111
[Y] –numbers rounded to nearest tenth
*Teriparatide-teriparatide vs. teriparatide-no active treatment
+computed as (change in LS mean BMD/group mean baseline BMD) x 100%

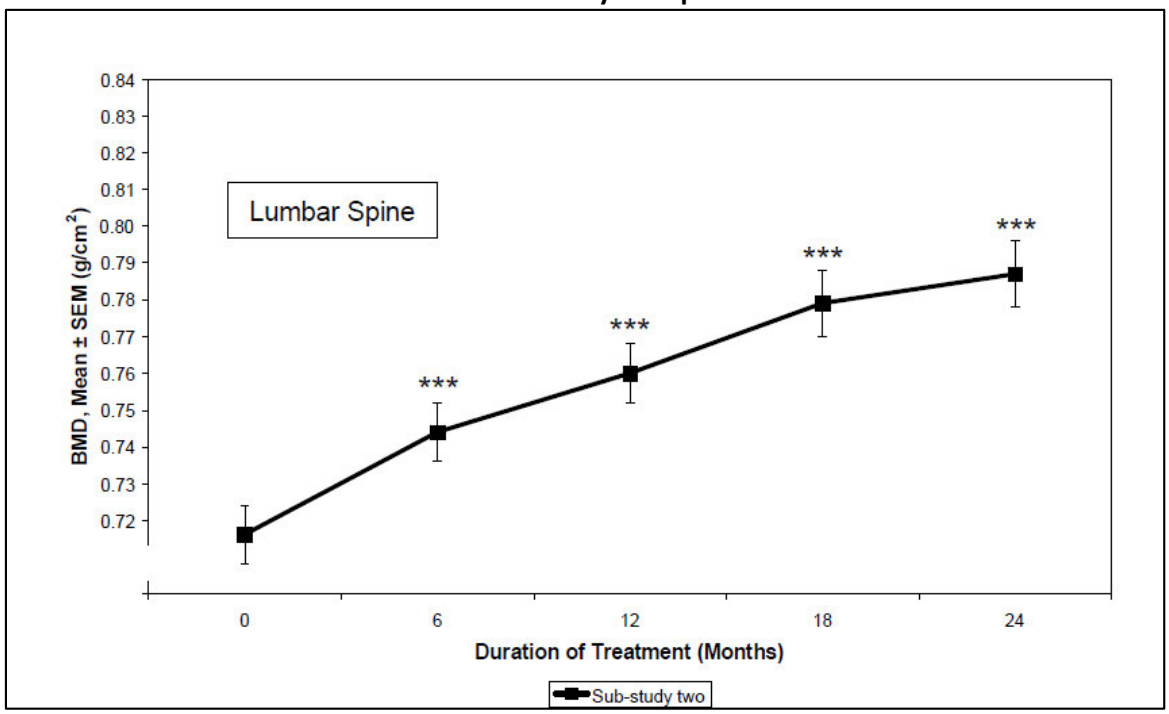
Change in LS BMD over the 24-month treatment period for sub-study 1 and sub-study 2 is depicted graphically in Figure 2 and Figure 3, respectively. Subjects receiving teriparatide for 24 months experienced continuous increases in LS BMD while LS BMD declined from months 12-24 in the other treatment groups.

Figure 2. Mean (Standard Error) LS BMD over Time (Sub-study 1) – Full Analysis Population



Source: NDA 021318 SD 1694, GHCA study report, Table GHCA.11.1, p. 95

Figure 3. Mean (Standard Error) LS BMD (g/cm2) over Time (Sub-study 2) – Full Analysis Population



Source: NDA 021318 SD 1694, GHCA study report, Table GHCA.11.2, p. 96

Secondary endpoints

Total Hip and Femoral Neck BMD

In sub-study 1, the change from baseline at month 24 in total hip and femoral neck LS BMD was greater in the teriparatide-teriparatide group than in the teriparatide-no active treatment arm and was similar to the teriparatide-raloxifene group (see Table 9). Similar increases in total hip and femoral neck LS mean BMD were observed in sub-study 2 (see Table 9).

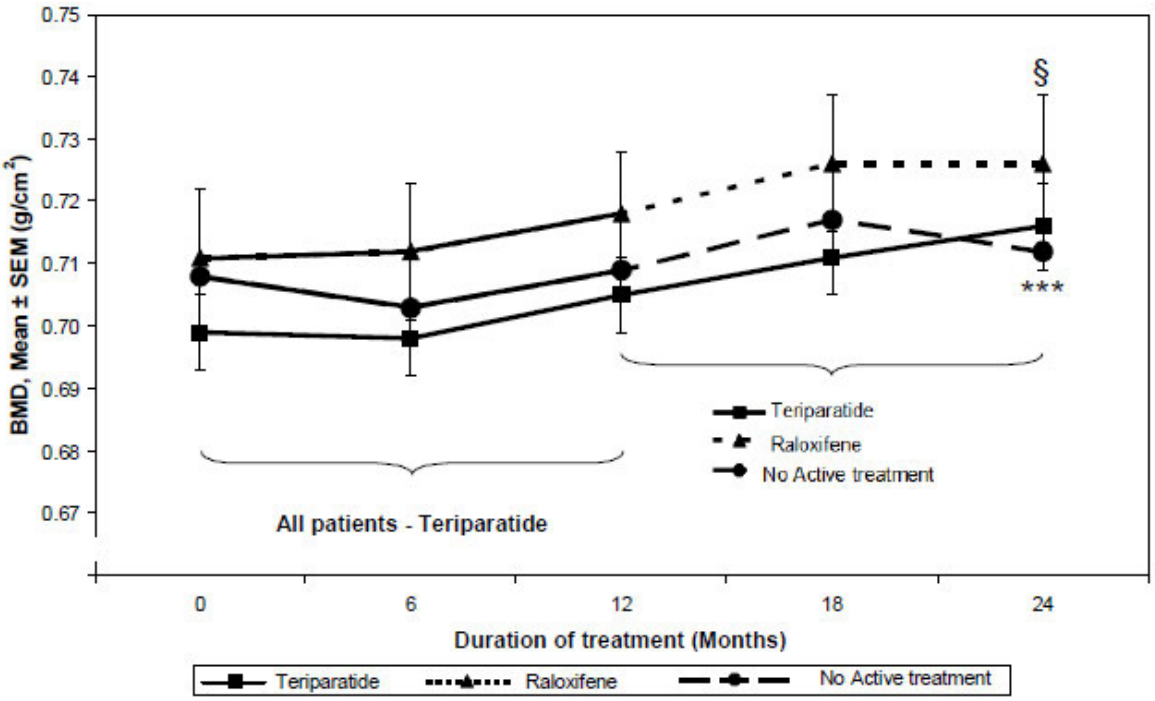
Table 9. total hip and femoral neck BMD (g/cm^2) Change from baseline at 24 months, Full Analysis population, MMRM analysis, Study GHCA

Total hip, Change at 24 months				Sub-study 2
	T-T (N=304)	T-R (N=97)	T-N (N=102)	T (N=234)
LS Mean	0.017	0.016	0.004	0.018
SE	0.002	0.004	0.004	0.004
95% CI	0.01 to 0.02	0.009 to 0.02	-0.004 to 0.011	0.01-0.03
% change	2.5%	2.4%	0.5%	2.6%
Femoral neck, Change at 24 months				
LS Mean	0.022	0.019	0.008	0.03
SE	0.002	0.004	0.004	0.004
95% CI	0.02 – 0.03	0.01-0.03	0.0-0.02	0.02 – 0.04
% change	3.5%	3.1%	1.3%	4.8%

Source: NDA 021318 SD 1694, GHCA study report, Table GHCA.11.20, p. 121 and Table GHCA.11.28, p. 132; table GHCA.11.25, p. 126 and Table GHCA.11.33, p. 137

Figure 4 and **Figure 5** graphically depict the change in mean total hip and femoral neck BMD over the 24-month study period in the three treatment groups. Only the teriparatide-teriparatide group showed a continuous increase from month 12-24.

Figure 4. Mean (SE) Total Hip BMD (g/cm²) over time (Sub-study 1) – full analysis population



Source: NDA 021318 SD 1694, GHCA study report, Figure GHCA.11.3, p. 119.

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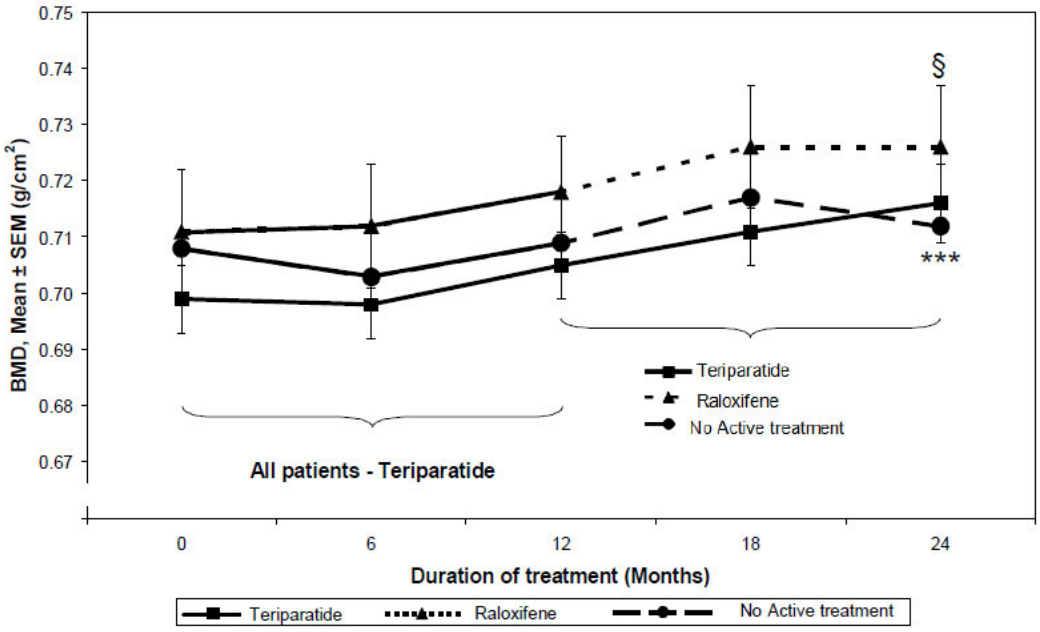
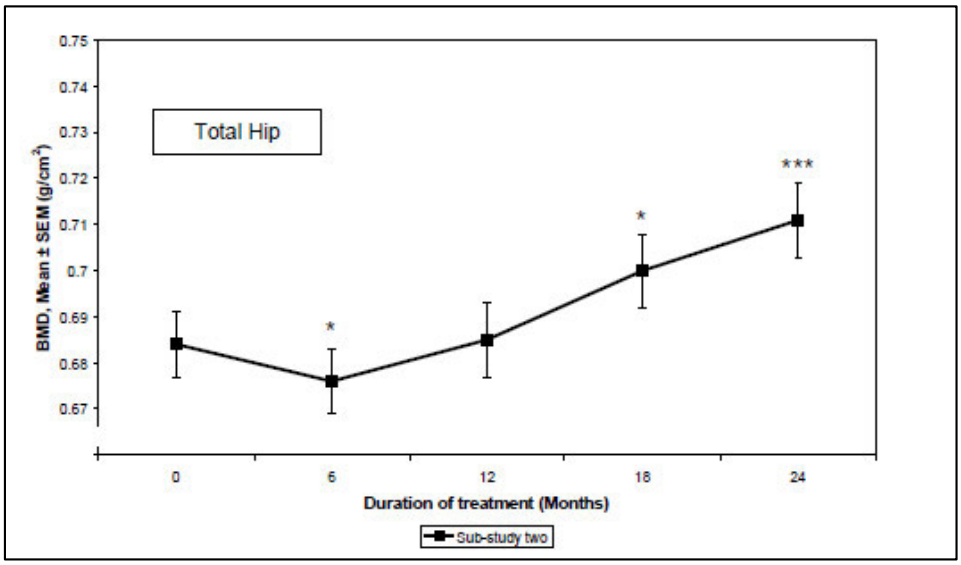
Figure 5. Mean (SE) Femoral Neck BMD (g/cm2) over time (Sub-study 1) – full analysis population, study GHCA



Source: NDA 021318 SD 1694, GHCA study report, Figure GHCA.11.5, p. 130

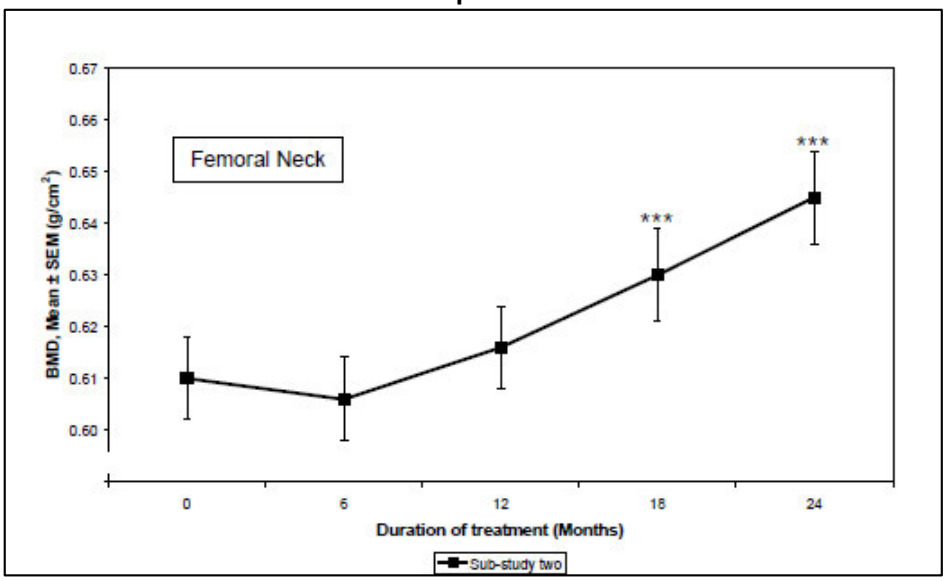
In sub-study 2, patients receiving teriparatide for 24 months showed an initial decrease in total hip and femoral neck BMD from month 0-6, followed by a steady increase out to month 24 (see **Figure 6** and **Figure 7**).

Figure 6. Mean (SE) BMD of total hip (g/cm2) over time (sub-study 2) – full analysis population



Source: NDA 021318 SD 1694, GHCA study report, Figure GHCA.11.4, p. 120

Figure 7. Mean (SE) BMD of the femoral neck (g/cm2) over time (Sub-study 2) – Full Analysis Population



Source: NDA 021318 SD 1694, GHCA study report, Figure GHCA.11.6, p. 131

Additional Analyses Conducted on the Individual Trial

The Applicant conducted a post-hoc analysis of all patients who received teriparatide for 24 months, merging subjects from sub-studies 1 and 2. This analysis, which was not included in the original study report but published later in the Journal of Bone and Mineral Research, showed that the absolute mean change in BMD increased at all skeletal sites regardless of previous treatment with, or response to, anti-resorptive therapy[11] (see Figure 8).

Figure 8. Absolute mean Change in BMD in Teriparatide-Treated Patients from baseline to 24 months according to previous history of and response to anti-resorptive (AR) therapy

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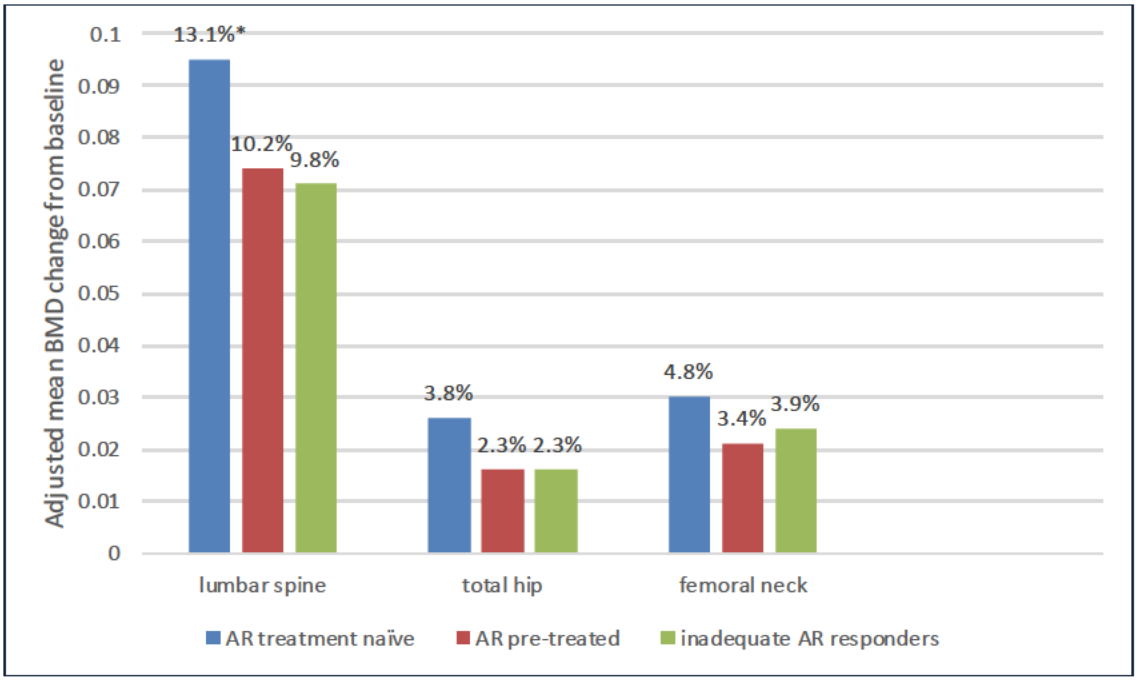
[11] Obermayer-Pietsch BM, Marin, F, McCloskey EV, et. al. Effects of Two Years of Daily Teriparatide Treatment on BMD in Postmenopausal Women with Severe Osteoporosis with and without Prior Antiresorptive Treatment. J Bone Miner Res 2008; 23: 1591:1600.



Source: NDA 021318 SD 1684, module 2.5, Figure 1, p. 31.
*Numbers at the top of the vertical bars indicate percentage change from baseline.

Reviewer comment: Treatment with teriparatide for 24 months is associated with continuous increases in BMD at the lumbar spine, total hip and femoral neck. Plateau of BMD response was not observed. Previous anti-resorptive therapy appears to blunt the BMD response to teriparatide.

8.2. Issue #2: Efficacy beyond 24 months

8.2.1. GHBZ: Comparison of the effects of teriparatide with those of alendronate sodium on lumbar spine bone mineral density in glucocorticoid-induced osteoporosis

Trial Design

The Applicant referred to this study report for information on the effects of teriparatide treatment beyond 24 months. Study GHBZ was previously reviewed by FDA as it served as the pivotal efficacy trial in support of the glucocorticoid-induced osteoporosis indication for which Forteo was approved in July 2009.[12, 13] For ease of review, key features of the trial are re-addressed in this document.

GHBZ was a global, multicenter, randomized, double-blind, double-dummy, active-comparator-controlled study in 428 adult men and women 21 years of age and older with osteoporosis associated

[12] Gassman, op. cit.
[13] Benson, op. cit.

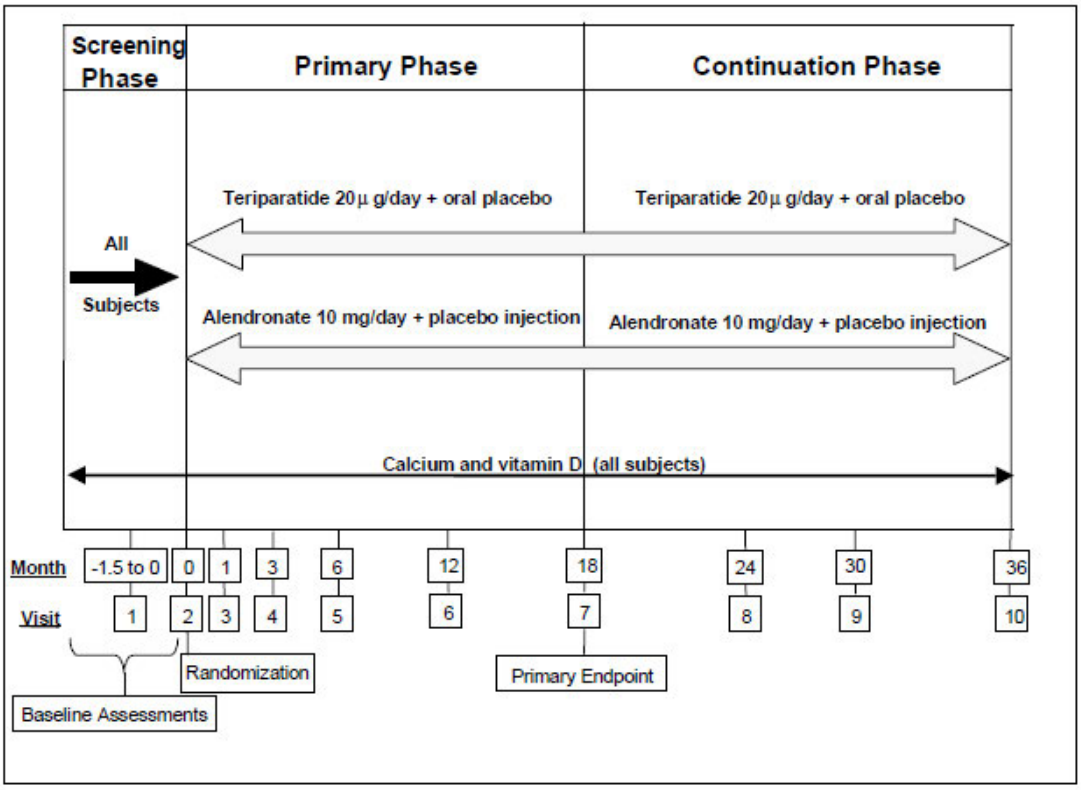
with sustained glucocorticoid therapy. Sustained GC was defined as taking an average dose of at least 5 mg/day prednisone or its equivalent for a minimum of three consecutive months immediately prior to screening. The protocol defined osteoporosis as BMD T score <-2.0 at total hip, femoral neck or lumbar spine; or, in patients with a known prior low trauma or atraumatic fracture, a BMD< -1.0.

There were three study periods:

- a 1.5 month screening phase
- an 18 month double-blind primary phase
- an 18 month double-blind continuation phase.

Patients were randomized 1:1 to either teriparatide 20 mcg daily (qd) + oral placebo or alendronate 10 mg qd + placebo injection. All patients also received calcium and vitamin D supplements for a minimum of one month prior to randomization. Study design is depicted in **Figure 9**.

Figure 9. GHBZ Study Design



Source: NDA 021318 Suppl 12, SD 191, submitted 5/29/2008, GHBZ study report, Figure GHBZ.9.1, p.38.

Study Endpoints

The primary endpoint was the change from baseline to 18 months in lumbar spine BMD

Secondary endpoints were:

- the change from baseline in femoral neck and total hip BMD at 18 months, 24 months,

and 36 months, and in lumbar spine BMD at 24 months and 36 months;
- the time course of BMD response at the femoral neck and total hip from baseline until 18 months; and
- the time course of BMD response at the lumbar spine, femoral neck, and total hip from baseline until 36 months.

Thoracic and lumbar spine x-rays were evaluated for the presence of vertebral fractures at baseline and months 18 and 36.

Reviewer's comment: For the purpose of this labeling supplement, efficacy findings at 24 and 36 months are of most interest. The 18-month efficacy results have already been reviewed and can be found in the Forteo package insert.

Statistical Analysis Plan

In the primary analysis of the primary outcome variable (change in lumbar spine BMD), a single comparison between the treatments was made for the primary and continuation phases. Analysis was conducted on the full analysis set (i.e. patients who received at least one dose of study medication and had one post-baseline measurement). No missing data were imputed except at endpoint for which a last observation carried forward (LOCF) method was used.

Hypothesis testing at the 0.05 level of significance occurred in the following pre-specified sequence:
- 36 months
- 24 months
- 18 months
- 12 months
- 6 months
- 3 months

At each time point, the test for the combined (males plus females) dataset was performed first. If the result was significant, the test for the females only dataset was performed.

The study was powered for the analysis of the primary efficacy variable in women only.

Patient Disposition

A total of 428 patients were randomized and treated. Just over half in both groups completed the 36-month trial. The most common reason for early discontinuation was patient decision, followed by an adverse event and lost to follow-up. The full analysis set (FAS) for the efficacy evaluation consisted of all patients who were randomized, treated and had at least one post-randomization efficacy evaluation. In this study , 92% of randomized patients were included in the FAS (see Table 10).

Table 10. Patient Disposition Study GHBZ

	Alendronate N(%)	Teriparatide N(%)
Randomized and treated	214	214
Completed 36-months	118 (55)	123 (57)
FAS population for efficacy evaluation	195 (91)	198 (93)
Withdrawn prematurely	96 (45)	91 (43)
Patient decision	42 (20)	29 (14)
Adverse event	18 (8)	30 (14)
Death	15 (7)	4 (1.9)
Lost to follow-up	13 (6)	4 (2)

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Protocol Violations/Deviations

More than half of patients reported at least one potentially significant protocol violation, but the incidence was balanced between the treatment groups (see Table 11).

Table 11 N(%) of patients with potentially significant protocol violations, GHBZ Full analysis set

	Alendronate	Teriparatide
Randomized and treated	214	214
Subjects with ≥1 impactful violation	107 (50)	104 (49)
BMD assessment not performed at both baseline and 18 months	66 (31)	58 (27)
Less than 70% compliant	25 (12)	31 (15)
Treated <15 months	63 (29)	55 (26)
Took protocol excluded medication	21 (10)	26 (12)

Reviewer's comment: To examine the effect of protocol violations on the primary variable, the Applicant repeated analyses using only those patients in the FAS who did not have major protocol violations (i.e., the per-protocol population).

Table of Demographic Characteristics

The majority of patients were middle-aged, Caucasian females. Characteristics were balanced between the treatment groups. For full details on patient characteristics, refer to the Forteo package insert and clinical reviews of NDA 21318 supplement 12.

Efficacy Results – Primary Endpoint

At both 24 months and 36 months, the mean change and percent change in LS BMD from baseline increased in both treatment groups but statistically significantly more for those receiving teriparatide than alendronate (see **Table 12**). Findings for both the full analysis set and the per protocol set were similar, showing that protocol violations did not significantly impact efficacy findings.

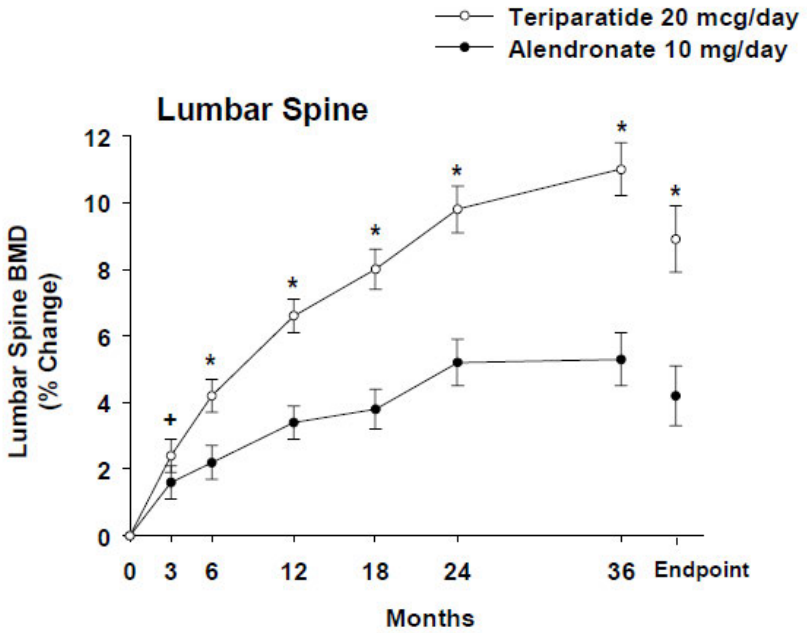
Table 12. Mean change and percentage change in LS BMD from baseline at Month 24 and Month 36, full analysis set and per protocol set, LOCF

Demographic Parameters	Alendronate N=214	teriparatide N=214	p-value*
Baseline mean (SE)	0.866 (0.014)	0.865 (0.014)	
Full analysis set			
LS Mean (SE) Change from baseline			
24 months	0.043 (0.006)	0.081 (0.006)	<0.001
36 months	0.044 (0.01)	0.090 (0.006)	<0.001
Mean (SE) percent change			
24 months	5.2% (0.7)	9.8% (0.7)	<0.001
36 months	5.3% (0.8)	11.0% (0.8)	<0.001
Per protocol set			
LS Mean (SE) Change from baseline			
24 months	0.050 (0.008)	0.086 (0.008)	<0.001
36 months	0.051 (0.008)	0.095 (0.008)	<0.001

Source: Source: NDA 021318 Suppl 12, SD 191, submitted 5/29/2008, GHBZ study report, Table GHBZ.11.10 p. 93, and Table GHBZ.14.31, p. 343 and GHBZ.14.32, p. 345.
*teriparatide vs. alendronate

As shown in **Figure 10**, from months 0-24, mean percent change in LS BMD increased sharply in the teriparatide group. The slope was smaller from months 24-36 but still in a positive direction. For alendronate, the increase in mean percent LS BMD was less pronounced for the entire 36 month treatment period than that observed with teriparatide.

Figure 10. Mean percent change in lumbar spine BMD, Study GHBZ



Source: NDA 021318 Suppl 12, SD 191, submitted 5/29/2008, GHBZ study report, Figure GHBZ.11.1, p. 79.

Efficacy Results – Secondary and other relevant endpoints

Within the teriparatide group, mean absolute and percent changes for femoral neck and total hip BMD were significantly greater than in the alendronate group at 24 and at 36 months (see Table 13).

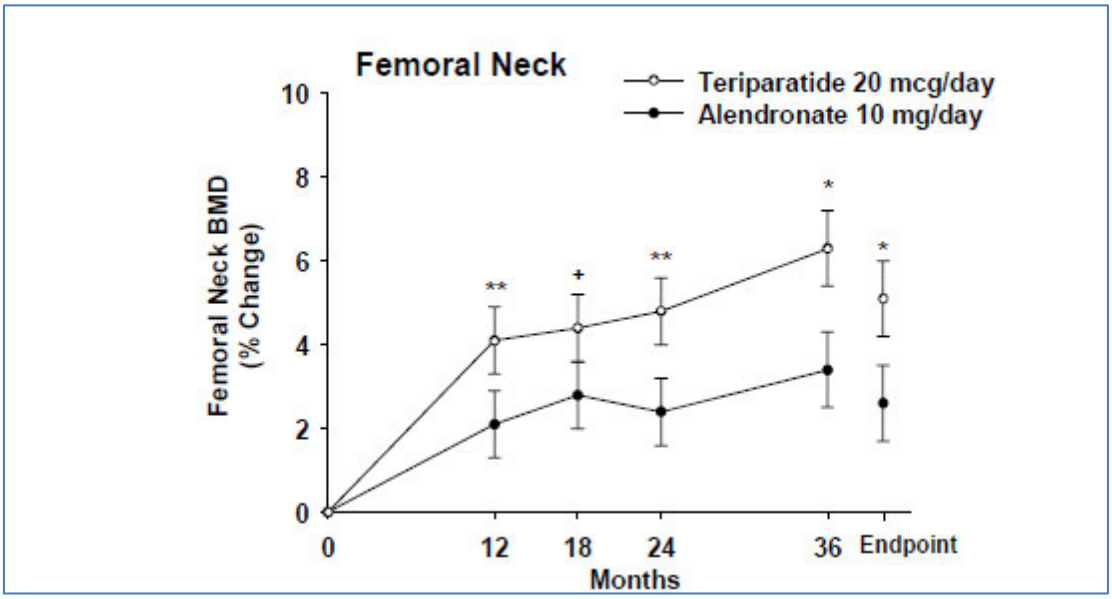
Table 13. Mean change and percentage change in femoral neck and total hip BMD from baseline to month 24 and month 36, full analysis set

	Alendronate N=214	teriparatide N=214	p-value*
Femoral Neck			
Baseline LS mean (SE)	0.729 (0.014)	0.708 (0.014)	
LS Mean (SE) Change from baseline			
24 months	0.015 (0.005)	0.030 (0.005)	<0.002
36 months	0.021(0.01)	0.041 (0.01)	<0.001
LS Mean (SE) percent change from baseline			
24 months	2.4% (0.8)	4.8% (0.8)	<0.001
36 months	3.4% (0.9)	6.3% (0.9)	<0.001
Total hip			
Baseline LS mean (SE)	0.786 (0.014)	0.770 (0.041)	
Mean (SE) Change from baseline			
24 months	0.018 (0.004)	0.034 (0.004)	<0.001
36 months	0.020 (0.005)	0.037 (0.005)	<0.001
Mean percent change from baseline			
24 months	2.5% (0.6)	4.7 (0.6)	<0.001
36 months	2.7% (0.6)	5.2% (0.6)	<0.001

Source: NDA 021318 Suppl 12, SD 191, submitted 5/29/2008, GHBZ study report, Table GHBZ.11.11 p. 96 and 11.12 p. 98
*teriparatide versus alendronate

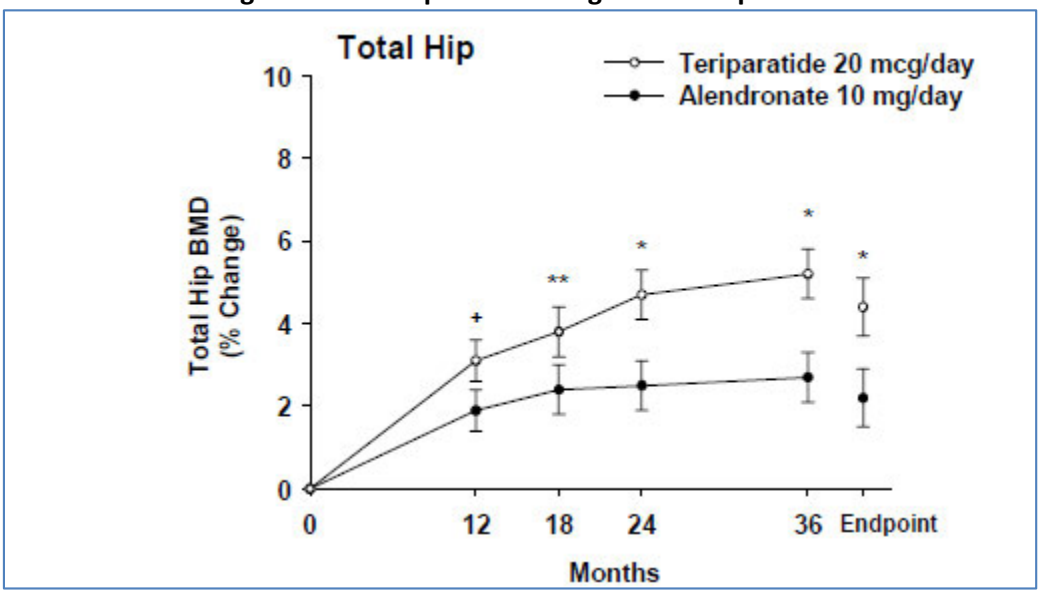
Femoral neck and total hip BMD continued to increase during the 36 month treatment period in the teriparatide treatment group (see Figure 11 and Figure 12).

Figure 11. Mean percent change in femoral neck BMD



Source: NDA 021318 Suppl 12, SD 191, submitted 5/29/2008, GHBZ study report, Figure GHBZ.11.2, p. 97

Figure 12. Mean percent change in total hip BMD



Source: NDA 021318 Suppl 12, SD 191, submitted 5/29/2008, GHBZ study report, Figure GHBZ.11.3, p. 99.

Efficacy from months 18 to 36 months

The extension phase lumbar spine BMD data was evaluated using the same analyses as the initial phase. However, the number of subjects entering the extension phase was approximately 2/3 of the original study population. Although the mean actual change in lumbar spine BMD from 18 months through 36 months was not statistically significantly greater for teriparatide compared to alendronate, both groups saw an increase during that time (see Table 14).

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Table 14. Lumbar spine BMD change from month 18 at month 36[14]

	Teriparatide (N=156)*	Alendronate (N=148)*	Treatment Difference Mean (95% CI)	P – value
Month 18				
LS Mean	0.928	0.891	0.037 (0.008, 0.066)	
Unadj. Mean (SD)	0.920 (0.130)	0.881 (0.136)		
Month 36				
Unadj. Mean	0.941	0.894		
Change	0.021	0.013	0.009 (-0.001, 0.018)	0.079
% Change	2.41%	1.44%	0.97% (-0.11%, 2.04%)	0.077

*N at month 18
Source: Benson, G., deputy directory memorandum of NDA 21318 Suppl 12, Table 3, p. 12 , filed in DARRTS 7/22/09.

Reviewer comment: The reduced sample size in the second half of the study provided insufficient power to achieve statistical significance. It is reassuring though that BMD continued to increase in those patients who remained on teriparatide for the duration of the study even if the improvement was not significantly larger than that observed with alendronate.

Fracture data

Subjects in study GHBZ were monitored for fractures through adverse event reporting and X-ray films at baseline, 18-months and 36-months. The incidence of fractures during the 36-month study was lower in the teriparatide group than in the alendronate group with the exception of any non-vertebral fracture which was slightly greater among teriparatide treated subjects (**Table 15**).

[14] Benson, op. cit.

Table 15. Summary of Fractures in Study GHBZ

Variable	Teriparatide subjects n(%)	Alendronate subjects n(%)
Initial 18 month phase – all subjects		
≥1 All vertebral and non-vertebral fractures	**13/214(6.1)**	**17/214(7.9)**
≥1 **New radiographic vertebral fractures**	1/171*(0.6)	10/165*(6.1)
≥1 Clinical vertebral fracture†	0	3/165*(1.8)
≥1 Any non-vertebral fracture	12/214(5.6)	8/214(3.7)
Overall 36-months – all subjects		
≥1 All vertebral and non-vertebral fractures	**19/214 (8.6)**	**27/214(12.6)**
≥1 **New radiographic vertebral fracture**	3/173*(1.7)	13/169*(7.7)
≥1 Clinical vertebral fracture†	0	4/169 (2.4)
≥1 Any non-vertebral fracture	16/214(7.5)	15/214(7.0)

**Vertebral fractures only include those subjects with baseline and post-baseline spinal radiographs
†Clinical fracture defined as radiographically confirmed fracture associated with a symptom such as back pain
Source: Benson G., Deputy Directory memorandum of NDA 21318 Suppl 12, Table 4, p. 13, filed in DARRTS 7/22/09.

Reviewer comment: At the time of approval of Forteo for the GIOP indication the Division concluded that (b) (4) [redacted] *At that time, however, there was considerable concern regarding the risk of osteosarcoma and data from the post-marketing surveillance studies were not yet available.*

8.2.1. Lindsay, et. al. Randomized controlled study of effect of parathyroid hormone on vertebral bone mass and fracture incidence among post-menopausal women on estrogen with osteoporosis[15]

(b) (4) [redacted]

[15] Lindsay R, Nieves J, Formica C, et. al. Randomized controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on estrogen with osteoporosis. Lancet 1997; 350: 550-55.

Study Design

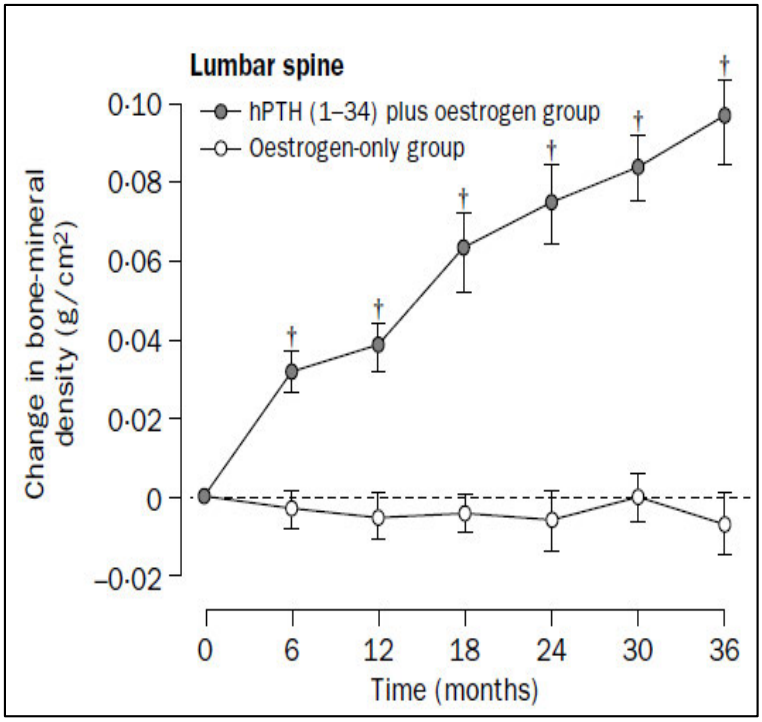
This was a 3-year randomized controlled trial of the effect of teriparatide 25 mcg daily plus hormone replacement therapy (HRT) compared to HRT alone in 34 post-menopausal women with osteoporosis (i.e., T-score <-2.5 and/or history of atraumatic fracture). After a one-year observation period on HRT, subjects were randomized in a 1:1 ratio to receive either teriparatide 25 mcg plus HRT or remain on HRT alone. HRT consisted of either orally administered equine estrogen 0.625 mg daily or transdermal estrogen 50 mcg daily with or without medroxyprogesterone (depending on presence of uterus). Bone mass was measured by DXA every six months. The primary endpoint was change in LS BMD.

Study Results

There were no significant differences between the study groups with respect to baseline characteristics. Mean age was 59.5 years in the combination group and 64.2 years in the HRT alone group. Racial grouping was not provided. Baseline lumbar spine BMD was 0.72 g/cm^2 in the teriparatide plus HRT group and 0.75 g/cm^2 in the HRT alone group. Baseline total hip was 0.70 g/cm^2 in the combination group and 0.72 g/cm^2 in the HRT alone group.

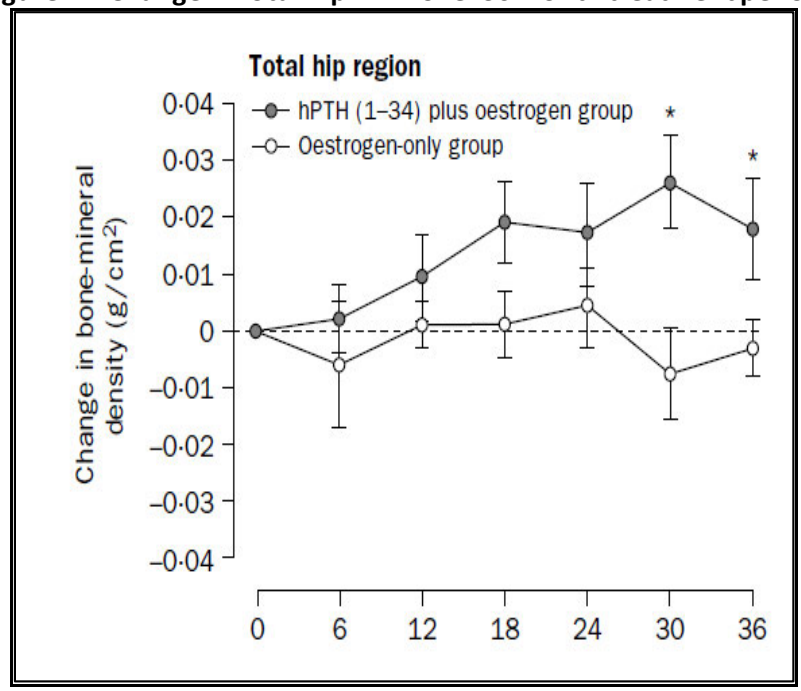
At the conclusion of 3 years of treatment, lumbar spine BMD had increased by 13% in the teriparatide-treated group and had "non-significantly declined" in the HRT alone group (percentage value not provided). Total hip BMD increased by 2.7% for teriparatide-treated patients and was stable in the estrogen-only group. Figure 13 and Figure 14 depict the change in BMD for both groups over the 36-month treatment period. Notable is that from months 30-36, total hip BMD declined slightly in the teriparatide group returning toward the 24-month value.

Figure 13. Change in LS BMD over 36 month treatment period



Source: Lindsay, et. al., Figure 2, p. 553.

Figure 14. Change in Total Hip BMD over 36 month treatment period



Source: Lindsay, et. al., Figure 2, p. 553.

The incidence of vertebral fractures during the treatment, was lower in the teriparatide group than in the control group whether using a 15% or 20% decrease in vertebral height as the diagnostic threshold.

Table 16. Fracture (using 15% and 20% decrease in vertebral height as diagnostic threshold) incidence during treatment

	Fracture diagnosed by 15% decrease in vertebral height	Fracture diagnosed by 20% decrease in vertebral height
Teriparatide plus HRT (N=17)	2 (11.2%)	1 (5.9%)
HRT alone (N=13)	7 (53.8%)	4 (30.8%)

Source: Lindsey et. al., Table 4, p. 554.

Reviewer comment: In this small study that utilized a dose of teriparatide slightly higher than the approved 20 mcg dose, LS BMD showed continued increase out to 36 months in post-menopausal women receiving teriparatide with HRT. Total hip increased out to 30 months and then decreased from months 30-36. Fracture incidence was lower than in the control group.

8.3. Issue #3: BMD Response to teriparatide after bisphosphonate use

8.3.1. GHBU: Bone effects of subcutaneous teriparatide following discontinuation of raloxifene or alendronate treatment in post-menopausal women with osteoporosis[16]

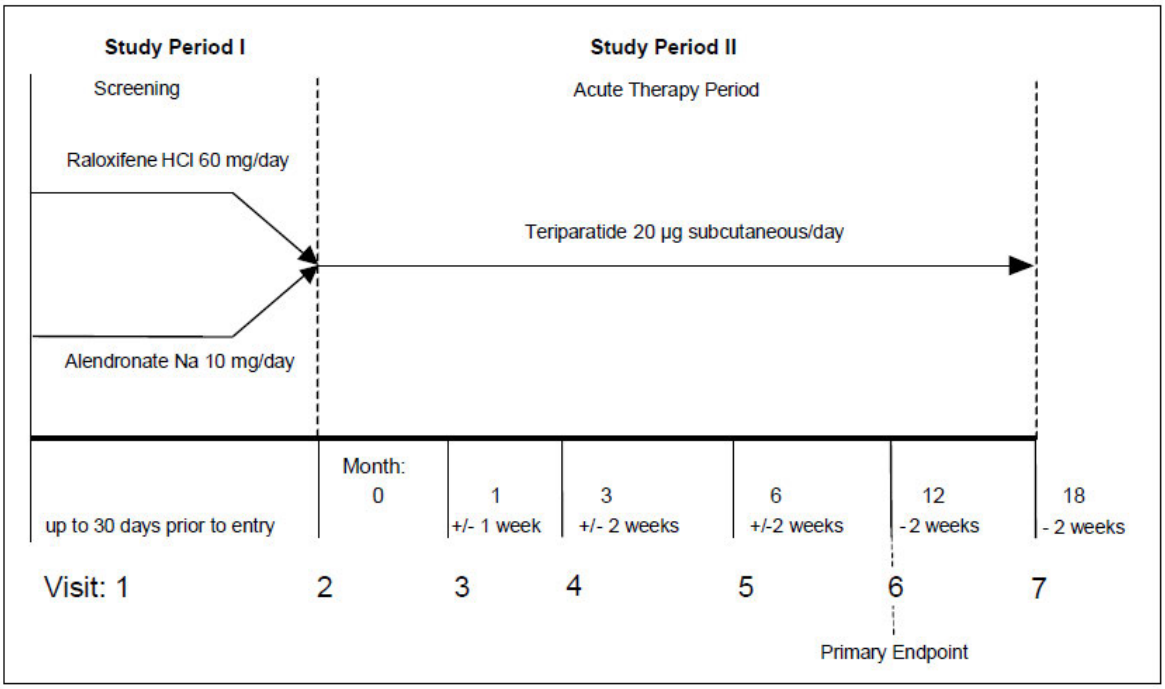
FDA requested information on BMD response to teriparatide after bisphosphonate use.
The primary objective of this study was to assess the effect of 18 months of teriparatide treatment on BMD in osteoporotic women previously treated with either alendronate or raloxifene.

Study GHBU was an open-label, single-center, phase 3, not-for-registration trial conducted in post-menopausal women ≥60 years previously diagnosed with osteoporosis (i.e., hip or lumbar spine BMD T-score<-2.5) and currently osteoporotic or severely osteopenic (i.e., hip or lumbar spine BMD T-score <-2.0). Subjects should have had normal baseline laboratory values (including serum calcium, 25-OH vitamin D and alkaline phosphate). They should also have received previous therapy for 18-36 months with either raloxifene 60 mg daily or alendronate 10 mg daily at study entry.

Enrolled subjects received teriparatide 20 mcg daily for 18 months. All patients also received daily calcium 1000 mg and vitamin D 400 IU. The study design is depicted in Figure 15.

[16] Ettinger B, San Martin J, et. al. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res. 2004 May; 19 (5): 745-51.

Figure 15. Design of Study GHBU



Source: NDA 021318 Suppl 54, SD 1684, GHBU study report, Figure GHBU.1, p. 23.

The primary outcome measure was the change in lumbar spine BMD measured by DXA.

A total of 59 patients were enrolled in the study. Most participants were white and had been treated with anti-resorptive therapy for about 29 months on average. Baseline characteristics were balanced between the two groups as shown in Table 17.

Table 17. Baseline Characteristics of patients in study GHBU

	Prior Raloxifene (N = 26)	*Prior Alendronate* (N = 33)
Age (years)	68.8 ± 5.6	71.2 ± 7.65
White (%)	100	85
Body mass index (kg/m^2)	23.8 ± 3.7	23.4 ± 4.7
Previous therapy duration (months)	29.0 ± 5.5	29.3 ± 5.2
Lumbar spine BMD (g/cm^2)	0.77 ± 0.08	0.79 ± 0.10
Total hip BMD (g/cm^2)	0.68 ± 0.06	0.67 ± 0.10
Lumbar spine BMD T-score	-2.5 ± 0.7	-2.3 ± 1.0
Total hip BMD T-score	-2.1 ± 0.5	-2.3 ± 0.8
PTH (pg/ml)	3.1 ± 1.2	3.2 ± 1.6
25 (OH) D (ng/ml)	72.5 ± 17.3	68.1 ± 20.6

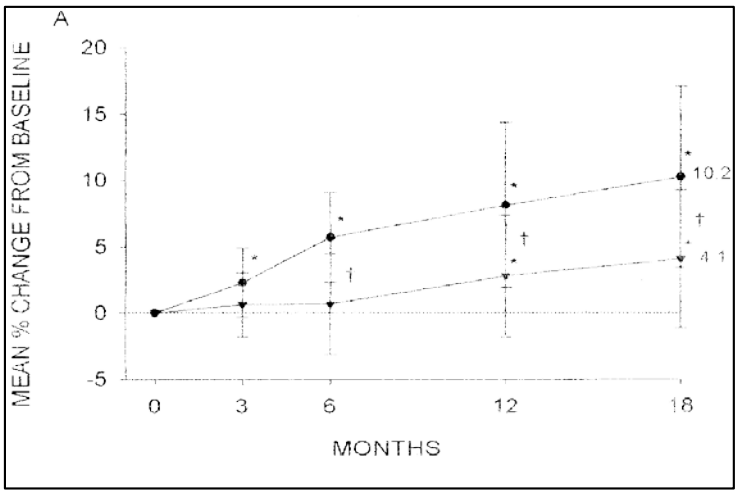
Source: Ettinger et. al., Table 1., p. 748.

Results

After 12 months of teriparatide, LS BMD increased by 7.66% in the previous raloxifene group and 2.49% in the previous alendronate group. At 18 months, 10.2% increase in lumbar spine BMD was observed for the prior RLX group, whereas the prior ALN group showed a 4.1% increase.

The change over the course of 18 months of teriparatide treatment in lumbar spine BMD is depicted in Figure 16. During the first 6 months of teriparatide, BMD was nearly unchanged in the previous alendronate group.

Figure 16. Mean percent change in LS BMD after 18 months of teriparatide according to previous treatment received (alendronate or raloxifene)



Top line=previous raloxifene

Source: Ettinger, Fig. 3, p. 750

Reviewer's comment: The authors concluded that prior treatment with alendronate blunts teriparatide-induced increases in BMD, particularly during the first six months of treatment.

8.4. Issue #4: Effect of teriparatide discontinuation on BMD and fracture risk

8.4.1. GHBJ: Extended follow-up of patients in LY333334 (Teriparatide) Trials

The Division requested information about the decrease in BMD when teriparatide is discontinued. GHBJ addresses this issue.

8.4.2. Study Design

Overview and Objective

The primary objective was to collect safety data for teriparatide following the withdrawal of teriparatide treatment.

Trial Design

GHBJ was a multi-center, international, five-year, observational study that enrolled subjects who completed up to 24 months of treatment with teriparatide 20 mcg/day, 40 mcg/day or placebo in one of seven long-term (≥3 month) clinical trials that had been conducted for the initial Forteo marketing application (eligible trials are shown in Table 18).

Table 18. Forteo Studies Included in GHBJ Follow-up Protocol

B3D-MC-GHAC	Effects of LY333334 in the Treatment of Postmenopausal Women with Osteoporosis
B3D-MC-GHAF	Effects of LY333334 in Postmenopausal Women on Estrogen and Progestin Therapy
B3D-MC-GHAH	LY333334 Compared with Alendronate in Postmenopausal Women with Osteoporosis
B3D-MC-GHAJ	Effects of LY333334 in the Treatment of Men with Osteoporosis
B3D-MC-GHAL	Effects of LY333334 in Postmenopausal Women Who Experience Rapid Bone Loss or Multiple Osteoporotic Fractures in Study B3D-MC-GHAC
B3D-MC-GHAU	Effects of LY333334 on Bone Mineral Density in Early Menopausal Women
B3D-MC-GHAV	Effects of Anti-Resorptive Drug on Bone Formation in Osteoporotic Postmenopausal Women Treated with LY333334

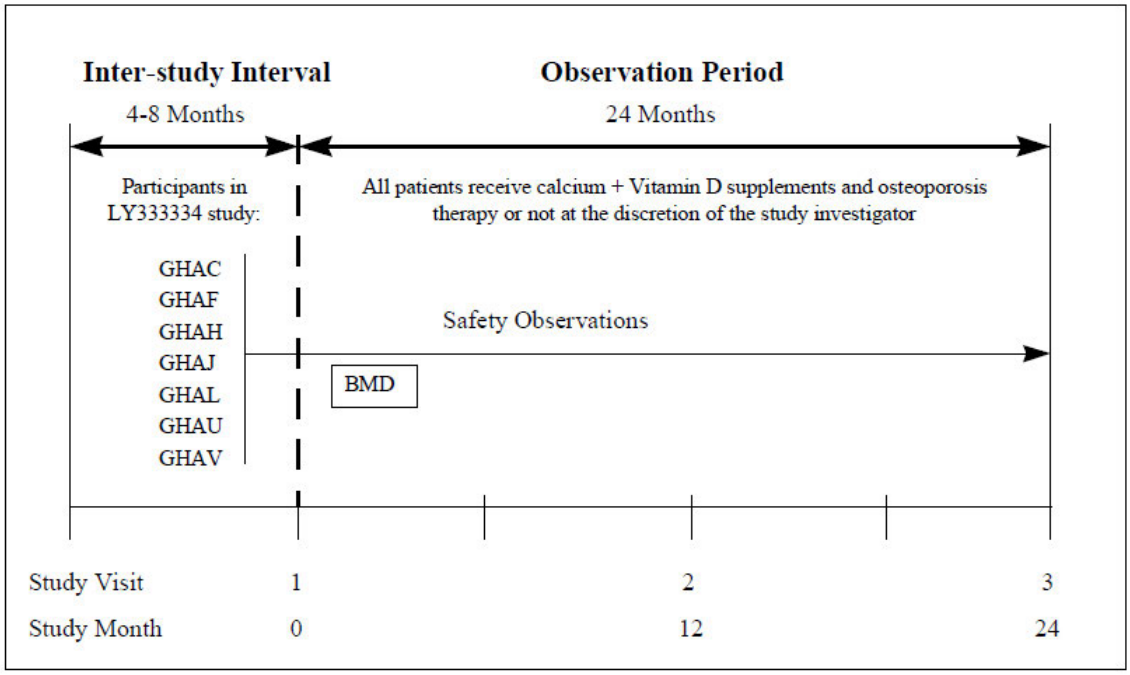
Source: NDA 021318 suppl 54, SD 1687, GHBJ study report, Table GHBJ.7.1, p. 58

Upon enrollment in GHBJ, patients were treated according to standard clinical practice by their physician. All patients were to continue on supplemental calcium 1000 mg/day and vitamin D 400 – 1200 IU/day. No patient received teriparatide, but subjects were allowed to receive other medication to treat osteoporosis.

The study consisted of a 24-month follow-up phase to monitor for both change in bone mineral density after teriparatide discontinuation, and for serious adverse events; and a 30-month extension phase to monitor for serious adverse events. Design is shown in Figure 17.

Hip and lumbar spine BMD was measured at previous study baseline, previous study discontinuation and at GHBJ Visit 1, Visit 2 (month 12) and Visit 3 (month 24).

Figure 17. Design of Study GHBJ



Source: NDA 021318 suppl 54, SD 1687, GHBJ study report, Figure GHBJ(a).2., p. 3449.

Study Endpoints

As this study was an observational safety study, there were no prespecified efficacy endpoints. However, the following parameters were measured during the 24-month follow-up phase to assess the effect teriparatide withdrawal:

- Vertebral fractures – all patients were interviewed to identify clinical vertebral fractures diagnosed since the previous study. An addendum to protocol GHBJ called for spinal radiographs at Visit 2 (month 12) for patients in the GHAC and GHAJ subsets.
- Nonvertebral fractures – patients were interviewed to identify fragility and traumatic non-vertebral fractures diagnosed since the previous study.

Lumbar spine and hip BMD at Visits 2 and 3.

Statistical Analysis Plan

This observational study was not sized on the basis of statistical power for any single outcome measure. The applicant conducted a variety of efficacy analyses but for the purpose of this review the following comparisons will be evaluated:

- change in spine and hip BMD from previous study baseline to GHBJ Visit 3.
- change in spine and hip BMD from previous study endpoint to GHBJ Visit 3
- incidence of vertebral and non-vertebral fractures during the 24-month follow up.

Data from study GHAC and GHAJ were analyzed separately.

The Applicant also conducted sub-group analyses according to use of osteoporosis medication during study GHBJ.

No adjustment for multiple comparisons were made.

8.4.3. Study Results

Compliance with Good Clinical Practices

The Applicant attests that the study was conducted in accordance with GCP.

Financial Disclosure

Not applicable since this is a non-covered study.

Patient Disposition

The majority (84%) of the 1930 patients enrolled in study GHBJ were previously enrolled in trials GHAC and GHAJ. The number of patients enrolled according to the treatment they received in the previous trial is shown in Table 19.

Table 19. Number of Patients enrolled into Study GHBJ from previous studies GHAC and GHAJ according to previous study treatment group

Prior study	Patient gender	Placebo	PTH 20	PTH40	Total enrolled in GHBJ
GHAC	Female	414	436	412	1262
GHAJ	Male	127	121	107	355
Total N		541	561	579	1617

Protocol Violations/Deviations

Because GHBJ was primarily a safety follow-up study, omission of physical examination at Visit 2 was considered the only significant protocol violation. Less than one percent of patients (18/1930) did not receive a physical examination at Visit 2.

Table of Demographic Characteristics

Nearly 100% of subjects enrolled in study GHBJ were Caucasian. Other demographic characteristics of patients enrolled from studies GHAC and GHAJ according to treatment received during previous study and use of osteoporosis treatment during GHBJ are shown in Table 20. Characteristics were similar across sub-groups with the exception of a larger percentage of smokers in the GHAJ subset not receiving osteoporosis treatment during study GHBJ. Baseline lumbar spine BMD was also slightly greater among subjects who did not receive osteoporosis treatment during study GHBJ.

Table 20. Baseline* demographic characteristics of subjects in study GHBJ according to previous study treatment group and use of osteoporosis treatment during study GHBJ

	GHAC subset (without osteoporosis treatment)			GHAC subset (with osteoporosis treatment)		
	Placebo	**PTH20**	**PTH40**	**Placebo**	**PTH20**	**PTH40**
N	150	188	169	264	248	243
Gender	Female (100%)			Female (100%)		
Mean age (years)	68	69	69	69	69	69
BMI (kg/m^2)	27	27	27	26	26	26
% Smoker	13	17	15	19	15	16
Baseline lumbar spine BMD (g/cm2)	0.9	0.9	0.9	0.8	0.8	0.8
	GHAJ (without osteoporosis treatment)			GHAJ (with osteoporosis treatment)		
	Placebo	**PTH20**	**PTH40**	**Placebo**	**PTH20**	**PTH40**
N	81	94	75	46	25	32
Gender	Male (100%)			Male (100%)		
Mean Age (years)	59	61	58	57	56	56
BMI (kg/m^2)	25	25	25	26	26	25
% smoker	27	27	28	20	9	7
Baseline lumbar spine BMD (g/cm2)	0.9	0.9	0.9	0.8	0.8	0.8

*Baseline – refers to previous study (i.e., study GHAC or GHAJ) baseline
Source: NDA 021318 suppl 54, SD 1687, GHBJ study report, Table GHBJ.11.1-2, p88 and p90.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Not applicable for this observational study.

Efficacy Results
The change from previous study endpoint to GHBJ visit 3 represents close to 30 months of off-drug follow-up. P-values, though included in the Applicant's study report, are not shown because there were no pre-specified endpoints and the study was not powered for any specific outcome measure.

Bone Mineral Density
Mean percent change in lumbar spine BMD from previous study endpoint to GHBJ visit 3 increased in subjects who had previously received placebo but decreased in patients who had previously received teriparatide. The degree of decrease in BMD was greater among patients who received teriparatide 40 mcg daily than in those on teriparatide 20 mcg daily. For total hip, BMD was nearly stable in all groups except among women previously treated with placebo who saw a slight increase during follow-up (see **Table 21**).

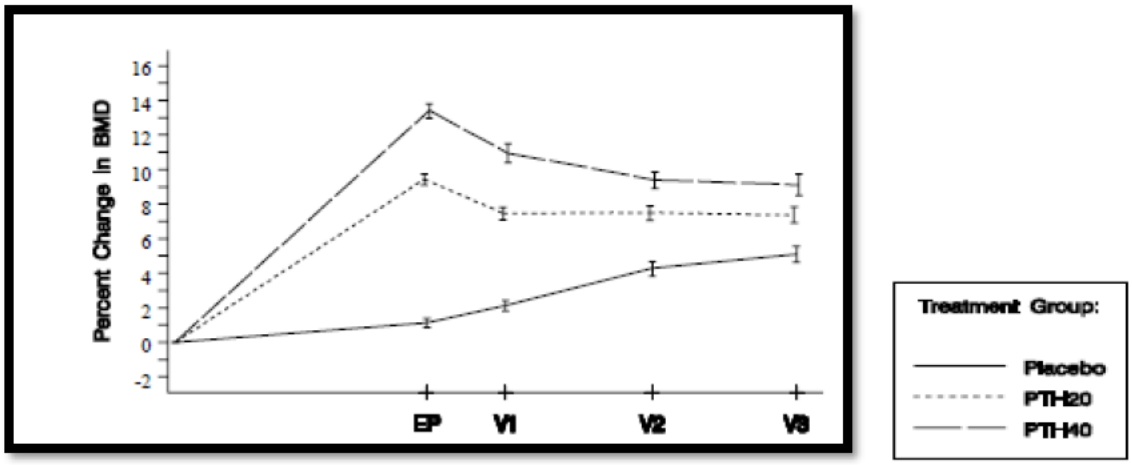
Table 21. Mean Percent Change (SD) from Previous Study Endpoint to GHBJ Visit 3 in BMD

	GHAC subset (females)				GHAJ subset (males)		
	Placebo	PTH20	PTH40		Placebo	PTH20	PTH40
Lumbar (L1-L4) spine (g/cm^2)							
N*	333	359	342		105	104	96
Change (SD)	3.9 (8)	-1.9 (7)	-3.9 (10)		1.8 (6)	-1.9 (5)	-4 (7)
Total hip (g/cm^2)							
N*	152	156	158		106	101	92
Change (SD)	1.3 (5)	-0.5 (6)	0.4 (6)		0.3 (4)	0.1 (4)	0.4 (6)

N*= number with visit 3 BMD measurement
Source: NDA 021318 suppl 54, SD 1687, GHBJ study report, Table GHBJ.11.16 p 126 and Table GHBJ.11.18 p 130.

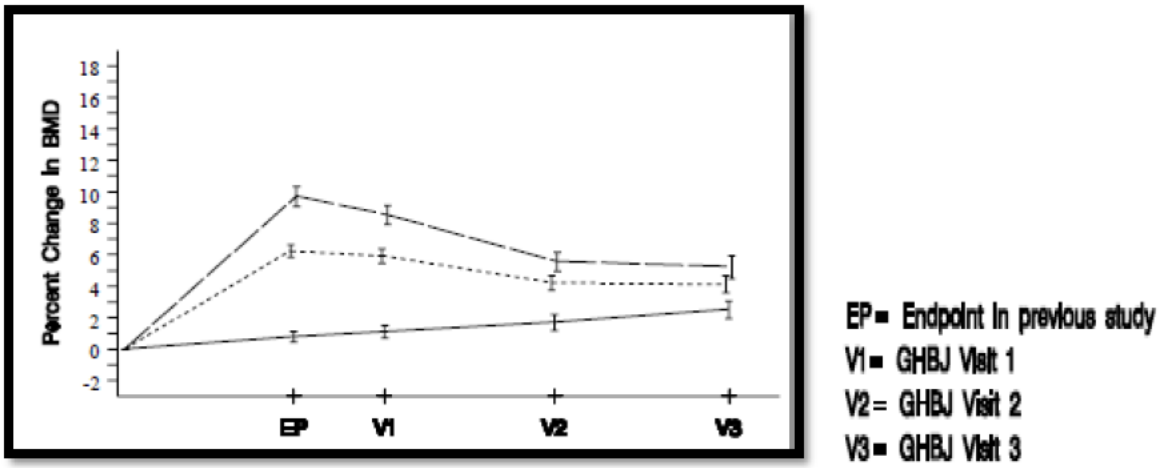
The mean percent change in lumbar spine and hip BMD for both sub-groups is depicted graphically in **Figure 18**, **Figure 19, Figure 20** and **Figure 21**.

Figure 18. Mean Percent Change (+/-SE) from GHAC baseline to GHBJ Visit 3 in Lumbar Spine BMD



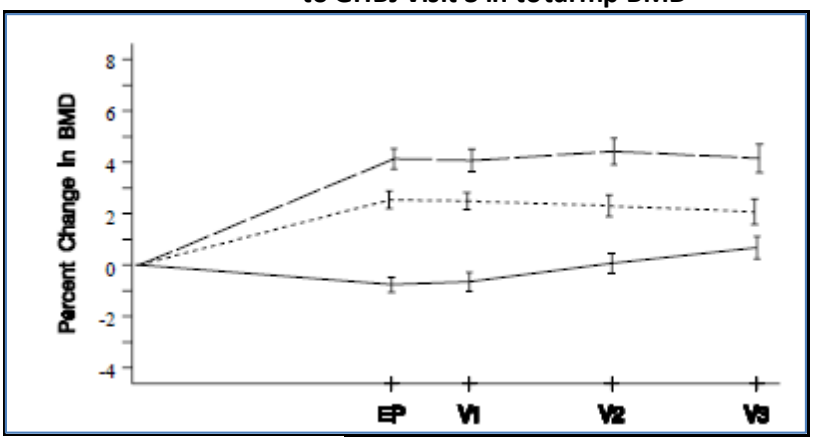
Source: NDA 021318 suppl 54, SD 1687, GHBJ study report, Figure GHBJ.11.5, p. 124

Figure 19. Mean Percent Change (+/-SE) from GHAJ baseline to GHBJ Visit 3 in Lumbar Spine BMD



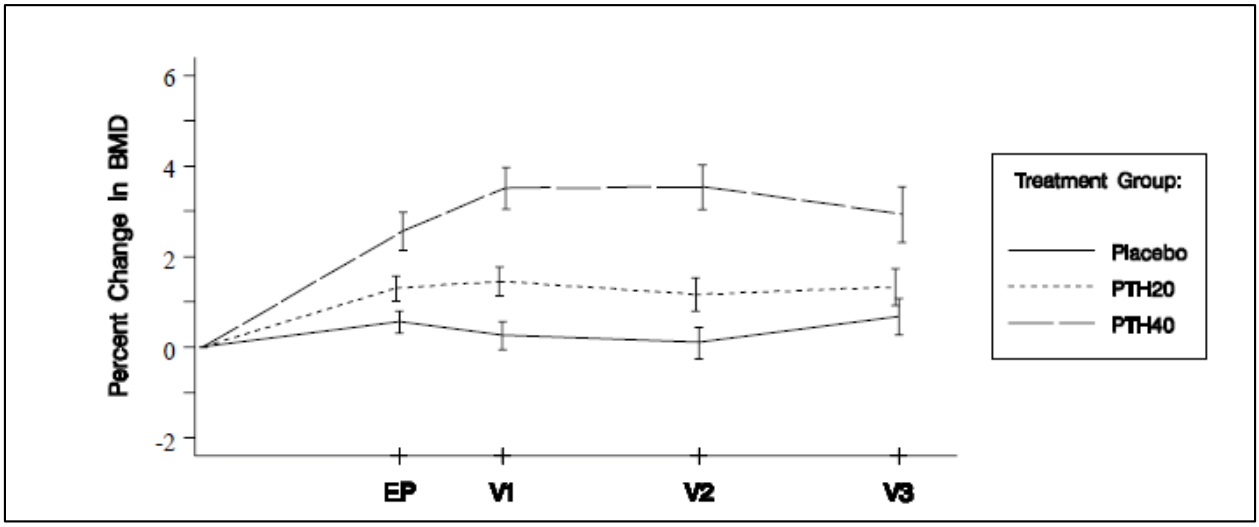
Source: NDA 021318 suppl 54, SD 1687, GHBJ study report, Figure GHBJ.11.10, p. 156

Figure 20. Mean Percent Change (+/-SE) from GHAC baseline to GHBJ Visit 3 in total hip BMD



EP = Endpoint in previous study
V1 = GHBJ Visit 1
V2 = GHBJ Visit 2
V3 = GHBJ Visit 3

Figure 21. Mean Percent Change (+/-SE) from GHAJ baseline to GHBJ Visit 3 in Total Hip BMD



Source: Figure GHBJ.11.11

Fractures

Fracture data at study endpoint are only available for participants from study GHAC.

In the GHAC subset, the incidence of vertebral fractures during the 30 months of off-teriparatide follow-up was lower among patients previously treated with teriparatide (either 20 or 40 mcg daily) than with placebo (Table 22).

Table 22. n (%) of patients with a new vertebral fracture occurring between GHAC endpoint and GHBJ Visit 3

	Placebo	PTH20	PTH40
Vertebral fracture			
N*	353	373	345
n (%)	67 (19)	42 (11)	36 (10)
Non-vertebral fracture			
N*	414	436	412
n (%)	60 (15)	54 (12)	43 (10)

*N=number of GHAC patients who had evaluate spine x-ray film at both endpoint and GHBJ visit 2.
Source: Tables GHBJ.11.8 and GHBJ.14.19

Reviewer comment:

- *Lumbar spine BMD decreased in both men and women after teriparatide discontinuation, but total hip BMD remained stable over thirty months following discontinuation.*
- *Addition of osteoporosis drug treatment following discontinuation of teriparatide mitigates the reduction in BMD.*
- *In post-menopausal women, prior treatment with teriparatide appeared to protect against subsequent fracture during thirty months of follow-up after teriparatide withdrawal.*

8.5. Issue #5: Effect of teriparatide re-treatment on BMD

8.5.1. Cosman et. al.- Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate[17]

The objective of this study was to determine whether a second course of teriparatide could produce similar biochemical and BMD changes as seen during the first teriparatide course of treatment. This was a follow-on study to a previous trial the authors conducted in which 126 women who had received alendronate 70 mg once weekly for >1 year were randomized to one of three treatment groups for 15 months:

- Alendronate 70 mg once weekly + teriparatide 25 mcg daily
- Alendronate 70 mg once weekly + cyclic teriparatide (teriparatide 25 mcg daily for three months alternating with three months of no teriparatide)

[17] Cosman F, Nieves J, Zion M, et. al. Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. J Bone Miner Res 2009; 24: 1110-1115.

- alendronate 70 mg once weekly alone.

After 15 months, teriparatide was discontinued and subjects were then to complete a 12-months of treatment with alendronate 70 mg once weekly alone. Upon completion of 12 months of alendronate therapy, subjects from the teriparatide treatment groups (daily and cyclic) who remained at high risk for fracture had the option of participating in the extension study during which they received another 15-month course of teriparatide 25 mcg once daily along with alendronate. High risk of fracture was defined as current spine, total hip or femoral neck BMD T-score of $\leq$-2.5 or have sustained an osteoporotic fracture in the previous three years.

Thirty-two women (n=17 from the prior daily teriparatide group and n=15 from the prior cyclic teriparatide group) enrolled in the extension study and received another 15-month course of teriparatide 25 mcg once daily in addition to alendronate 70 mg once weekly. All subjects also received calcium and vitamin D supplementation. The baseline characteristics of the two treatment groups were similar except for a lower total hip T-score in the prior daily treatment group (see Table 23).

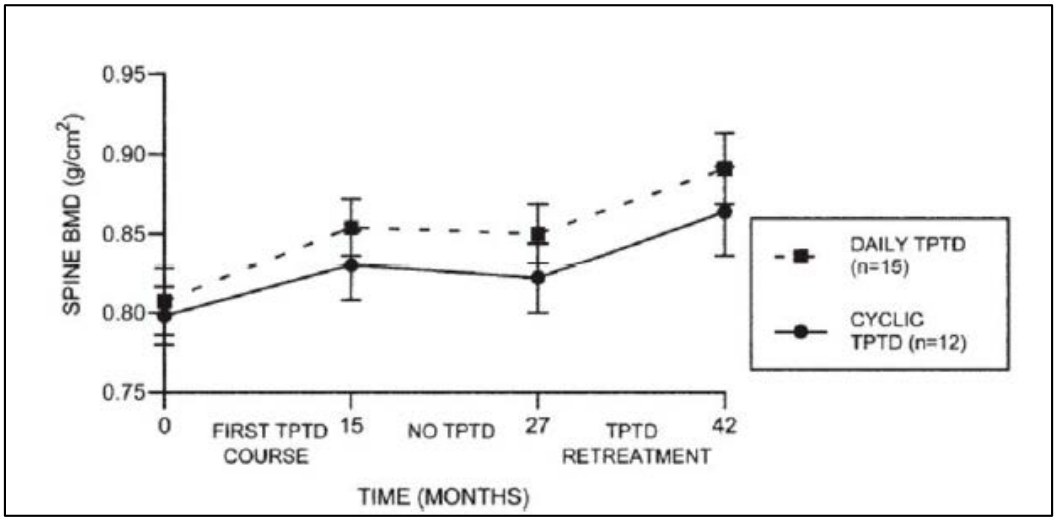
Table 23. Baseline Characteristics of the study population at retreatment

	Prior daily group (n=17)	Prior cyclic group (n=15)
Descriptive characteristics (mean)		
Age (yr)	69.1	69.6
Years from menopause	21.0	21.2
Years on alendronate	5.3	5.2
Prior fracture of spine, hip or wrist [n(%)]	12 (71)	8 (53)
BMD (mean ± SD)		
Spine BMD (g/cm^2)	0.85 ± 0.09	0.83 ± 0.07
Spine T-score	22.9± 0.7	23.0± 0.6
Total hip BMD (g/cm^2)	0.79 ± 0.10	0.72 ± 0.06
Total hip T-score	21.8± 0.8	22.4± 0.5

Source: Cosman, et. al., Table 1, p. 1112.

Results:
Mean change in BMD at 15 months during initial teriparatide treatment and teriparatide retreatment was compared for the two teriparatide treatment paradigms (daily and cyclic). In the initial treatment, mean spine BMD increased 0.047 gm/cm^2 in the daily group and 0.033 gm/cm^2 in the cyclic group. BMD was stable in both groups during the 12 month alendronate alone treatment period. During teriparatide re-treatment, mean spine BMD increased again – by 0.040 gm/cm^2 in the daily group and by 0.042 gm/cm^2 for the cyclic group (Figure 22).

Figure 22. Mean spine BMD through the original teriparatide course and the teriparatide retreatment for the original daily (n=15) and cyclic (n=12) groups for all subjects who completed the full 42-month protocol



TPTD = teriparatide
Source: Cosman, et. al. Figure 3, p. 1113.

Reviewer comment: In this small study (N=32), post-menopausal women with osteoporosis who remained at high risk for fracture after an initial fifteen month course of teriparatide 25 mcg daily followed by 12 months of alendronate experienced a positive response in LS BMD to a second 15-month course of teriparatide 25 mcg daily.

8.5.2. Finkelstein, et. al. Effects of teriparatide retreatment in osteoporotic men and women[18]

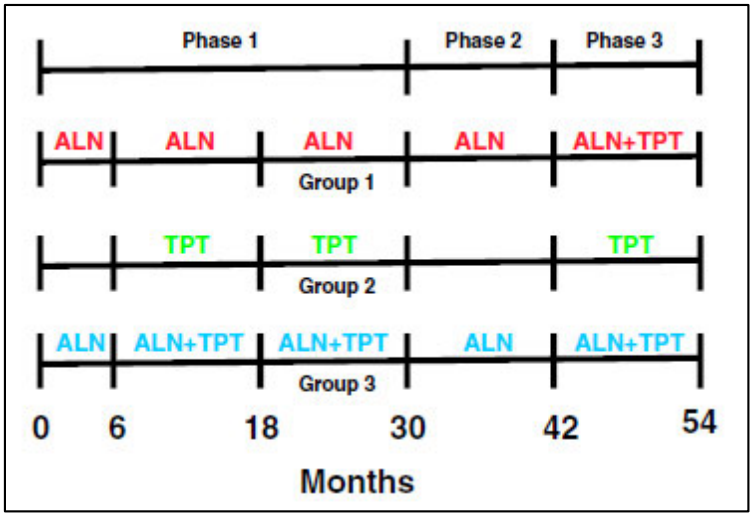
The objective of this study was to determine the BMD response to teriparatide re-treatment after a drug-free period in men and post-menopausal women aged 46 to 85 years with osteoporosis (defined as LS or femoral neck BMD T-score ≤-2.0).

The study was conducted in three phases (see Figure 23):

[18] Finkelstein JS, Wyland JJ, Leder, BZ, et. al. Effects of Teriparatide Retreatment in Osteoporotic Men and Women. *J Clin Endocrinol Metab* 94: 2495-2501, 2009.

- Phase 1 (thirty months): participants were randomized to receive alendronate alone (10 mg orally once daily, group 1), teriparatide alone [37 µg subcutaneously (sc) once daily, group 2], or both (group 3, n = 59). Alendronate was started at the baseline visit and continued for 30 months in groups 1 and 3. Teriparatide was started at month 6 and continued for 24 months in groups 2 and 3. Treatment was not blinded.
- Phase 2 (12 months): Subjects who completed phase 1 on their assigned treatment were eligible to continue into phase 2 (months 30–42), during which teriparatide was discontinued in groups 2 and 3. Alendronate was continued in groups 1 and 3 during phase 2. No other osteoporosis medications were permitted during phase 2.
- Phase 3 (12 months): Subjects who completed phase 2 on their assigned treatment and had a LS or proximal femur T score <-1 were eligible to continue into phase 3 (months 42–54), during which teriparatide was administered for 12 months to all three groups. Alendronate was continued in groups 1 and 3. Calcium intake was estimated by a research dietitian and maintained at 1000 to 1200 mg daily through diet or supplements. All subjects received 400 IU of vitamin D daily.

Figure 23. Diagram of the study protocol



Source: Finkelstein, et. al., Fig. 2, p. 2496.

Reviewer comment: To qualify for teriparatide re-treatment, subjects were not required to be at high risk for fracture.

The prespecified primary efficacy end point was the difference in the change in posterior-anterior lumbar spine BMD during months 6 to 18 and months 42 to 54 in subjects receiving teriparatide alone. The primary efficacy analysis was conducted on the per-protocol population (all subjects who remained on teriparatide until at least month 48 of retreatment phase).

Results A total of 21 subjects (12 males, 9 females) who had received teriparatide alone in the previous phases continued on teriparatide alone in phase 3. Mean age was 60 years and baseline BMD T-scores

were -2.3 (PA spine), -1.9 (lateral spine), -2.1 (femoral neck) and -1.4 (total hip). No subject had previously used bisphosphonates or other prescription osteoporosis medications.

The change in BMD at each skeletal site during the first 12 months of the initial teriparatide treatment and the first 12 months of teriparatide re-treatment is shown in Table 24. The gain in BMD at the PA lumbar spine was statistically significantly greater during the first teriparatide treatment year than during the first re-treatment year.

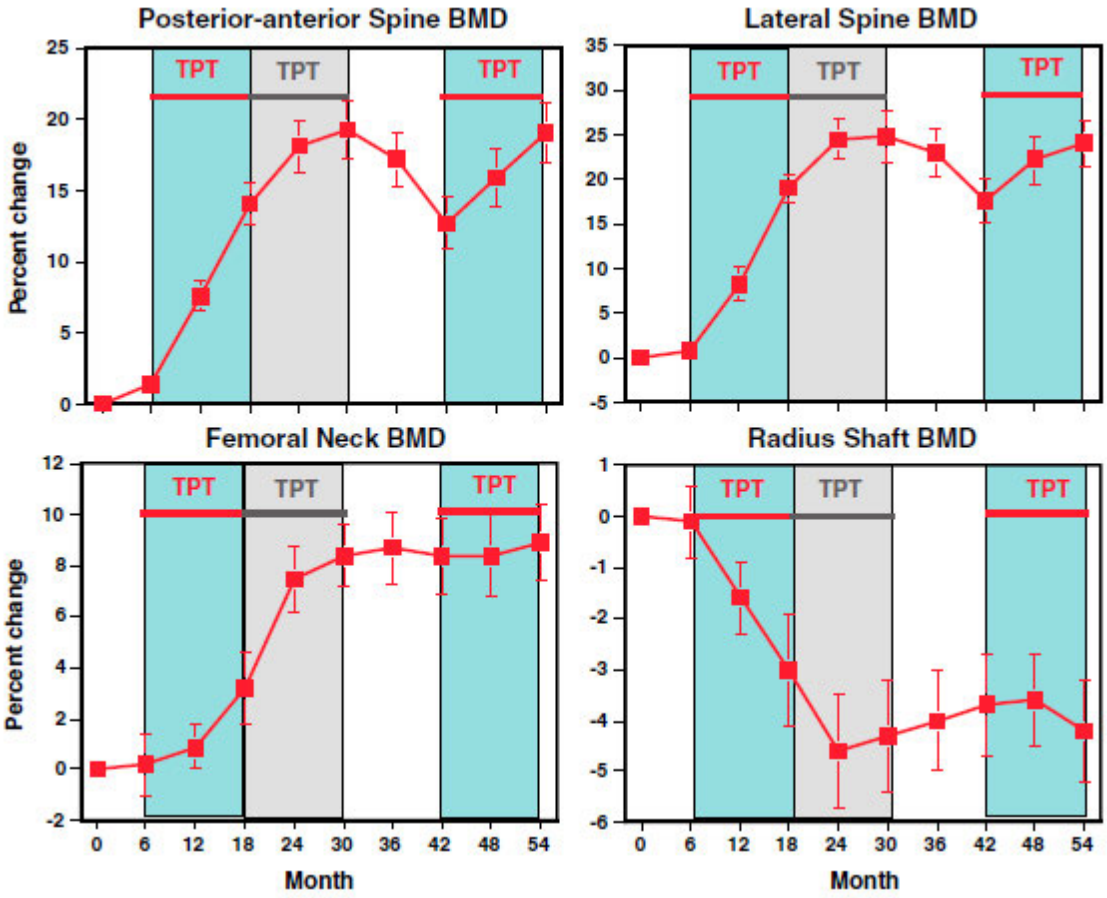
Table 24. Absolute Mean (Percent) Change in BMD (g/cm2) during first 12 months of initial teriparatide treatment and first 12 months of teriparatide re-treatment

	Initial 12 months of teriparatide (tptd)	12 months of teriparatide re-treatment	
Skeletal site	**BMD change, months 6–18**	**BMD change, months 42–54**	***P* value***
PA spine	0.102 ± 0.011 (12.5 ± 1.5%)	0.048 ± 0.008 (5 2 ± 0.8%)	<0.001
Lateral spine	0.111 ± 0.012 (16 9 ± 1.7%)	0.045 ± 0.015 (6 2 ± 1.8%)	0.001
Femoral neck	0.016 ± 0.008 (2.8 ± 1 3%)	0.0004 ± 0.005 (0 2 ± 0.8%)	0.08
Radius shaft	-0.019 ± 0.007 (-2.8 ± 1.1%)	0.0004 ± 0.002 (0.001 ± 0.4%)	0.02
Total body	0.023 ± 0.007 (2.5 ± 0 8%)	0.004 ± 0.003 (0.5 ± 0.4%)	<0.001

*comparison of BMD change during first 12 months of initial treatment and first 12 months of re-treatment
Source: Finkelstein, Table 2, p. 2498

The change in BMD at each skeletal site over the duration of the 54 month study period is depicted in Figure 24. PA and lateral Lumbar spine BMD increased during the initial teriparatide treatment (months 6-30), declined after teriparatide stopped, and increased again during teriparatide re-treatment (months 42-54), although the response was less than during initial treatment. Femoral neck BMD increased during the initial treatment and then was stable during re-treatment. BMD of the radius shaft decreased during initial teriparatide treatment, increased after teriparatide withdrawal, and remained stable during the second treatment.

Figure 24. Change in BMD during initial teriparatide treatment (months 6-30), teriparatide withdrawal (months 30-42) and teriparatide re-treatment (months 42-54)



Source: NDA 021318 Suppl 54, SD 1684, Clinical overview, Figure 6, p. 48

Reviewer comment: In this small study of men and post-menopausal women with osteoporosis who were not at high risk for fracture, response to teriparatide re-treatment is attenuated when re-administered after a 12 month hiatus. Of note, this study used a dose of teriparatide (37 mcg daily) that is greater than the approved dose of 20 mcg daily.

6.5.3 Mana, et. al. Retreatment with teriparatide: our experience in three patients with severe secondary osteoporosis[19]

This case series reports the results of re-treatment with teriparatide in three post-menopausal women with "severe" secondary osteoporosis. Etiology of osteoporosis was glucocorticoid-induced in two and hyperthyroidism in one.

Case 1: 62 year old female with osteoporosis (L2-4 T-score -4.8) received teriparatide for 18 months. LS BMD increased by 22% during treatment. After teriparatide discontinuation, the patient then received oral ibandronate monthly for three years. LS T-score at the conclusion of ibandronate was-3.5 so the patient was re-treated with teriparatide for 18 months with an observed increase in LS BMD by 18% at the conclusion of re-treatment.

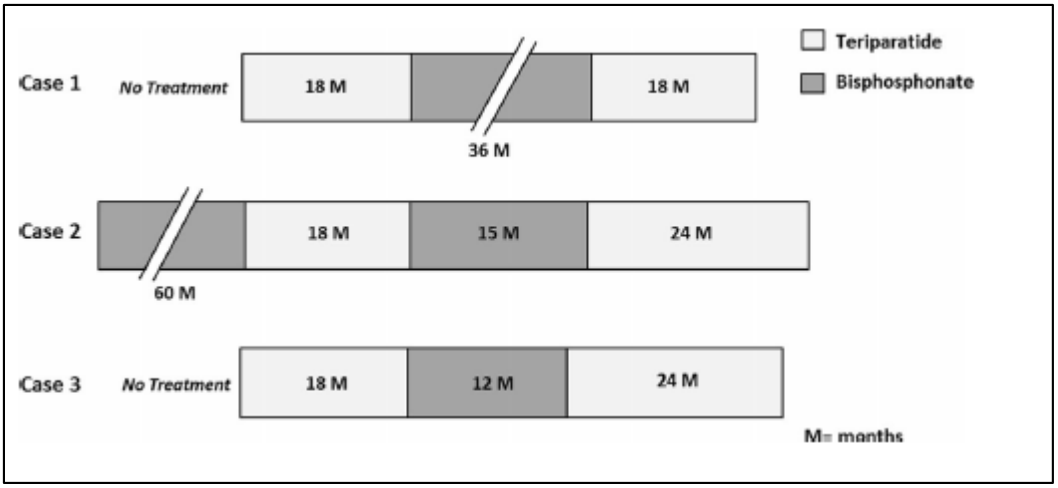
Case 2: A 60 year old female initiated teriparatide for treatment of severe osteoporosis (LS T-score -4.5). Following 18 months of teriparatide treatment, LS BMD had increased by 12%. Fifteen months after finishing teriparatide and despite interim treatment with a single infusion of zoledronic acid 5 mg, LS BMD decreased by 6% and LS T-score was -4.2. The patient resumed teriparatide for 24 months. LS BMD increased by 13% during the re-treatment.

Case 3: A 60-year old woman with osteoporosis (LS BMD T-score -5.3) and history of atraumatic fracture received teriparatide for 18 months. LS BMD increased by 39%. After teriparatide was discontinued the patient received IV ibandronate every 3 months for one year after which LS BMD declined by 10% (LS BMD T-score -5.1). She was re-treated with teriparatide for 24 months. BMD at the end of re-treatment showed an increase in LS BMD by 15%.

Treatment regimen for each of the three patients, and LS BMED percent change during initial and follow-up teriparatide treatments are shown in Figure 25 and Figure 26.

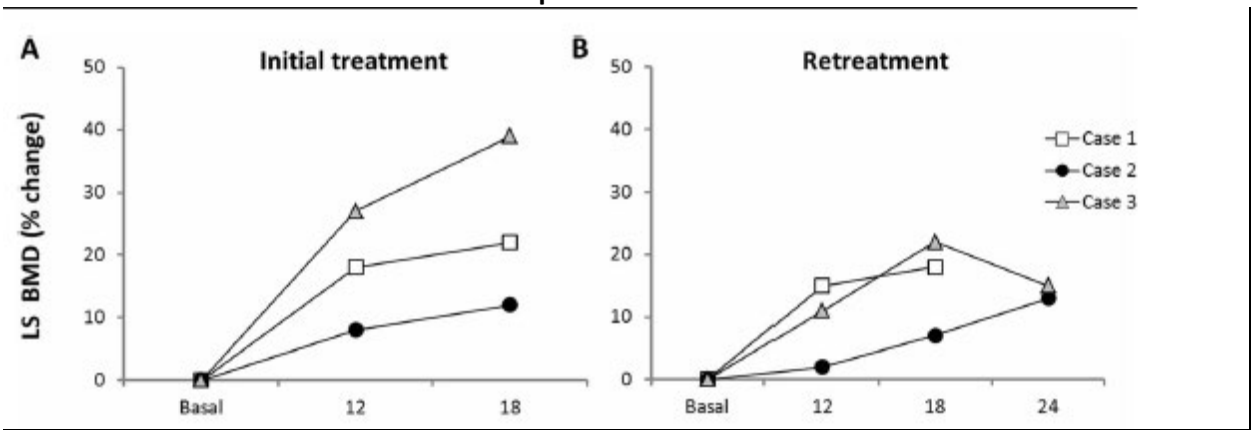
[19] Mana DL, Zanchetta MB, Zanchetta JR. Retreatment with teriparatide: our experience in three patients with severe secondary osteoporosis. *Osteoporos Int.* 2017;28(4):1491–1494.

Figure 25. Treatments received by each patient



Source: Mana, et. al., Fig 1, p. 1492.

Figure 26. Percentage change in LS BMD during initial teriparatide treatment and teriparatide re-treatment



Source: Mana, Fig. 2, p. 1493

Reviewer comment: In this small case series of post-menopausal women with secondary osteoporosis at high risk for fracture, BMD increased again during teriparatide re-treatment, but the response was less than during initial treatment.

9. Integrated Review of Effectiveness

9.1. Integrated Assessment of Effectiveness

The following efficacy considerations (b) (4) (b) (4) will be summarized below.

9.1.1. Efficacy up to 24 months

The intended duration of the pivotal registration trial of teriparatide for fracture prevention in post-menopausal osteoporosis was 36 months. However, the study was terminated early when osteosarcomas were observed in a rat carcinogenicity study. This resulted in a mean exposure to teriparatide of 18±5 months with <1% of participants in the fracture prevention trial cohort reaching the 24- month visit.

As discussed in section 6.1.1, Study GHCA in post-menopausal women with osteoporosis at high risk for fracture showed the BMD at the lumbar spine, total hip and femoral neck did not plateau prior to 24 months but continued to increase up to 24 months. Previous anti-resorptive therapy appears to blunt, but not negate, the BMD response to teriparatide.

9.1.2. Efficacy beyond 24 months

Study GHBZ in adults with glucocorticoid associated osteoporosis at high risk for fracture demonstrated continued efficacy of teriparatide with respect to increasing BMD out to 36 months. Although the mean change in LS BMD from 18 months to 36 months increased in both teriparatide and alendronate groups, the difference was not statistically significantly different between the two groups. However, the number of subjects entering the extension phase was approximately 2/3 of the original study population, which resulted in insufficient power to detect a significant difference. The lower incidence of fractures during the 36-month treatment period in the teriparatide treatment group supports the benefit of teriparatide beyond 2 years.

In a three-year study of post-menopausal women at high risk for fracture, LS BMD increased out to 36 months in participants receiving teriparatide 25 mcg daily in combination with hormone replacement therapy and more so than HRT alone. Total hip BMD also increase from baseline to 30 months and then appeared to decline in the combination treatment group. Fracture incidence over the 36 month treatment period was lower for the combination than for the HRT alone group. The limitation of this study is that the dose of teriparatide utilized is higher than the approved U.S. dose of 20 mcg daily.

9.1.3. Effect of teriparatide discontinuation on BMD

Study GHBJ showed that lumbar spine BMD decreased in both men and women after teriparatide discontinuation, but total hip BMD remained stable over thirty months following discontinuation. Addition of osteoporosis drug treatment following discontinuation of teriparatide mitigates the reduction in BMD. In post-menopausal women, prior treatment with teriparatide appeared to protect against subsequent fracture during thirty months of follow-up after teriparatide withdrawal.

9.1.4. Effect of re-treatment with teriparatide

The sponsor submitted data from two uncontrolled trials and one case series regarding the efficacy of teriparatide re-treatment that involved a total of 53 patients. Patient population, severity of osteoporosis, and dose of teriparatide administered differed in the individual trials which are summarized in Table 25.

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Table 25. Summary of studies of teriparatide (TPTD) re-treatment

	Population and sample size	Re-treatment regimen	Osteoporosis criteria	outcome
Cosman (2009)	post-menopausal women N=32	TPTD 25 µg qd plus alendronate 70 mg q week x 15 months (preceded by alendronate 70 mg q week x 12 months)	T-score <-2.5 or osteoporotic fracture in previous three years	Positive LS BMD response and of similar magnitude as initial treatment
Finkelstein (2009)	Men and post-menopausal women aged 46-85 years N=21	TPTD 37 µg x 12 months (initial treatment was 37 µg x 24 months)	T score <-1	Positive LS BMD response but less than initial treatment
Mana (2017)	Post-menopausal women with secondary osteoporosis (glucocorticoid-induced in two, hyperthyroidism in third) N=3	Teriparatide (dose not specified); duration range 18-24 months	T-score range -3.5 to -5.1	Positive response in LS BMD though less than initial treatment

.

The two publications (Cosman and Mana) that involved patients at high risk for fracture suggest a benefit to BMD of teriparatide re-treatment. However, those data are limited by small sample sizes (N=32 and N=3, respectively) and differences in treatment regimen and enrollment criteria. Additional controlled data in a larger and uniform population with a consistent dose regimen is needed to provide more robust evidence of the efficacy of teriparatide re-treatment.

10. Review of Safety

10.1. Safety Review Approach

Safety issues addressed in this application are the following:

- risk of osteosarcoma
- safety of teriparatide use beyond 24 months
- late effects of teriparatide use.

The Division of Pharmacovigilance II (DPV II) reviewed in depth the post-marketing observational studies that the Applicant conducted to evaluate the risk of osteosarcoma. The DPVII memoranda were finalized in DARRTS on May 3, 2019, and March 3, 2020. This review will summarize DPVII's conclusions.

This review will also address results of the Applicant's search of their own post-marketing safety surveillance data for cases of osteosarcoma. (b) (4) . Finally, during the course of this review, DPV II became aware of a case of dystrophic calcification in an osteoporotic patient treated with teriparatide. This report prompted DPVII to open a tracked safety issue (TSI) regarding the risk of calciphylaxis associated with teriparatide. The risk of calciphylaxis is also addressed in this review.

10.2. Analysis of Submission-Specific Safety Issues

10.2.1. Osteosarcoma Risk

Clinical trial data
There have been no reports of osteosarcoma during clinical trials to date involving 1952 patients exposed to teriparatide.

Post-marketing Observational Studies
The Applicant has completed the required post-marketing studies evaluating the risk of osteosarcoma which were reviewed by the Division of Epidemiology II in memoranda finalized in DARRTS on May 3, 2019 (see Appendix 16.2) , and March 3, 2020 (see Appendix 16.3). DEPI II concluded that

- the patient registry did not identify an elevated risk for osteosarcoma with teriparatide use
- the two claims studies [GHBX(2.2A) and GHBX(2.3B)] showed a balanced risk of osteosarcoma between teriparatide users and their comparators
- the two case series studies [GHBX(1) and GHBX(B)] did not identify a safety concern for osteosarcoma.

Reviewer's comment: There is no evidence in the submitted data of an increased risk of osteosarcoma among patients treated with Forteo for up to two years.

Post-marketing Safety Surveillance
The Applicant searched the Lilly Safety System (LSS) database from time of product launch (2002) through September 30, 2019, for the following preferred terms coded to the Medical Dictional for Regulatory Activities (MedDRA) version 22.0: *extra-skeletal osteosarcoma*, *osteosarcoma*, *osteosarcoma metastatic*, and *osteosarcoma recurrent*.

In an estimated exposure of 2,470,000 patients, the search identified 35 cases, of which 32 were coded as osteosarcoma, 2 as osteosarcoma metastatic, and 1 as extra-skeletal osteosarcoma. Affected patients ranged in age from 43 years to 90 years. Of these 35 cases:

- Diagnosis of osteosarcoma was not confirmed in seven
- Narratives contained insufficient information to make an assessment in 15
- In the remaining 13 cases,
    - osteosarcoma diagnosis occurred less than 2 years after Forteo initiation in six cases

- There were confounding factors that are known risk factors for developing osteosarcoma in 7 cases. Risk factors were employment as an Xray technician (n=1), Crohn's disease (n=1), history of arthroplasty and/or spinal fusion surgery (n=2) and previous treatment with external beam radiation involving the skeleton (n=3).

In two of the three cases involving patients with a history of external beam radiation, the interval between teriparatide initiation and diagnosis of osteosarcoma (one month after and one month prior, respectively) precludes a contribution from teriparatide. In the third case, the time interval was not specified but the narrative indicated it was less than one year.

The Applicant provided the narrative summary for the case of the X-ray technician which is provided below:

> *Case US201608003841* was identified during the post-marketing surveillance study GHBX and involved a 60 year old female with a family history of lung cancer and a personal history of multiple sclerosis who worked as an X-ray technician for an unspecified number of years. She had never had a positive radiation badge and was not under radiation exposure since 2001. Concomitant medications were glatiramer for MS (discontinued on an unspecified date), estradiol, ibuprofen and alprazolam.
>
> In January 2008, the patient started Forteo, which she took "for about two years," for treatment of osteoporosis. In April 2015 the patient was diagnosed with osteoblastic osteosarcoma during evaluation of a right mandibular abnormality identified on a routine panoramic dental X-ray. Osteosarcoma was removed surgically, and the patient recovered from the procedure. No further information was provided as to her clinical status.

Reviewer comment: This patient's workplace exposure to radiation seems to have been minimal. A contributory role for teriparatide in this case cannot be excluded.

Risk in patients with a history of external beam radiation or implant radiation involving the skeleton

Current Forteo labeling warns against using the product in patients who have an increased baseline risk of osteosarcoma, which includes have had prior external beam or implant radiation therapy involving the skeleton. The Applicant proposes (b) (4)

- In a sensitivity analysis in study B3D-MC-GHBX(2.2), 3061 out of 105794 Medicare patients in the teriparatide cohort were documented to have a history of radiation treatment. No cases of osteosarcoma were identified in the teriparatide study cohort.
- In study B3D-MC-GHBX(b), 1173 patients with osteosarcoma were interviewed. Three of the 1173 patients reported treatment with teriparatide prior to diagnosis. However, there is no information as to whether any of the three had had previous x-ray or radiation treatment.

- The Applicant identified three cases of osteosarcoma that reported a history of radiation treatment in their search of the LSS database. However, in those cases teriparatide was administered shortly prior to diagnosis or after diagnosis of osteosarcoma.

Reviewer's comment: Overall, findings from the post-marketing safety database do not identify a safety concern for osteosarcoma. There are insufficient data to demonstrate an increased risk of osteosarcoma in patients who have received external beam radiation. (b) (4)

10.2.2. **Safety of teriparatide beyond 24 months**

Due to current labeling restricting duration of use, there are limited data on the safety of Forteo beyond two years of use. The Applicant submitted results of one Lilly-sponsored clinical trial and from three publications in the scientific literature to support safety of teriparatide use beyond 24 months (see Table 26).

In the studies summarized in Table 26, a total of 192 patients were exposed to teriparatide for up to 42 months (either continuously or cumulatively). There were no reports of osteosarcoma in any of the studies.

Previous clinical review of study GHBZ identified no new safety signals in patients exposed up to 36 months and the data were found to be acceptable for approval of the GIOP indication.[20, 21]

[20] Gassman, A. op cit.
[21] Benson G., op. cit.

Table 26. Summary of Studies submitted that evaluated teriparatide use for longer than 24 months

Study	Population and sample size exposed to TPTD	TPTD dose and duration of exposure
GHBZ	men and women aged ≥21 years with GIOP at high risk for fracture N=123 exposed for 36 months	TPTD 20 mcg SC daily x 36 months
Lindsay (1997)	Post-menopausal women N=13 exposed for 3 years	TPTD 25 mcg SC daily x 3 years
Cosman (2009)	post-menopausal women N=32	First treatment: TPTD 25 mcg qd x 15 months or TPTD 25 mcg qd x 3 months alternating with no TPTD x 3 months x 15 months Second treatment (following 12 months of alendronate): TPTD 25 mcg qd plus alendronate x 15 months Total duration of TPTD: 30 months
Finkelstein (2009)	Men and post-menopausal women aged 46-85 years N=21	First treatment: TPTD 37 µg qd x 24 months Second treatment: TPTD 37 µg qd x 12 months Total duration of TPTD: 36 months
Mana (2017)	Post-menopausal women with secondary osteoporosis (glucocorticoid-induced in two, hyperthyroidism in third) N=3	First treatment: TPTD (dose not specified) x 18 months Second treatment: TPTD (dose not specified) x 18 months (n=1) or x 24 months (n=2)

Lindsay et al: The most common adverse reactions (incidence not specified) were pain and redness at the injection site. Four of seventeen patients in the teriparatide group withdrew prior to study completion for the following reasons:

- after six months for back pain attributed to TPTD
- after 1.5 years because of subcutaneous nodule development at the injection site
- after one year because of diagnosis of breast cancer
- after 1.5 years because of development of otosclerosis and initiation of sodium fluoride.

No other safety data were provided in the article.

Cosman, et. al.: There were no withdrawals due to treatment emergent adverse events. Re-treatment was "well-tolerated."

Finkelstein, et. al.: Hypercalcemia occurred in 7 of 130 blood samples collected 4 to 6 hours after teriparatide dosing during the re-treatment period. Hypercalciuria occurred in 5 of 81 collections during re-treatment. The number of patients affected was not specified in the paper. No subject developed anti-teriparatide antibodies. No other safety findings were addressed.

Mana et. al: None of the three patients showed "side effects related to the treatment."

Reviewer's comment: Although extent of exposure is limited, there are no new safety signals apparent from data in patients exposed to teriparatide for longer than 24 months and up to 42 months.

10.2.3. **Safety of teriparatide following discontinuation**

B3D-MC-GHBJ (GHBJ study), which enrolled 1930 patients from previous phase 3 pivotal efficacy studies, assessed the effects of teriparatide after treatment discontinuation. Subjects were followed for 54 months after discontinuation from the previous studies and monitored for occurrence of serious adverse events.

Early discontinuations due to an adverse event was no greater among patients who received teriparatide than those previously treated with placebo (0.7% and 0.4% for previous teriparatide 20mcg and 40 mcg, respectively, and 0.9% for placebo). There were no events of osteosarcoma during the median 4.65 years of off-drug follow-up. The incidence of any fracture was similar among prior treatment groups – 6.7% for prior placebo, 7.2% for prior teriparatide 20 mcg qhs and 6.0% for teriparatide 40 mg qhs.

The Applicant coded all serious adverse events using the MedDRA dictionary. SAE preferred terms that occurred more often among teriparatide-treated subjects and proportional to previous teriparatide dose were *localized osteoarthritis*, *inguinal hernia*, *chronic lymphocytic leukemia* (CLL) and *pneumonia*. This reviewer then searched the GHBJ dataset for other preferred terms that could also represent osteoarthritis, inguinal hernia, CLL and pneumonia in order to determine the true proportion of such events. Findings from this analysis are shown in Table 27, and show that those adverse events increased in frequency according to previous teriparatide dose.

Table 27. N (%) of patients experiencing a serious adverse event following teriparatide discontinuation during study GHBJ

Adverse event	Placebo N=541	Teriparatide 20 mcg N=558	Teriparatide 40 mcg N=519
N with a SAE	176 (32.5)	194 (34.7)	156 (30.0)
Osteoarthritis*	8 (1.5)	10 (1.8)	13 (2.5)
Pneumonia+	9 (1.7)	15 (2.7)	14 (2.7)
Inguinal hernia**	1 (0.2)	3 (0.5)	3 (0.6)
Chronic lymphocytic leukemia++	0	0	3 (0.6)

*includes preferred terms of *localized osteoarthritis*, *spinal osteoarthritis* and *osteoarthritis*
+pneumonia includes preferred terms of *bronchopneumonia*, *lung infection*, *pneumonia primary atypical* and *pneumonia*.
**no other preferred terms were searched
++no other preferred terms were searched

Reviewer comments:

- *Incidence of inguinal hernia is unlikely to be related to prior treatment with teriparatide based on the drug's mechanism of action.*

- *Narrative summaries for events of osteoarthritis were reviewed. In the majority of cases, the patients had a history of osteoarthritis that pre-dated initiation of teriparatide. In no case did teriparatide use appear to be related to the development of osteoarthritis which is already common in the age cohort affected by osteoporosis.*
- *Cases of pneumonia developed between 109 days and 685 days following initiation of study drug. Eleven of the affected patients were current smokers – 2/9 (22%) from prior placebo, 5/15 (33%) from prior teriparatide 20 mcg and 4/14 (29%) from prior teriparatide 40 mcg. The excess number of current smokers among teriparatide-treated patients could in part explain the imbalance in cases of pneumonia. There is no indication that previous teriparatide treatment was related to pneumonia in any patient.*
- *The three cases of CLL were reviewed. In one case, the patient developed lymphocytosis and subsequent CLL while taking teriparatide. CLL was diagnosed 36 months and 58 months after discontinuing teriparatide in the other two cases. However, in one of the latter cases the patient had lymphadenopathy noted prior to randomization. Teriparatide was not considered related to leukemia in any of the three reports because of the drug's mechanism of action and other available clinical safety data for teriparatide.*

10.2.4. **Calciphylaxis**

On February 12, 2019, DPV II received an email literature alert from Embase of a citation entitled, "*Worsening of soft tissue dystrophic calcification in an osteoporotic patient treated with teriparatide*." [22] The article by Htet et. al. described a 74-year-old male patient who experienced symptomatic worsening of previously stable dystrophic calcification four months after teriparatide initiation. Following discontinuation of teriparatide, the patient's symptoms resolved within one week.

DPV II evaluated this potential safety signal by searching the following sources for reports of cutaneous calcification associated with parathyroid hormone (PTH) agonists [Forteo (teriparatide) and Tymlos (abaloparatide)] and PTH product [Natpara (parathyroid hormone)]:
Periodic safety reports submitted to FDA from September 13, 2015 through September 12, 2018
FDA Adverse Event Reporting System (FAERS) reports and the medical literature through February 12, 2019. DPV II also requested information from the European Medicines Agency and International Post Market Surveillance about their investigation of this potential safety signal.

According to a memorandum filed to DARRTS on February 7, 2020 (see Appendix 16.4), DPV II identified 15 cases with sufficient evidence to support teriparatide use as a contributory factor in development of new, or exacerbation of existing, cutaneous calcification. DPV II believes that teriparatide in concert with an underlying risk factor for cutaneous calcification (e.g., autoimmune disease or concomitant medications) can trigger this adverse event. Furthermore, because teriparatide is an analogue of endogenous parathyroid hormone and exhibits similar pharmacologic activities, there is biologic plausibility to the risk of calciphylaxis.

[22] Htet TD, Eisman JA, Elder GJ, et al. Worsening of soft tissue dystrophic calcification in an osteoporotic patient treated with teriparatide. *Osteoporos Int* 2018;29:517-8.

10.3. Integrated Assessment of Safety

- The totality of data submitted does not suggest an increased risk of osteosarcoma among patients treated with Forteo for up to two years.
- Although extent of exposure is limited, there are no new safety signals apparent from data in patients exposed to teriparatide for longer than 24 months and up to 42 months.
- Five years of follow-up following teriparatide discontinuation shows no increased risk of osteosarcoma or other delayed adverse effects.
- Teriparatide, in concert with an underlying risk factor for cutaneous calcification (e.g., autoimmune disease or concomitant medications), may be associated with development of calciphylaxis. An association is biologically plausible give teriparatide's pharmacologic activity.

11. Advisory Committee Meeting and Other External Consultations

Not applicable.

12. Pediatrics

Not applicable for this labeling supplement

13. Labeling Recommendations

13.1. Prescription Drug Labeling

Based on the data submitted to this application, the review team recommends the following changes to labeling content:

- Highlights:
  - Remove boxed warning regarding risk of osteosarcoma
- Section 2 (Dosage and Administration): allow for treatment for more than two years in patients who remain at or return to having a high risk for fracture
- Section 5 (Warnings and Precautions)
  - Add information regarding risk of cutaneous calcification including calciphylaxis to the existing warning entitled, "Hypercalcemia and hypercalcemic disorders." Rename title of the warning, "Hypercalcemia and Cutaneous Calcification."
- Section 6.2 (Adverse Reactions/Postmarketing Experience): update to include data from the two osteosarcoma surveillance safrety

- Section 7 (Drug Interactions): Remove hydrochlothiazide and furosemide sub-headings as the information contained in these only inform the prescriber that co-administration of teriparatide with these drugs does not result in clinically important changes in serum calcium. The Physician Labeling Rule advises that the Drug Interactions section only contain clinically relevant information such as the need to modify a dose.

14. Risk Evaluation and Mitigation Strategies (REMS)

None.

15. Postmarketing Requirements and Commitments

None.

16. Appendices

16.1. Financial Disclosure

New studies submitted to this labeling supplement are non-covered studies. Study GHBZ was a covered study and financial disclosure for that trial was reviewed with the original submission to NDA 021318 Suppl 12.

16.2. Division of Epidemiology II Review of PMR Studies Re: Osteosarcoma Risk, May 2019

APPEARS THIS WAY ON ORIGINAL

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Review: PMR Studies on the Risk of Osteosarcoma of Teriparatide (Teriparatide®)

Date: 5/3/2019

Reviewers:	Jie Li, PhD Division of Epidemiology II
Team Leader:	Jie Li, PhD Division of Epidemiology II
Division Director:	CAPT David Moeny, RPh, MPH, USPHS Division of Epidemiology II
Subject:	Final study report review
Drug Name:	Teriparatide (Forteo)
Application Number:	NDA 21318
Applicant:	Eli Lilly
OSE RCM #:	2018-2193

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Teriparatide (Teriparatide®) was approved by FDA in 2002 with two post-marketing requirements (PMRs) in place to examine the risk for osteosarcoma with teriparatide use. This review summarizes the final study results of three PMR studies and provides regulatory recommendations on the risk of osteosarcoma with teriparatide use.

The first PMR, a case-series study issued in 2002, aimed to interview osteosarcoma cases in the Nordic countries and U.S. and identify any teriparatide exposure prior to cancer onset. As of 31 December 2013, 129 cases of osteosarcoma cases were reported by the participating Nordic countries and 112 cases underwent medical chart review; none were exposed to teriparatide before the cancer onset. The U.S. study component identified 1,173 cancer cases from 30 state cancer registries, with 5,432,764 person-years at risk. Three cases had prior teriparatide use, yielding an estimate of the incidence rate of osteosarcoma of 3.2 cases per million per year. The observed number of cases with prior exposure was within the range of the expected number of cases of osteosarcoma exposed to teriparatide treatment (n=4.17), with an estimated standardized incidence rate ratio of 0.72 (90% CI, 0.20-1.86). DEPI did not find a safety signal from the case series studies and we do not recommend any regulatory action based on this case series study result due to the hypothesis generating nature of the study.

The second PMR, a prospective patient registry study, was designed to estimate the incidence of osteosarcoma among teriparatide-treated patients (aged ≥18 years) in the U.S., with a target of accruing 1.7 million patient-years of follow-up to 'demonstrate a relative risk of 3', according to the study protocol. According to the most recent periodic safety report (no final report submitted), as of September 30, 2018, 71,417 teriparatide users had been enrolled. No incident cases of osteosarcoma have been identified among enrolled patients. DEPI agrees to release the PMR as requested by the sponsor due to the low use of teriparatide in the US and the slow enrollment of the study.

Lastly, two claims-based safety studies were initiated in 2015 to supplement the prospective patient registry study. The primary objectives of the studies were to estimate the incidence of osteosarcoma among patients who received treatment with teriparatide as compared to an unexposed, matched comparator cohort in two claims databases. The two claims studies show a balanced risk between teriparatide users and their comparators. The strengths of the two claims studies included the linkage to the state cancer registries to identify cancer cases. DEPI concurs with the sponsor and recommends adding the study results into the Adverse Reaction Section of the labeling (suggested label language in the last section of this review).

1 INTRODUCTION

Teriparatide, a recombinant human parathyroid hormone analog (1-34), was approved in the U.S. in 2002 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. In 2009, two additional indications were approved (increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, and treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture). Teriparatide stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. A multi-dose prefilled delivery device (pen) is used for subcutaneous injection containing 28 daily doses of 20 mcg.

In pre-license, non-clinical studies, teriparatide showed a higher incidence of osteosarcoma in rats (but not in monkeys) at a higher systemic exposure than in humans; and the risk appears to be dose- and treatment duration-dependent. It is hypothesized that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of parathyroid hormone (PTH) in the formation of new bone and osteosarcomas. Since the bone metabolism in rats differs from that in humans, the relevance of the animal finding to humans is uncertain. There were no human cases of osteosarcoma identified in the pre-license clinical trials.

A boxed warning for the potential risk for osteosarcoma is in the label and the use of the product is limited to patients in the absence of other risk factors for osteosarcoma (e.g., Paget's disease of bone, or unexplained elevations of alkaline phosphatase, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton). The label recommends two years or less of lifetime use, since the clinical safety and efficacy beyond two years of treatment has not been demonstrated.

Since approval, there have been five post-marketing requirements (PMRs) for observational studies for teriparatide examining the drug-associated risk of osteosarcoma in humans. See below. This review is for DEPI to examine sponsor's submissions of the final study reports and provide regulatory recommendations.

(1) a case-series study in Europe, GHBX [1]

(2) a case-series study in the US, GHBX [b]

(3) a prospective patient registry in the U.S. (GHBX 2.1 study)

(4) two claims based retrospective cohort studies in Medicare D and IQVIA Longitudinal Prescription Database (GHBX 2.2 and 2.3)

2 METHODS

2.1 PHARMACOEPIDEMIOLOGY EVALUATION METHODS

DEPI reviewed the following submissions, as well as the prior PMR study protocols and DEPI review reports/memo.

- GHBX Post-Approval Safety Study (PASS) report (1.0): Case Series Study in EU
- GHBX[B] Post-Approval Safety Study report: Case Series Study in the US
- GHBX Post-Approval Safety Study (PASS) report (2.2a): Medicare D Database
- GHBX Post-Approval Safety Study (PASS) report (2.3b): IQVIA Longitudinal Prescription Database
- Regulatory Response: FDA Information Request: Study B3D-MC-GHBX October 26, 2017
- Regulatory Rebuttal Document: Response to Safety Labeling Change Notification Letter for Teriparatide, January 25, 2018

3 STUDY RESULTS

We present the study results in Sections 1-4 below. In addition, we present the study results of an ongoing prospective patient registry as the sponsor requested that FDA consider the release of the patient registry PMR for the reasons specified in Section 5.

3.1 STUDY GHBX [1]: CASE-SERIES STUDY IN NORDIC COUNTRIES

The case-series study was initiated in 2003 to evaluate a potential association between teriparatide and adult osteosarcoma in humans. This final report follows the conclusion of the 10-year surveillance period in Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). The study was hypothesis generating in nature: "if the study generates a signal of possible association between teriparatide use and osteosarcoma, a subsequent case-control study may be conducted." The primary objective was to identify newly diagnosed cases of osteosarcoma among men and women aged 40 years or older in selected countries and identify incident osteosarcoma cases with a history of teriparatide treatment.

National or regional cancer registry data were used in Finland, Sweden, and Iceland to identify cases of osteosarcoma. In the other two countries, Denmark and Norway, coordinating country investigators from medical centers specializing in treatment of adult osteosarcoma were responsible for identifying and reporting cases to the Scandinavian Sarcoma Group (SSG) because the national cancer registries were not able to provide cases due to privacy restrictions.

The case reports from the SSG included the patient's age, date of diagnosis, and tumor site so that patient eligibility could be confirmed by the coordinating centers. Once confirmed, the coordinating country investigator was notified and shipped a study packet for patient contact and data collection. Once consent was obtained (or waived due to local requirements or a patient being deceased), the medical record from the physician who was responsible for treating the patient was obtained from the treatment facility and, if necessary, the medical record was obtained from the patient's general practitioner's office. Study variables were abstracted from the medical record by research nurses or coordinating country investigators that had completed training for this study onto a standard data collection form. The data collection form was reviewed by the SSG for quality and completeness, patient identifiers were removed, and the anonymized form was transferred to the study center (RTI-HS) for quality checks. Data queries were sent to the investigators if additional information or clarification was required.

Patients were eligible if they were aged 40 years or older at the time of cancer diagnosis and had histological confirmation of osteosarcoma or one of five other tumor types with a primary bone site (ICD-O-3 codes meeting the case definition of osteosarcoma are provided in Appendix 1). Demographic information, personal cancer information, osteoporosis history and treatments (including teriparatide), brief personal and family medical history, and lifestyle and occupational exposures were ascertained from the patient's general practitioner/primary care physician medical records. Due to the inherent lag time between diagnosis and reporting to the cancer registry, the final study results were focused on the 8-year period from 2004-2011.

As of 31 December 2013, a total of 129 cases of osteosarcoma were diagnosed since January 2004 and were reported by the participating Nordic countries. There were 14 patients who did not provide consent, and medical records could not be obtained for an additional 3 patients. More than 90% of identified cases had their medical records abstracted in each study country, except for Sweden (75% of the cases were abstracted in Sweden due to lack of patient consent). A total of 112 patient medical records were abstracted. All 112 cancer patients were white, and more than half were men (56%). The mean age at the time of diagnosis of osteosarcoma was 60 years (range, 41-92 years). Nearly half of the patients were deceased (52 of 112) at the time they were reported to the SSG registry. Of the 112 cancer patients, 94 (84%) were diagnosed with osteosarcoma NOS (not otherwise specified), 14 with chondroblastic osteosarcoma, 2 with parosteal osteosarcoma, and 1 each with fibroblastic and telangiectatic osteosarcoma. The tumor site varied, but there was predominance in the lower extremities, with more than half of the cases occurring in the legs and pelvic region. Nearly one-third of the cancer patients (30 of 112) had a recorded history of another type of cancer before the osteosarcoma diagnosis, and 25 patients had a recorded history of radiation treatment before the osteosarcoma diagnosis. Twelve patients had a recorded history of some kinds of injury or

infection at the site of the osteosarcoma. Of the patients with osteosarcoma, 8 had a family history of breast cancer and 1 had a family history of leukemia.

In medical chart review, none of these 112 cancer patients had a record of teriparatide use. For one patient, the specific medication history of teriparatide treatment could not be determined. This patient did not have a history of osteoporosis or other medications for osteoporosis listed in the medical record. Four patients had a history of osteoporosis recorded in the medical record.
No patients had a documented history of bisphosphonate use. Six patients had a history of supplement use (i.e., calcium or vitamin D or both).

3.2 STUDY GHBX[B]: CASE SERIES STUDY IN THE U.S.

The U.S. case-series design identified incident cases of osteosarcoma from participating state cancer registries in the US. Information on patients' medical history and antecedent exposures, including drug exposures, was collected through telephone interview, and responses were validated by medical record review in a random sample. Information on age at diagnosis, sex, race, vital status, tumor morphology, and primary tumor site was collected from participating cancer registries for eligible patients, regardless of whether the patient was interviewed. No formal hypothesis testing for statistical inference was planned because there was no control group.

The study identified 3,808 patients diagnosed with osteosarcoma from 2003 through 2016 from the 30 cancer registries that contributed data during the study (4,940 cases expected from the US within the study period with incidence rate 2.5 per million population per year (95% CI, 2.3-2.7), age-adjusted to the 2000 US standard population). Of the 3,808 patients identified by the registries, 2,549 met enrollment requirements, and 1,173 patients or their proxies were interviewed (questionnaire response rate 46% and the interview rate was 24%). Of the 1,173 cancer cases interviewed, the majority were white (84%), and more than half were men (53%). The mean age at the time of diagnosis of osteosarcoma was 61 years (range, 40-94 years). Approximately 38% of interviews were completed with a proxy.

Among the interviews completed for patients diagnosed with osteosarcoma, 144 respondents (12%) reported history of osteoporosis and 12 (1%) reported possible prior use of teriparatide. After additional follow-up to confirm exposure (with patient, caregiver, and/or provider), 3 of the 12 cases with possible exposure to teriparatide were considered valid exposures. The sponsor estimated that, with 5,432,764 person-years at risk, the incidence rate of osteosarcoma was 3.2 cases per million per year. The observed number of cases with prior exposure (n=3) was within the range of the expected number of cases of osteosarcoma exposed

to teriparatide treatment (n=4.17), with a standardized incidence rate ratio of 0.72 (90% CI, 0.20-1.86).

3.3 STUDY GHBX [2.2A]: MEDICARE D DATABASE

The primary objective of Study GHBX 2.2a was to estimate the incidence rate ratio and 95% confidence interval of osteosarcoma among patients aged 65 years or older with a prescription claim for teriparatide versus a cohort of matched comparators in Medicare Part D prescription claim data. The study is a population-based retrospective comparative cohort study.

Patients were eligible if they were aged 65 years or older and enrolled in Medicare Part D with at least 4 months of continuous enrollment prior to the index date (date of the first prescription of interest within the study period) and had at least one prescription for teriparatide (exposed) or had a non-teriparatide prescription (comparator) within the same calendar month and year as the index date of the exposed patients. Patients were followed from 01 January 2007 until death, a diagnosis of osteosarcoma, or the end of the study period (31 December 2014). Teriparatide users and comparators were matched (1:4) on age, sex, 3-digit zip code during the index year, a filled prescription of any medication during the same calendar year and month, and the number of unique therapeutic classes of medications dispensed during the 4 months prior to the index date. The primary outcome of incident osteosarcoma was ascertained through linkage between the study cohorts and state cancer registries. Osteosarcoma cases identified using the ICD-O-3 codes met the case definition of osteosarcoma (Appendix 1) and were pathologically confirmed and reported any time after the index date.

The study identified 153,316 patients in the teriparatide and 613,247 patients in the comparator cohort. On average, patients in the teriparatide cohort were treated for 10 months.

The teriparatide cohort was predominantly female (91%), and 59% were aged 75 years or older on the index date. Notably, the baseline use of medications in most of the unique therapeutic classes was higher in the teriparatide cohort than the comparator cohort. For example, corticosteroid use was higher among the teriparatide cohort than the comparator cohort both during the baseline period (39% vs. 31%) and during study follow-up (45% vs. 36%). Osteoporosis drugs other than teriparatide were more frequently dispensed in the teriparatide cohort than the comparators (60% vs. 27%). Other baseline differences in medication use included antineoplastic agents (7% vs. 4.7%), autonomic drugs (31% vs. 27%), cardiovascular drugs (73% vs. 83%), and electrolytic, caloric and water balance drugs (37% vs. 50%) between teriparatide users and comparators.

The teriparatide users also reported more baseline medical conditions than the comparators in a sensitivity analysis of a subset of patients with Medicare A, B and D coverage where medical diagnosis codes were available. When comparing variables used as proxies for health status during the baseline period, the proportion of patients with a baseline vertebral or hip/pelvic fracture in the teriparatide subcohort (23%, n=105,794) was nearly triple that of the percentage of patients with a fracture in the comparator subcohort (8%, n=297,509). Radiation use was higher among comparators than teriparatide users (4.3% vs. 2.9%). There were more inpatient and outpatient visits among the teriparatide cohort. However, the mean Charlson comorbidity index was nearly the same for the two groups.

During study follow-up, the use of medications in most of the unique therapeutic classes was higher in the teriparatide cohort than the comparator cohort, except for cardiovascular drugs and electrolytic, caloric and water balance drugs, where the use was higher among the comparators.

A total of 26 cancer registries participated in the study. Of the study cohorts, 100,033 teriparatide users were from participating states and 53,283 from non-participating states. The participating cancer registries submitted 811 cases of osteosarcoma for linkage against the study cohorts, which represented 68% of all osteosarcoma cases expected (n=1,197, total number of cases of osteosarcoma diagnosed in the US reported in SEER in 2017) during the study period (coverage fraction estimated by the sponsor). A total of 1,895,715 person-years (397,000 personyears in the teriparatide cohort; 1,498,715 in the comparator cohort) were observed, after adjusting for the 68% coverage fraction.
There was no case of osteosarcoma observed in the teriparatide cohort (incidence rate estimate,
0.0; 0.0 to 9.3), and fewer than 11 cases observed in the comparator cohort. As a condition of the Medicare data use agreement, to protect patient privacy, non-zero cell counts less than 11 cannot be disclosed; thus, the exact number of cases cannot be reported since it is more than zero but less than 11. The sponsor claims that the confidence interval (95% CI, 1.5 to 8.7) of the incidence rate estimate among the comparators indicates that the incidence rate is similar to what would be expected in the general U.S. population aged 65 years or older, given the estimated background incidence rate of osteosarcoma and the person-years observed in this cohort. As shown in Table 1 below, the incidence rate ratio, exposed vs. comparison cohort, was 0.0 (95% CI, 0.0 to 3.2) after coverage fraction (CF) adjustment (IRR before CF adjustment was not provided).

Table 1. Incidence rate and incidence rate ratio (IRR) between teriparatide and comparator cohorts, adjusting for coverage fraction (CF).

	Teriparatide Users	Matched Comparators
Patient number	153,316	613,247
Cancer case	0	< 11
F/U time from participating states in PYs*	378,631	1,426,199
Incidence rate per million PYs	0 (0-9.94)	(1.54-9.16)
IRR	n/a	
IRR adjusted for CF	0 (0.00-3.21)**	

*A total of 100,033 and 400,119 patients were from the participating states, respectively. F/U represents study follow up time in person-years and PYs represents person-years of follow-up. **CF coverage fracture 68%

3.4 STUDY GHBX [2.3B]: IQVIA DATABASE

The primary objective of study B3D-MC-GHBX (2.3b) was to estimate the incidence of osteosarcoma among patients who received treatment with teriparatide as compared to (1) an unexposed matched osteoporosis comparator cohort and (2) an unexposed matched general population comparator cohort using incidence rate ratios (IRRs) and 95% confidence intervals (CIs). This population-based comparative cohort study included patients aged ≥18 years and linked data from a U.S. pharmacy dispensing database (IQVIA) containing exposure details and data from 29 U.S. state cancer registries (SCRs) to examine the relationship between teriparatide exposure and osteosarcoma. The study results included U.S. data during the study period 01 January 2005 - 31 December 2014.

Study cohorts were selected from the IQVIA Longitudinal Prescription database (formerly known as the IMS LRx Database), a commercial claims database where prescription dispensing and demographic data were obtained. LRx data were linked to osteosarcoma diagnosis data from the participating SCRs. Detailed methods for the linkage to the SCRs are provided in Appendix 2. The study population included patients age 18 years or older with at least one dispensed prescription for teriparatide or a non-teriparatide medication specifically indicated for (osteoporosis (OP) comparator) or a non-teriparatide medication (general population comparator). Patients were excluded from both comparator cohorts if they had ≥1 pharmacy dispensing for teriparatide between 01 September 2004 and 31 December 2014. Detailed methods for cohort matching are provided in Appendix 3. Teriparatide users and comparators were matched on index date (the date of the first prescription of interest within the study period), age, sex, 3-digit zip code during the index year, payer type, a filled prescription of any medication during the same calendar year and month, and the number of unique therapeutic classes of medications dispensed during the 4 months prior to the index date.

A total of 29 SCRs participated in the study which provided demographic variables for linking and osteosarcoma diagnosis information including diagnosis code (i.e., histology, as coded by ICD-O-3 codes in the list below), primary site, diagnostic confirmation, and month (when available) and year of osteosarcoma diagnosis. It was estimated that the participating registry data included approximately 70% of all U.S. osteosarcoma cases aged 20 years and older during the study period (coverage fraction).

In the final study report, the study identified 429,486 patients with ≥1 dispensed teriparatide from an outpatient pharmacy during the study period. Of those patients, 94.1%

prescription for (n=404,130) were eligible for matching to control study cohorts. Of the teriparatide-exposed patients eligible for matching, 82.9% (n=335,191) were matched with at least 1 unexposed OP comparator patient (teriparatide-OP cohort) and 93.9% (n=379,283) were matched with at least 1 unexposed general population comparator patient (teriparatide-GP cohort). There were 329,166 teriparatide-exposed patients who were included in both the teriparatide-OP cohort and the teriparatide-GP cohort. The majority of teriparatide users were 65 years and older (70.5% and 66.9% respectively); the patients were mostly female (93.2% and 89.1%, respectively); and from the South (43.9% and 44.7%, respectively).

The incidence rate and rate ratio estimates were similar when teriparatide users were compared to the osteoporosis cohort or the general patient cohort. Therefore, we present only the results of comparisons between the teriparatide and osteoporosis cohorts.

Baseline medication use was more common among teriparatide users than OP nonusers for analgesics-opioid (42.3% vs. 20.4%), antianxiety agents (17.4% vs. 11.4%), anticonvulsants

(15.5% vs. 9.7%), antidepressants (27.9% vs. 21.2%), corticosteroids (16.2% vs. 9.2%), dermatologicals (18.6% vs. 13.8%), fluoroquinolones (13.2% vs. 8.9%), medical devices (11% vs. 3.2%), musculoskeletal therapy agents (11.9% vs. 5.6%) and ulcer drugs (31.9% vs. 22.2%). However, baseline medication use was higher among OP nonusers than teriparatide users for endocrine/metabolic agents (84.0% vs. 38.7%), antihypertensive (34% vs. 30%), and antihyperlipidemics (37% vs. 30%). The mean number of prescriptions dispensed was 7.9 (SD 8.0), median 5.0 in the teriparatide cohort; and the mean and median numbers of months of teriparatide exposure was 8.4 (SD 8.1) and 5.5.

A total of 29 participating SCRs represented 65% of the U.S. population aged ≥18 years and approximately 70% of all osteosarcoma cases. The linkage to cancer registries identified 3 cases of osteosarcoma among the teriparatide exposed patients (one case resided in a non-participating state and was therefore excluded from the primary incidence rate calculation); 6 cases in the unexposed OP cohort; and 9 cases in the unexposed General Population cohort.

As shown in Table 2 below, among patients residing in the states with participating SCRs (2 cancer cases from the user cohorts), the incidence rate per 1,000,000 person years (PYs) was 1.6 (95% CI: 0.2, 5.9) for the teriparatide cohort, compared to 2.6 (95% CI: 0.9, 5.6) among the unexposed OP cohort, and the incidence rate ratio was 0.6 (95% CI: 0.1, 3.6). If we include the third cancer case who lived in the non-participating state into this analysis, the incidence rate for the teriparatide cohort was 2.5 per 1,000,000 PYs, similar to the osteoporosis cohort. The results were similar to the ones above when teriparatide users were compared to the general patient cohort (IRR 0.8, 0.1-4.0).

Table 2. Incidence rates and rate ratio (IRR) estimates from participating states

	Teriparatide Users	Osteoporosis Patients
Patient number*	335,191	637,387
Cancer case	2**	6
F/U time from participating states in PYs	1,218,635	2,333,295
Incidence rate per million PYs	1.64 (0.20-5.93)	2.57 (0.94-5.60)
IRR	0.64 (0.06-3.57)	

*Number of patients from participating states was not provided. Only the follow-up (F/U) time from patients in participating states was provided. PYs represent person-years of follow up.

**One case was excluded in the analysis limited to the participating states but included in the coverage fraction adjusted analysis.

3.5 STUDY GHBX 2.1 – PROSPECTIVE PATIENT REGISTRY IN THE US

Per the sponsor's meeting request in December 2018, the sponsor asked FDA to consider releasing them from their U.S. patient registry study requirement. However, they did not submit the study results of the currently available data collected from the patient registry study, despite an Information Request issued in December 2018. Therefore, DEPI reviewed the most recent progress report for the ongoing U.S. study GHBX (2.1) submitted on 19 October 2018.

The Teriparatide Patient Registry was launched on July 23, 2009, following FDA approval of teriparatide for use in the treatment of men and women with glucocorticoid-induced osteoporosis. The objective of this study is to estimate the incidence of new cases of osteosarcoma in patients who have received treatment with teriparatide. To achieve this objective, the study target is to observe 1.7 million PY within the study population.

The study is a voluntary prospective cohort study that allows a one-time registration of consenting adult patients using teriparatide in the United States. The study population includes adult patients (aged $\geq$ 18 years) in the U.S. who receive teriparatide during the enrollment period and who provide voluntary consent. Following patient consent, appropriate information is collected from the patients to confirm actual teriparatide use and to facilitate linkage of patient information to state cancer registries. On an annual basis, starting in the third quarter of 2010 and continuing through 2024, data from the registered patients are linked to participating cancer registries to ascertain any new confirmed cases of osteosarcoma among patients registered in the Teriparatide Patient Registry. Cancer outcomes are ascertained through linkage with cancer registries to identify pathologically confirmed cases of osteosarcoma newly reported any time after the patient began treatment with teriparatide.

This study is descriptive, with no formal statistical hypothesis testing. Each identified case is reviewed (e.g., histology, stage, grade, anatomical site and laterality, reporting site and specialty of reporting physicians). Incidence rates and 95% confidence intervals will be calculated for the occurrence of osteosarcoma, adjusting for the proportion of total national adult osteosarcoma cases represented by the participating registries.

As of September 30, 2018, 71,417 teriparatide users had been enrolled. Patient characteristics were not presented in the progress report. A total of 40 registries that cover approximately 93% of U.S. adult osteosarcoma cases participated in the ninth annual linkage that was completed

on October 5, 2018. Based on the current number of registered patients (n = 71,417), and after 9 years of follow-up, the sponsor estimates there are approximately 302,719 PYs of follow-up, which is far lower than the target 1.7 million PYs of follow-up.

No incident cases of osteosarcoma have been identified among enrolled patients. One cancer case with prior teriparatide use was identified in 2016; however, at the time of enrollment, 'the patient had already been diagnosed with osteosarcoma.' Because this case did not qualify as newly diagnosed after study enrollment, this match was reported by Lilly to the FDA as a spontaneously identified adverse event but was not included as a 'reportable study outcome.'

By DEPI's estimate, when we apply the "Rule of Three", we are 95% confident that the probability of osteosarcoma is less than 1 case per 23,806 teriparatide users (3 per 71,417 users), based on the current number of patients enrolled in the study.

4 DISCUSSION

The two case series studies did not identify a safety concern for osteosarcoma. Due to the descriptive nature of the case series study, we do not recommend adding the case series results into the current labeling.

The patient registry enrolled 71,417 teriparatide users, and no incident cancer case was identified through linkage to the 40 cancer registries in the US. Although underpowered, the study results so far do not suggest a risk for osteosarcoma. After 9 years of enrollment and follow-up, with an estimated 302,719 person-years of follow-up, we do not anticipate the registry could meet the sample size target in near future (target is 1.7 million PYs). Therefore, we recommend granting the sponsor's request to be released from this requirement.

The two claims-based studies show balanced incidence rates between teriparatide users and their comparators. Strengths of the two claims studies included the linkage to the state cancer registries to identify cancer cases and use of comparators. We recommend adding the study results into the Adverse Reaction Section of the labeling. DEPI proposed labeling language is provided in the section below.

The limitations of the claims-based studies lie in the low use of teriparatide and the rarity of osteosarcoma. In the Medicare study, there were no cases of osteosarcoma observed in the teriparatide cohort (IR, 0.0; 0.0 to 9.3), and fewer than 11 cases observed in the comparator cohort. In the IQVIA study, there were only 2 cancer cases identified from the states of participating state cancer registries. In addition, both studies seem to suggest that teriparatide patients represent a sicker population of patients at baseline. For example, the IQVIA study

showed baseline differences in medication use between teriparatide users and comparators. It is unclear how these baseline differences bias the risk estimates. Finally, these studies do not allow for the assessments of detailed baseline patient characteristics (due to the prescription only data sources) and the utilization of advanced statistical methods, such as propensity score matching, to control for confounding.

5 CONCLUSIONS

DEPI concurs with the sponsor request to release the PMRs. We recommend inclusion of the claims-based studies in the Adverse Events section of the label, as detailed in the comments to sponsor below.

6 DEPI'S COMMENTS TO THE SPONSOR

We have reviewed your submission of the PMR study final reports. The two claims studies show a balanced risk between teriparatide users and their comparators. We agree to add the study results into the Adverse Reaction Section of the labeling with the following proposed label language:

> Two (b) (4) studies (b) (4) , respectively, (b) (4) a similar risk for osteosarcoma between (b) (4) users and their comparators. However, the interpretation of the study results calls for caution owing to the limitations of the data sources (b) (4) which do not allow (b) (4) and control for confounders.

7 APPENDICES

Appendix 1 ICD-O-3 codes meeting the case definition of osteosarcoma

- 9180/3 Osteosarcoma NOS,
- 9181/3 Chondroblastic osteosarcoma,
- 9182/3 Fibroblastic osteosarcoma,
- 9183/3 Telangiectatic osteosarcoma,
- 9184/3 Osteosarcoma in Paget's disease of bone,
- 9185/3 Small cell osteosarcoma,
- 9186/3 Central osteosarcoma,

- 9187/3 Intraosseous well-differentiated osteosarcoma,
- 9192/3 Parosteal osteosarcoma,
- 9193/3 Periosteal osteosarcoma,
- 9194/3 High-grade surface osteosarcoma, and
- 9195/3 Intracortical osteosarcoma.

Appendix 2. Cohort Matching Methods

Osteoporosis (OP) Cohort: For each calendar year of the study period, OP patients were selected for potential matching if they had ≥1 prescription dispensing for a qualifying osteoporosis medication (other than teriparatide) during the study year, were ≥18 years of age during the study year, and had a 3-digit ZIP code associated with any teriparatide-exposed patient indexing in the same study year. From the potential OP matches selected, for each calendar year of the study period, patients were then pre-matched to teriparatide-exposed patients on month of dispensing, sex, and age. A potential OP match could have been pre-matched with several teriparatide-exposed patients. Final matching priority was given to teriparatide-exposed patients who pre-matched to only 1 OP patient. Once those matches had been made, then, for each calendar year of the study period starting with 2005, the remaining pre-matched OP patients were randomly selected for final matching (up to 2:1) to teriparatide exposed patients on month and year of dispensing, sex, age, payer type, and number of GPI medication classes.

General Population Cohort: The General Population patients were selected for potential matching and were pre-matched similarly to the OP patients, but had ≥1 prescription dispensing for any medications (including the qualifying OP medications). A potential General Population match could have been prematched with several teriparatide-exposed patients. Due to the size of the commercial pharmacy database, a 10% random sample of pre-matched General Population patients were randomly selected for each calendar year of the study period for final random matching (up to 4:1) to teriparatide-exposed patients, with final matching priority given to teriparatide-exposed patients who pre-matched to <4 General Population patients. The remaining pre-matched General Population patients were randomly selected for each calendar year of the study period starting with 2005 for final matching (up to 4:1) to teriparatide exposed patients.

Appendix 3. Linkage to Cancer Registries

First, each participating state cancer registry (SCR) created a data file containing all osteosarcoma (OS) cases diagnosed in their state during the study period. The prepared data file included demographic variables for linking (i.e., first name, last name, date of birth, sex, street address, and ZIP code) and OS diagnosis codes, primary site, diagnostic confirmation, and date (year and month, when available) of OS diagnosis. The participating SCRs either installed the IQVIA de-identification and encryption software internally or provided the OS data files to the trusted third-party data processor, (b) (4) (b) (4) for de-identification. A deterministic data linkage method was used to match on

demographic variables across the study cohorts and SCR data using encryption and de-identification technology. The data linkage rate was 89%. The following variables utilized for linkage were deidentified and encrypted into a patient token:

- Patient first and last name;
- Date of birth;
- Patient sex;
- Patient address 1 (patient's primary correspondence address 1); and
- Patient ZIP code (patient's primary correspondence ZIP code).

Second, SCRs sent the file to a third party for de-identification of the variables required for linkage and creation of encrypted patient tokens via the IQVIA encryption engine. Alternatively, some SCRs installed and ran the IQVIA de-identification and encryption engine locally and transferred the resulting encrypted patient tokens, along with the variables to be utilized for the study analyses, to (b) (4) Lastly, (b) (4) compiled data files from all participating SCRs and sent the encrypted patient tokens and the variables for the study analyses to the research team at IQVIA where they were linked to the study cohorts (i.e., the 2 teriparatide-exposed cohorts and the 2 matched comparator cohorts) created using the LRx database.

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/s/

JIE J LI
05/03/2019 11:13:17 AM

DAVID G MOENY
05/03/2019 12:43:44 PM

16.3. Division of Epidemiology Ii Review of Osteosarcoma Risk, March 2020

APPEARS THIS WAY ON ORIGINAL

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Review: PMR Studies on the Risk of Osteosarcoma of Teriparatide (Teriparatide®)

Date: 3/2/2020

Reviewer/Team Leader:	Jie Li, PhD Division of Epidemiology II
Acting Deputy Director:	Monique Falconer, MD, MS Division of Epidemiology II
Subject:	Final study report of patient registry PMR study
Drug Name:	Teriparatide (Forteo)
Application Number:	NDA 21318
Applicant:	Eli Lilly
OSE RCM #:	2016-1499; 2020-319

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EXECUTIVE SUMMARY

Teriparatide (Teriparatide®) was approved by FDA in 2002 with Post-Marketing Requirements (PMR) to examine the risk for osteosarcoma with teriparatide use, including two case series studies, one patient registry, and two claims-based studies.

The Division of Epidemiology (DEPI) previously reviewed (by Jie Li, dated 5/3/2019, OSE RCM# 2018-2193), the final study results from a case-series study and two claims-based studies, and none of which indicated an elevated risk for osteosarcoma. However, DEPI recommended adding the two claims-based study results to Section 6 of the Forteo label due to the large sample size of the two studies.

This is the DEPI review of the final study report titled 'Forteo® Patient Registry B3DMC-GHBX (2.1) Final Study Report' for the US patient registry, dated November 19, 2019, under **Supplement S53**. But, the applicant's proposal for the labeling of those observational studies was submitted under a separate **Supplement, S54**. The applicant requested FDA consider an early release of the US patient registry PMR due to the low use of Forteo in the US and the rareness of the cancer outcome which did not allow the study to accrue the target 1.7 million PYs as planned.

The prospective patient registry study was designed to estimate the incidence of osteosarcoma among teriparatide-treated patients (aged ≥18 years) in the U.S., with a target of accruing 1.7 million patient-years of follow-up to 'demonstrate a relative risk of 3', according to the study protocol. As of September 2019, the patient registry enrolled 75,247 teriparatide users, and no incident cancer case was identified through linkage to the 42 cancer registries in the US. Although underpowered, the study results so far do not suggest a risk for osteosarcoma with teriparatide use. After 10 years of enrollment and follow-up, with an estimated 361,763 personyears of follow-up, we do not anticipate the registry could meet the target sample size in near future (target is 1.7 million PYs). Therefore, DEPI recommends granting the applicant's request to release them from the patient registry PMR. DEPI does not recommend (b) (4)

In addition, the applicant's proposed the following labeling language (under Supplement 54) for adding the observational studies to section 6 of the current label. This proposal is aligned with DEPI's recommendation from the prior DEPI review; therefore, DEPI concurs with adding the following PMR language into teriparatide's label:

6.3 (b) (4) (b) (4) *osteosarcoma surveillance safety studies designed to obtain data on the incidence rate of osteosarcoma among FORTEO-treated patients.* (b) (4) (b) (4) *studies* (b) (4) *three and zero osteosarcoma cases* (b) (4) *379,283 and 153,316* (b) (4) *users, respectively,* (b) (4) *The study results suggest a similar risk for osteosarcoma between* (b) (4) *users and their comparators. However, the interpretation of the study results calls for caution owing to the*

limitations of the data sources which do not allow for complete measurement and control for confounders.

1 INTRODUCTION

Teriparatide, a recombinant human parathyroid hormone analog (1-34), was approved in the U.S. in 2002 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. In 2009, two additional indications were approved (1) increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, (2) and treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture. Teriparatide stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. A multi-dose prefilled delivery device (pen) is used for subcutaneous injection containing 28 daily doses of 20 mcg.

In pre-license, non-clinical studies, teriparatide showed a higher incidence of osteosarcoma in rats (but not in monkeys) at a higher systemic exposure than in humans; and the risk appears to be dose- and treatment duration-dependent. It is hypothesized that the rat skeleton is more sensitive than monkey or human skeletons to the pharmacological effects of parathyroid hormone (PTH) in the formation of new bone and osteosarcomas. Since the bone metabolism in rats differs from that in humans, the relevance of the animal finding to humans is uncertain. There were no human cases of osteosarcoma identified in the pre-license clinical trials.

A boxed warning for the potential risk for osteosarcoma is in the label and the use of the product is limited to patients in the absence of other risk factors for osteosarcoma (e.g., Paget's disease of bone, or unexplained elevations of alkaline phosphatase, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton). The label recommends two years or less of lifetime use, since the clinical safety and efficacy beyond two years of treatment has not been demonstrated.

Five study components were issued under a Post-Marketing Requirement (PMR) for the postmarketing safety surveillance program for teriparatide examining the drug-associated risk of osteosarcoma in humans.

(1) a case-series study in Europe, GHBX [1]

(2) a case-series study in the US, GHBX [b]

(3) a prospective patient registry in the U.S. (GHBX 2.1 study)

(4) two claims based retrospective cohort studies in Medicare D and IQVIA Longitudinal Prescription Database (GHBX 2.2 and 2.3)

DEPI has already reviewed the final study reports for study components 1, 2 and 4, and consider these study components fulfilled under the PMR surveillance program. DEPI recommended adding the two claims-based study results (study component 4) into the Forteo label (by Jie Li, dated 5/3/2019, OSE RCM# 2018-2193).

This is the DEPI review of the final study report (study component 3) titled 'Forteo® Patient Registry B3D-MC-GHBX (2.1) Final Study Report' for the US patient registry, dated November 19, 2019, under **Supplement S53**. Sponsor proposed labeling languages was submitted under a separate **Supplement S54**. See below. The applicant requested FDA consider an early release of the US patient registry PMR due to the low use of Forteo in the US and the rareness of the cancer outcome which did not allow the study to accrue the target 1.7 million PYs as planned.

6.3 (b) (4) (b) (4) osteosarcoma surveillance safety studies designed to obtain data on the incidence rate of osteosarcoma among FORTEO-treated patients.

(b) (4) studies (b) (4) three and zero osteosarcoma cases (b) (4) 379,283 and 153,316 i (b) (4) users, respectively, (b) (4) (b) (4). The study results suggest a similar risk for osteosarcoma between (b) (4) users and their comparators. However, the interpretation of the study results calls for caution owing to the limitations of the data sources which do not allow for complete measurement and control for confounders.

2 METHODS

DEPI reviewed 'Forteo® Patient Registry B3D-MC-GHBX (2.1) Final Study Report' for the US patient registry, dated November 19, 2019, under **Supplement S53**. DEPI also reviewed the applicant's labeling proposal for NDA 021318/S-54 and provided labeling recommendations.

3 STUDY RESULTS OF GHBX 2.1

The objective of this study is to estimate the incidence of new cases of osteosarcoma in patients who have received treatment with teriparatide. To achieve this objective, the study target is to observe 1.7 million PY within the study population to detect a 3-fold increase for the risk for osteosarcoma.

The study is a voluntary prospective cohort study that allows a one-time registration of consenting adult patients using teriparatide in the United States. The study population includes adult patients (aged $\geq$ 18 years) in the U.S. who receive teriparatide during the enrollment

period and who provide voluntary consent. Following patient consent, appropriate information is collected from the patients to confirm actual teriparatide use and to facilitate linkage of patient information to state cancer registries. Exposure to teriparatide is ascertained based on selfreported data from the one-page registration form that included month/year of teriparatide start and demographic and other information necessary to complete linkage with participating cancer registries. Osteosarcoma cases diagnosed on or after 01 January 2009 were identified from data files held at each of the participating state cancer registries. Incident cases occurring among patients enrolled in the Forteo Patient Registry were identified by participating cancer registries using a standard linkage algorithm. See **Appendix 1**. Each identified case was characterized by histology, stage, grade, anatomical site and laterality, reporting site and specialty of reporting physicians.

This study is descriptive, with no formal statistical hypothesis testing. Incidence rates and 95% confidence intervals were calculated for the occurrence of osteosarcoma, adjusting for the proportion of total national adult osteosarcoma cases represented by the participating registries.

By 2019, 75,247 patients were enrolled in the Forteo Patient Registry (representing 361,763 cumulative person-years after adjusting for mortality). Patient data were linked to the research databases of 42 participating state cancer registries (covering 93% of the US population). These cancer registries represented 6,180 cases of osteosarcoma in adults aged 18 years or older diagnosed in the US since 01 January 2009.

After the 10th and final annual linkage (completed 25 September 2019), no participant in the patient registry was matched as an incident case of osteosarcoma following the registry enrollment; therefore, the crude incidence rate was estimated as 0 (95% CI, 0-10.2) cases per million person-years among Forteo users. One cancer case with prior teriparatide use was identified in 2016; however, at the time of enrollment, 'the patient had already been diagnosed with osteosarcoma.' Because this case did not qualify as newly diagnosed after study enrollment, this match was reported by Lilly to the FDA as a spontaneously identified adverse event but was not included as a 'reportable study outcome.'

4 DISCUSSION

The patient registry enrolled 75,247 teriparatide users, and no incident cancer case was identified through linkage to the 42 cancer registries in the US. Although underpowered, the study results so far do not suggest a risk for osteosarcoma with teriparatide use. Using the rule of three, the worst case scenario is that the proportion of patients with osteosarcoma will be approximately 1/25,000 teriparatide users (3/75,247), when 0 cases occur in the enrolled 75,247 teriparatide users. Given the low use of teriparatide in the US and the rareness of the cancer outcome (explained in prior DEPI review), we consider the public health impact to be relatively low. After 10 years of enrollment and follow-up, with an estimated 361,763 person-

years of followup, DEPI does not anticipate the patient registry will meet the target 1.7 million PYs sample size in near future.
In prior DEPI review, we recommended adding the two claims-based study results into the Adverse Reaction Section of the labeling due to the large sample size of the two studies. Under **Supplement S54**, the applicant's proposed labeling language is aligned with what DEPI proposed in our prior review of the observational studies PMR (by Jie Li, dated 5/3/2019, OSE RCM# 2018-2193). .

5 CONCLUSIONS

The patient registry did not identify an elevated risk for osteosarcoma with teriparatide use.
DEPI concurs with the applicant's request to release the patient registry PMR.
In addition, DEPI finds the applicant's proposed labeling language (under **Supplement 54**) for the two observational studies acceptable.

6 RECOMMENDATIONS

DEPI recommends granting the applicant's request to release them from the patient registry PMR. DEPI does not recommend (b) (4) (b) (4). In addition, the sponsor proposed labeling language below is aligned with what DEPI proposed in our prior review of the other PMR study results; therefore, DEPI agrees to labeling language below:

6.3 Observational (b) (4) Studies in (b) (4) (b) (4) osteosarcoma surveillance safety studies designed to obtain data on the incidence rate of osteosarcoma among FORTEO-treated patients. (b) (4) (b) (4) studies (b) (4) three and zero osteosarcoma cases among 379,283 and 153,316 (b) (4) users, respectively, (b) (4). The study results suggest a similar risk for osteosarcoma between (b) (4) users and their comparators. However, the interpretation of the study results calls for caution owing to the limitations of the data sources which do not allow for complete measurement and control for confounders.

7 APPENDICES

Appendix 1. ICD-O-3 codes meeting the case definition of osteosarcoma

- 9180/3 Osteosarcoma NOS,
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- 9185/3 Small cell osteosarcoma,
- 9186/3 Central osteosarcoma,
- 9187/3 Intraosseous well-differentiated osteosarcoma,
- 9192/3 Parosteal osteosarcoma,
- 9193/3 Periosteal osteosarcoma,
- 9194/3 High-grade surface osteosarcoma, and
- 9195/3 Intracortical osteosarcoma.

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JIE J LI
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03/02/2020 11:21:12 AM

16.4. Division of Pharmacovigilance Calciphylaxis Review

APPEARS THIS WAY ON ORIGINAL

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	August 30, 2019
Reviewers:	Jenny Kim, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance II Karen Konkel, MD, Medical Officer Division of Pharmacovigilance II
Team Leader:	Lynda McCulley, PharmD, BCPS Division of Pharmacovigilance II
Division Director:	S. Christopher Jones, PharmD, MS, MPH Division of Pharmacovigilance II
Product Names:	Forteo (teriparatide) Tymlos (abaloparatide) Natpara (parathyroid hormone)
Subject:	Cutaneous calcification including calciphylaxis
Application Type/Number:	NDA 021318, NDA 208743, BLA 125511
Applicant/Sponsor:	Eli Lilly, Radius Health Inc., NPS Pharms Inc.
OSE RCM #:	2019-661
TSI #:	2060

Special acknowledgement to Melissa Reyes, MD, MPH, DTMH Division of Pharmacovigilance, for her contribution to this review.

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EXECUTIVE SUMMARY

This Division of Pharmacovigilance (DPV) review evaluates periodic safety reports (submitted to FDA in 2018), FDA Adverse Event Reporting System (FAERS) reports and the medical literature through February 12, 2019 for parathyroid hormone (PTH) agonists [Forteo (teriparatide) and Tymlos (abaloparatide)] and PTH product [Natpara (parathyroid hormone)] associated with cutaneous calcification, including calciphylaxis. Additionally, DPV requested information from the European Medicines Agency and International Post Market Surveillance about their investigation of this potential safety signal. This review was initiated following identification of a published case report of cutaneous calcification and teriparatide during routine pharmacovigilance.

DPV identified 15 cases with sufficient evidence to support teriparatide use as a contributory factor in the outcome of cutaneous calcification, an unlabeled adverse event. New onset calciphylaxis was the most commonly reported adverse event (12) followed by three cases of worsening pre-existing unspecified cutaneous calcification (2) and dystrophic calcification (1) that were stable prior to teriparatide initiation. We did not identify any cases related to abaloparatide or parathyroid hormone, which may be due to the longer marketing status of teriparatide (2002) compared to parathyroid hormone (2015) and abaloparatide (2017).

All of the probable and possible cases were reported by an HCP and the majority had a biopsy and/or imaging that confirmed the diagnosis. While all the cases had underlying risk factors for cutaneous calcification, we differentiated our probable cases from possible based on the following criteria: unlikely to be attributed to chronic kidney disease (CKD) (as assessed by either reported metabolic parameters or CKD reported to be stable), less likely to be attributed to co-existing confounding disease because it is in remission, and less likely to be attributed to confounding concomitant medication because of stable chronic use.

We posit that administration of teriparatide coupled with underlying risk factors such as autoimmune disease and concomitant medications, triggered cutaneous calcification observed in our case series. There is biologic plausibility to support teriparatide as a cause of these adverse events since it is a recombinant human PTH analog (1-34) and exhibits similar activities as endogenous PTH.

In conclusion, we find an association between teriparatide and cutaneous calcification, including calciphylaxis. We believe it is reasonable to consider adding calciphylaxis to the teriparatide and abaloparatide labels given the significant morbidity and potential life-threatening outcome associated with the adverse event. Evidence of worsening of previously stable cutaneous calcification was observed in a few cases and adding this adverse event should be taken into consideration.

Based on this review, DPV recommends the following:

- Add to the *Warnings and Precautions* (5) of the teriparatide label the adverse event of calciphylaxis and worsening of pre-existing cutaneous calcifications, including a list of risk factors that could work synergistically with teriparatide to predispose patients to calciphylaxis (e.g., autoimmune disease, concomitant warfarin or systemic corticosteroids, end-stage renal disease, obesity)

- Consider adding a similar *Warnings and Precautions* to the abaloparatide label2

1 INTRODUCTION

This Division of Pharmacovigilance (DPV) review evaluates periodic safety reports (submitted to FDA in 2018), FDA Adverse Event Reporting System (FAERS) reports and the medical literature through February 12, 2019 for parathyroid hormone (PTH) agonists [Forteo (teriparatide) and Tymlos (abaloparatide)][23] and PTH product [Natpara (parathyroid hormone)][b] associated with cutaneous calcification, including calciphylaxis. Additionally, DPV requested information from the European Medicines Agency (EMA) and International Post Market Surveillance (IPMS) about their investigation of this potential safety signal. This review was initiated following identification of a published case report of cutaneous calcification and teriparatide during routine pharmacovigilance.

For the purposes of this document, the Medical Dictionary for Regulatory Activities (MedDRA) lower level term (LLT) *Calcinosis cutis* used to describe cases in this review is linked to the preferred term (PT) *Cutaneous calcification*, which will be used herein to describe the adverse event in this document.

1.1 BACKGROUND

On February 12, 2019, DPV received an email literature alert from Embase of a citation titled: *Worsening of soft tissue dystrophic calcification in an osteoporotic patient treated with teriparatide*.[1] Htet et al described a 74-year-old male patient without a pre-existing autoimmune disease, who experienced symptomatic worsening of previously stable dystrophic calcification four months after teriparatide initiation. Following discontinuation of teriparatide alone, the patient's symptoms resolved within one week.

There are several medical terminologies utilized in the medical literature to describe cutaneous calcification, which includes the subtypes outlined below. Calcinosis cutis is synonymous to cutaneous calcification as identified in MedDRA; however, it appears that calcinosis cutis is commonly used by medical experts who have published on this topic. As noted above, in MedDRA, the LLT *Calcinosis cutis* is linked to PT *Cutaneous calcification*, which we opted to use in this review as the general description of the adverse event.

Cutaneous calcification is characterized by the deposition of insoluble calcium salt in the skin and soft tissue and includes five subtypes: calciphylaxis, dystrophic calcification, iatrogenic calcification, idiopathic calcification, and metastatic calcification.[2] The underlying associated disease determines the subtype as the pathogenesis is different for each subtype. For example, dystrophic calcification occurs secondary to tissue damage from an autoimmune disease such

[23] Forteo (teriparatide) is a recombinant human parathyroid hormone (PTH) analog (1-34), [rhPTH(1-34)]. Tymlos (abaloparatide) is a human PTH related peptide [PTHrP(1-34)]. [b] Natapara (parathyroid hormone) is a recombinant PTH product.

as dermatomyositis or lupus erythematosus.[3] Also, serum calcium and/or phosphorus levels may be normal or abnormal depending on the subtype. Refer to **Appendix A** for a detailed description of each subtype.

APPEARS THIS WAY ON ORIGINAL

Calciphylaxis is the most severe subtype and is potentially fatal; the one-year mortality rate has been estimated to be 45-80%.[4] It is a small-vessel occlusive disease in which the medial layer of the vessel wall becomes calcified, the endothelial cells proliferate, and the sub-intimal layer becomes thickened and fibrotic.[5] This results in lumenal narrowing followed by thrombosis and ischemia. The process is similar to myocardial infarction. Calciphylaxis mainly affects vessels in the dermis and subcutaneous fat; however, vasculopathy may occur in visceral organs and skeletal muscle.[2] In addition to vessel damage, extravascular calcified deposits form and lesions appear. Clinically, patients present with painful, violaceous skin lesions resembling livedo reticularis that may progress to nonhealing ulcers, with subsequent tissue necrosis and superimposed infection (see **Figure 1**).[2,4] The lesions may be located centrally, in the adipose tissue of abdomen and thighs, or peripherally in areas with less adiposity, such as the digits.[6] The central distribution is more prevalent in patients who have end-stage renal disease (ESRD), are female, or have a higher body mass index. Sepsis is the leading cause of death in patients with calciphylaxis.[4]

Although calciphylaxis is a rare condition, it predominantly affects patients with ESRD due to the imbalance in calcium and phosphorus metabolism and secondary hyperparathyroidism. The incidence of calciphylaxis in dialysis or kidney transplant patients is estimated to be 1 to 4%.[2] Calciphylaxis occurring in patients with both normal renal function and parathyroid function, also referred to as non-uremic calciphylaxis (NUC), has been described as extremely rare.[7] As of 2016, there were 116 case reports of NUC in the literature.[5] Other risk factors that predispose patients to the development of calciphylaxis include female sex, age 40 to 49 years old, primary hyperparathyroidism, obesity, autoimmune disease, chronic liver disease, including alcoholic liver disease, hypoalbuminemia, infection, diabetes, protein C or S deficiency, localized skin trauma from subcutaneous injections, and malignancy.[4,7] Medications such as warfarin[8, 24,],

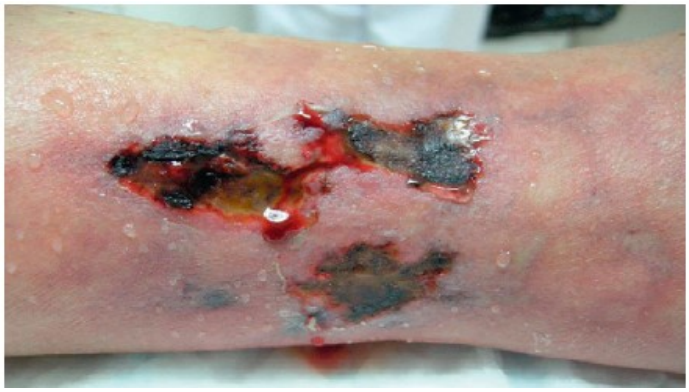
[24] Coumadin (warfarin) product label contains a warning regarding calciphylaxis (section 5.3): *Coumadin can cause fatal and serious calciphylaxis or calcium uremic arteriolopathy, which has been reported in patients with or without end-stage renal disease. When calciphylaxis is diagnosed in these patients, discontinue Coumadin and treat calciphylaxis as appropriate. Consider alternative anticoagulation therapy.*

systemic corticosteroids, calcium and active vitamin D supplementation, and chemotherapy have also been associated with calciphylaxis.[4]

The gold standard for diagnosis of calciphylaxis is a skin biopsy; however, there are associated risks including non-healing wounds and infections.[3] Other non-invasive diagnostic tests include imaging (e.g., X-ray, CT, MRI), ultrasound, or bone scintigraphy.[3] Treatment options for calciphylaxis are limited to aggressive wound care management and surgical debridement if necessary, pain management, and intravenous sodium thiosulfate, an inorganic salt that induces dissolution of calcium deposits by forming soluble calcium-thiosulfate complexes.[3,4] Successful treatment with pamidronate and cinacalcet have been reported.[2] One case report described treatment of severe refractory calciphylaxis with teriparatide as last-line therapy following intensive dialysis with low calcium dialysate concentration and citrate anticoagulation.[9] The rationale for the use of teriparatide was to activate bone turnover by increasing bone-specific alkaline phosphatase activity to target the patient's adynamic bone disease. The patient did experience subsequent improvement in pain, though she died a few weeks later from septic

shock. The authors noted that it was difficult to conclude if intensified dialysis or teriparatide was the major contributor to the improvement of bone metabolism.

Figure 1. Calciphylaxis of the lower extremity, adapted image from Leis-Dosil et al[10]



The pathophysiologic mechanisms of calciphylaxis have not yet been fully elucidated, but a clearer picture has emerged in recent years. The disorder begins in the vascular smooth muscle cell (VSMC), which has the capacity to reversibly differentiate from a contractile phenotype to an osteoblastic phenotype.[11]

According to a recently published model, the VSMC normally maintains a balance between calcification inhibition and promotion.[6] In the presence of conditions that include hypercalcemia, hyperphosphatemia, use of Vitamin D, and diabetes mellitus, the VSMC transdifferentiates into an osteochondrogenic phenotype, initiating a cascade leading to vascular calcification. This phenotype allows for upregulation of RUNX2, a transcription factor that enables matrix vesicles containing calcium and phosphorus to expel into the vessel's extracellular matrix and crystallize into calcium hydroxyapatite. Promoters of this process include Bone Morphogenic Proteins 2 and 4 (BMP-2, BMP-4) and Vascular Endothelial Growth Factor-A (VEGF-A)[25], which positively feedback either directly or indirectly to RUNX2 to potentiate the process. Inhibitors include inorganic pyrophosphate[e], carboxylated Matrix Gla Protein (MGP), and Fetuin-A. Factors that interfere with these inhibitors aggravate the cycle and allow calcification to proceed. These factors include Vitamin K deficiency (due to poor nutrition or antagonism by warfarin) and chronic inflammatory states like chronic kidney disease (CKD), diabetes, or autoimmune disease. It is likely that multiple factors and a triggering event, such as repeated subcutaneous injections or rapid weight loss, instigate calciphylaxis; unfortunately, the trigger is not usually apparent.

A second model of calciphylaxis considers other possible mediators.[10,12] Here, the osteoblastic VSMC phenotype expresses the receptor activator of nuclear factor-κB (RANK), its ligand, RANKL, and a RANKL antagonist called osteoprotegerin. RANK and RANKL are necessary for normal bone development and osteoclast function.[12] NFκB, an important transcription factor

[25] VEGF-A is released by adipocytes, which may partly explain how obesity may be a risk factor for calciphylaxis. [e] Interestingly, bisphosphonates are analogues of pyrophosphate and have been used to treat calciphylaxis.

for many cellular functions, is activated either directly through RANK-RANKL or indirectly via decreased osteoprotegerin inhibition. This results in calcium loss from bone with deposition in the vasculature. Factors that promote NFκB activation include chronic inflammatory disease, glucocorticoid use, and PTH.

1.2 REGULATORY HISTORY

To our knowledge, there are no pending regulatory actions for the products of interest related to cutaneous calcification.

Table 1 summarizes FDA approval information for PTH agonists (teriparatide and abaloparatide) and parathyroid hormone product.

Table 1. FDA Approval Information for Products of Interest[8-10]

Product Name	Forteo (teriparatide)	Tymlos (abaloparatide)	Natpara (parathyroid hormone)
FDA Application #	NDA 021318	NDA 208743	BLA 125511
Approval Date(s)	November 26, 2002 and July 22, 2009	April 28, 2017	January 23, 2015
Manufacturer	Eli Lilly	Radius Health, Inc.	NPS Pharms Inc.
Indication(s)	• Treatment of postmenopausal women with osteoporosis at high risk for fracture (2002) • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture (2002) • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture (2009)	□ Treatment of postmenopausal women with osteoporosis at high risk for fracture	□ Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism
Dosing Regimen	• 20 mcg subcutaneously once a day • Use of drug for more than 2 years during a patient's lifetime is not recommended	• 80 mcg subcutaneously once daily • Cumulative use of abaloparatide for more than 2 years during a patient's lifetime is not recommended	□ Initial dose is 50 mcg injected subcutaneously once daily and then adjusted to achieve serum calcium in the lower half of normal range □ No limitation on the duration of therapy

1.3 PRODUCT LABELING

None of the products are labeled for cutaneous calcification. However, hypercalcemia is included in the product labeling, specifically the ***Warnings and Precautions*** section, for all the products of interest: teriparatide (5.5), abaloparatide (5.3), parathyroid hormone (5.3).[13-15] Teriparatide also includes a warning to avoid use in patients with metabolic bone diseases other than osteoporosis (5.4).[13] Refer to **Appendix B** for complete labeling information regarding hypercalcemia for each product.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

DPV selected relevant cases associated with PTH and PTH agonist products and cutaneous calcifications using the following case definition:

Inclusion criteria:

- Adverse event following exposure to teriparatide, abaloparatide, or parathyroid hormone

AND

- Diagnosis of cutaneous calcification[26] confirmed by a healthcare professional (HCP)[27]

Exclusion criteria:

- Insufficient case details
- Calciphylaxis occurred only prior to drug initiation
- Duration of therapy beyond the labeled two-year limit of teriparatide or abaloparatide

2.2 CAUSALITY ASSESSMENT

We modified the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality System[16] to assess the relationship of cutaneous calcification and PTH agonists. We categorized the cases as probable, possible, unlikely, or unassessable based on the strength of the evidence for a causal association as described in **Table 2**. We used clinical judgement based on the case details provided if a case did not clearly meet the criteria for either probable or possible. All cases were reviewed independently by two reviewers and with any discordance,

[26] Lower Level Term (LLT) Calcinosis cutis (PT *Cutaneous calcification*) with five subtypes: dystrophic calcification (PT *Dystrophic calcification*), metastatic calcification (PT *Calcification metastatic*), calciphylaxis (PT *Calciphylaxis*), idiopathic calcification (not in MedDRA), iatrogenic calcification (not in MedDRA)
[27] Confirmed by HCP defined as one of the following: case reported by an HCP or reported by a consumer and it was reported that the patient was diagnosed and/or treated by an HCP

consensus was reached. Additionally, cases that met the criteria for either unlikely or unassessable were excluded from further analysis.

Table 2. Modified WHO-UMC Causality Assessment Scale

Causality term	Assessment criteria
Probable	• Event or laboratory test abnormality, with reasonable time relationship to teriparatide initiation • Unlikely to be attributed to chronic kidney disease (CKD)* • Unlikely to be attributed to other disease Unlikely to be attributed to other drug(s) • Less likely to be attributed to co-existing confounding disease because it is in remission or concomitant drug† that is in a stable pattern of use
	• Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Lack of information on status of co-existing confounding disease, CKD, or concomitant medication • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory Data cannot be supplemented or verified

*Determined by either reported serum calcium, phosphate, and parathyroid hormone within reference range or status of CKD reported as "stable"
†Concomitant medication described as "chronic" by HCP

2.3 FAERS SEARCH STRATEGIES

DPV searched the FAERS database with the strategies described in **Table 3**.

Table 3. FAERS* Search Strategies

	Search #1	Search #2	Search #3
Date of Search	February 13, 2019		
Time Period of Search	All reports through February 12, 2019		
Search Type	FBIS Quick Query		
Product Terms Product Active Ingredient:	Teriparatide; teriparatide acetate	Abaloparatide	Parathyroid hormone; parathyroid hormone (1-84) human recombinant
MedDRA Search Terms (Version 21.1)	Preferred Term (PT)†: *Calciphylaxis, Calcification metastatic, Cutaneous calcification, Dystrophic calcification*		

*See **Appendix C** for a description of the FAERS database.
†Two subtypes (i.e., iatrogenic calcification, idiopathic calcification) are not MedDRA terms and therefore could not be searched in FAERS.

2.4 PERIODIC SAFETY REPORTS

DPV reviewed the following periodic safety reports for abaloparatide, parathyroid hormone, and teriparatide:

- Abaloparatide: Periodic Adverse Drug Experience Report (PADER), reporting period from July 28, 2018 to October 27, 2018
- Parathyroid hormone: Periodic Benefit-Risk Evaluation Report (PBRER), reporting period from April 24, 2018 to October 23, 2018
- Teriparatide: Periodic Safety Update Report (PSUR), reporting period from September 13, 2015 to September 12, 2018

2.5 LITERATURE SEARCH

DPV searched the medical literature with the strategies described in **Table 4**.

Table 4. Literature Search Strategies

	Search #1	Search #2	Search #3	Search #4	Search #5	Search #6
Date of Search	February 13, 2019					
Database	Embase	Pubmed	Embase	PubMed	Embase	PubMed
Search Terms	"parathyroid hormone [134]" AND "skin calcification"	"teriparatide" AND "calcinosis"	"abaloparatide" AND "skin calcification"	"abaloparatide" AND "calcinosis"	"recombinant parathyroid hormone [184]" AND "skin calcification"	"recombinant parathyroid hormone" AND "calcinosis"
	"parathyroid hormone[134]" AND "calcinosis"	"teriparatide" AND "calciphylaxis"	"abaloparatide" AND "calcinosis"	"abaloparatide" AND "calciphylaxis"	"recombinant parathyroid hormone [184]" AND "calcinosis"	"recombinant parathyroid hormone" AND "calciphylaxis"
Years Included in Search	All citations through February 13, 2019					
Limits	Humans, English only					

3 RESULTS

3.1 CASE SERIES SELECTION FROM FAERS AND PERIODIC SAFETY REPORTS

DPV identified 15 cases, from FAERS (n=14) and the PSUR for teriparatide (n=1) with sufficient evidence to support teriparatide use as a contributory factor in the outcome of cutaneous calcification (see Figure 2).

3.1.1 FAERS

DPV retrieved 39 FAERS reports associated with teriparatide. No FAERS reports were retrieved associated with either abaloparatide or parathyroid hormone. After applying the case definition and causality assessment in **Sections 2.1 and 2.2**, 14 cases were included in the case series of cutaneous calcification reported with teriparatide use (see **Figure 2**). Refer to **Appendix D** for a line listing of the FAERS cases.

3.1.2 Periodic Safety Reports

DPV reviewed the periodic safety reports for abaloparatide, parathyroid hormone, and teriparatide to evaluate for additional cases of cutaneous calcification. Three reports were identified for further analysis, one related to parathyroid hormone and two related to teriparatide. After applying the case definition and causality assessment in **Sections 2.1 and 2.2**, only one case was included in the case series (see **Figure 2**).

Abaloparatide

DPV reviewed the PADER for abaloparatide covering the reporting period from July 28, 2018, to October 27, 2018, and did not identify any reports of cutaneous calcification including calciphylaxis.

Parathyroid hormone

DPV reviewed the PBRER for parathyroid hormone covering the reporting period from April 24, 2018 to October 23, 2018. One report of calciphylaxis following parathyroid hormone administration was reported in Table 3.1.1 Study-Emergent Adverse Event Summary by Study Cohort.

On April 25, 2019, DPV submitted an information request (IR) to the Sponsor, NPS Pharms Inc., for the case details of the one report of calciphylaxis from a postmarketing study (Mfr Case Control Number not reported). On May 1, 2019, the Sponsor submitted the requested information. DPV evaluated the report and determined that it did not meet the case definition as the patient had calciphylaxis 2.5 years prior to the initiation of parathyroid hormone. This case was also reviewed by a clinical reviewer in the Division of Metabolic and Endocrine Products. The clinical reviewer commented that the case lacked a temporal relationship between calciphylaxis and Natpara and there were multiple confounding factors.

Teriparatide

DPV reviewed the PSUR for teriparatide covering the reporting period from September 13, 2015 to September 12, 2018. The Sponsor, Eli Lilly, identified 14 cumulative reports related to the PT *Calciphylaxis*. Of the 14 reports, 12 were submitted to FAERS and two postmarketing study reports were not submitted to FAERS. Eli Lilly concluded that "there was not adequate evidence to identify non-uraemic calciphylaxis as an adverse drug reaction."

On March 21, 2019, DPV submitted an information request (IR) to Eli Lilly for case details of the two postmarketing study reports **(Mfr Case Control Number: FI201312000913 and US201504006540)**. On March 26, 2019, Eli Lilly submitted the requested information. DPV evaluated both cases; however, one U.S. case **(US201504006540)** was excluded as it did not meet the case definition as the patient had "pre-existing calciphylaxis" prior to teriparatide initiation. The remaining foreign case report **(FI201312000913)** was included in the case series.

Figure 2. Case Series Selection

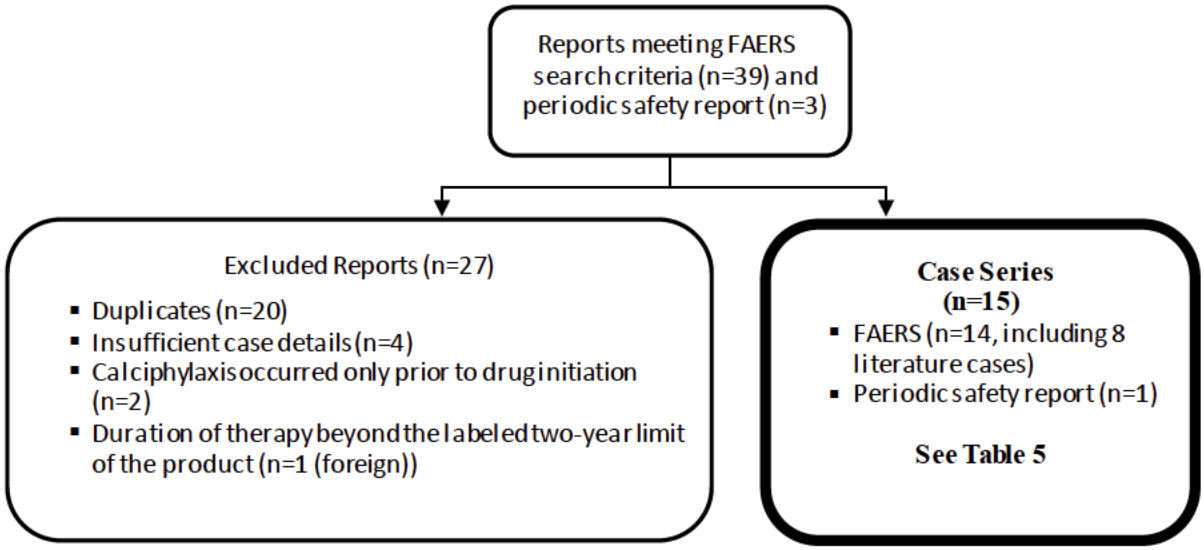


Table 5 provides descriptive characteristics of the case series (including 8 also published in the literature)[1,10,17-21] of cutaneous calcification reported with teriparatide. All events of cutaneous calcification were either reported by an HCP or reported by a consumer who described diagnosis and treatment of cutaneous calcification by an HCP.

Table 5. Descriptive Characteristics of Cases of Cutaneous Calcification with Teriparatide, Received by FDA through February 12, 2019 (N=15)

Characteristic	Results
Sex	
Female	13
Male	2
Age	
47-54 years	3
≥ 65 years	12
Mean (±SD)	72.3 (±13.3)
Median (range)	74 (47 to 86)
Country	
Foreign	8
United States	7
Report type	
Expedited	12
Direct	2
Periodic report*	1
Serious outcome†	
Death‡	2
Hospitalization	3
Life-threatening	1
Required intervention	1
Other serious	10
Teriparatide dosing regimen	
20 mcg daily	9
Not reported	6

Type of calcification	
Calciphylaxis	12
Unspecified cutaneous calcification§	2
Dystrophic calcification§	1
Confirmatory diagnostics	
Biopsy	9
Imaging (x-ray or CT)	3
Both biopsy and imaging	2
Not reported	1
Time to onset (N=13)	
Mean (±SD) months	5.3 (±5.2)
Median (range) months	3 (1 to 20)
Unspecified time	2
Location of calcification	
Lower extremity (unilateral or bilateral)	11
Other sites‖	3
Not reported	1
Reported intervention¶	
Discontinuation of teriparatide ± calcium/vitamin D only	6
Sodium thiosulfate (intravenous or intralesional)	4
Bisphosphonates	3
Wound care	3
Aluminum hydroxide	1
Plastic surgery	1
Intervention outcome	
Improved or stable	9
Worsened or not recovered	4
Death‡	1
Not reported	1
Causality assessment	
Probable	6
Possible	9

Table 5. Descriptive Characteristics of Cases of Cutaneous Calcification with Teriparatide, Received by FDA through February 12, 2019 (N=15)

*One case identified from PSUR of teriparatide (see **section 3.1.2**).
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have more than one serious outcome.
‡ Two cases reported death; however, only one case was related to the progression of calciphylaxis as the patient was not a candidate for surgical debridement. The second death case reported the patient died due to the progression of congestive heart failure; however, lesions were completely resolved (improved or stable) at the time of death.
§ Three cases reported worsening of pre-existing unspecified cutaneous calcification (2) and dystrophic calcification (1) that were stable prior to teriparatide initiation.
‖ Other sites included buttock (2) and breast and lower extremities (1).
¶ Intervention was not mutually exclusive.

Table 6 summarizes risk factors identified for cutaneous calcification following teriparatide use.

Characteristic	**Results**
Number of risk factors for calcification	
Mean (±SD)	3.9 (±1.1)
Median (range)	4 (2 to 6)

Table 6. Risk Factors for Cutaneous Calcification with Teriparatide, Received by FDA through February 12, 2019 (N=15)

Type of risk factor*	
Female	13
Autoimmune disease	10
Other inflammatory disorder	3
Obesity	3
Caucasian	3
Chronic kidney disease (CKD)	2
Age 40-49 years	1
Alcohol use	1
Cirrhosis	1
Diabetes	1
Concomitant confounding medications† (n=14)	
Systemic corticosteroid	9
Warfarin‡	7
Calcium	3
Calcitriol	1
Methotrexate	1

*A case may have had more than one risk factor.
†A case may include more than one concomitant confounding medication.
‡ Of the 7 cases that included concomitant warfarin, 3 were reported as "chronic" use by the reporter.

Table 7 provides a line listing of the six probable and nine possible cases based on the modified WHO-UMC causality assessment criteria (see **Section 2.2**).

Table 7. Summary of Probable/Possible Cases Received by FDA (N=15)

Case	FAERS or Mfr Case Control #/ Country/ Event Year	Age/ Sex	Confounding risk factors	Time to onset (months)	Biopsyproven diagnosis	Imaging	Intervention	Intervention outcome	WHO-UMC causality
1	13400991 Spain 2016[20]	51/F	Cirrhosis, female, obesity, CKD*, white	4	Yes	X-ray and CT showed calcification of upper lung lobes; mammography showed multiple bilateral calcifications with vascular morphology	IV pamidronate, IV sodium thiosulfate, then IV ibandronate	Improved	Probable
2	14355163 Australia 2018[1]	74/M	Alcohol use, white	3	NR	CT of pelvis showed no change in size of lesions	D/C of teriparatide and calcium only	Resolved	Probable
3	12215941 Columbia 2016[19]	54/F	Dermatomyositis (in remission), female, prednisone	9	NR	X-ray showed worsening calcifications on left buttock and new lesions on right buttock	Aluminum hydroxide and alendronate	Stable	Probable
4	7275323 Spain 2009[10]	80/F	Female, obesity, polymyalgia rheumatica, prednisone	2	Yes	NR	D/C of teriparatide only	Improved	Probable

5	10084142 U.S. 2014[18]	86/F	Female, calcium[†], polymyalgia rheumatica, prednisone[†], warfarin[†], white	2	Yes	NR	Aggressive wound care and zoledronic acid	Resolved	Probable
6	8384826 U.S. 2012	86/F	Female, calcium, warfarin[†]	"a few weeks" [‡]	Yes	NR	NR	NR	Probable
7	3931407 U.S. 2003	47/M	Age, amyloidosis, ESRD on dialysis[§], calcitriol, fludrocortisone	1	Yes[§]	NR	D/C of teriparatide only	Resolved	Possible
8	10008893 U.S. 2014[17]	66/F	Female, obesity, rheumatoid arthritis, prednisone, warfarin	2	Yes	NR	IV sodium thiosulfate	Death	Possible
9	12215948 Columbia 2016[19]	66/F	CREST, female, methotrexate	6	NR	Knee x-ray showing huge calcification in the right patella and multiple soft-tissue calcifications in the anterior right knee	D/C of teriparatide only	Stable	Possible
10	8537234 Finland 2012	67/F	Female, rheumatism, cortisone, methylprednisolone	NR	Yes	NR	Unspecified route of sodium thiosulfate	Not resolved	Possible
11[‖]	FI201312000913 Finland 2014	74/F	Female, rheumatism,	20	Yes	NR	Unspecified route of	Improved	Possible

Table 7. Summary of Probable/Possible Cases Received by FDA (N=15)

Case	FAERS or Mfr Case Control #/ Country/ Event Year	Age/ Sex	Confounding risk factors	Time to onset (months)	Biopsyproven diagnosis	Imaging	Intervention	Intervention outcome	WHO-UMC causality
			prednisolone, warfarin				Sodium thiosulfate		
12	6160764 U.S. 2006	81/F	Female, Sjogren's syndrome, vascular blockage, calcium	9	Yes	CT (unspecified type) was negative for cancer reported by patient	D/C of teriparatide, calcium, and vitamin D only	Not resolved	Possible
13	11698775 U.S. 2015	82/F	Female, PVOD, unspecified corticosteroid, warfarin[†]	3	Yes	NR	Wound care	Not resolved	Possible
14	12808058 Israel 2016	84/F	COPD, diabetes, female, warfarin	6	NR	NR	Plastic surgery	Resolved	Possible

15	8349167 U.S. 2012	86/F	Female, polymyalgia rheumatica, rheumatoid arthritis, warfarin	2	Yes	NR	D/C of teriparatide only	Not resolved	Possible

*Although Case ID 13400991 reported CKD, the patient had a serum calcium of 10.8 mg/dL (reference 9-10 5 mg/dL)[22], phosphorus of 3.9 mg/dL (reference 3-4 5 mg/dL)[22] and serum parathyroid hormone of 0 016 pg/mL (reference 8-51 pg/mL)[23], all of which were assessed to not be risk factors for calciphylaxis. †Reported as "chronic" concomitant medications ‡A specific time to onset was not reported.
§Case ID 3931407 reported ESRD on dialysis for 25 years (which was assessed to be stable) and the patient developed calciphylaxis one month after teriparatide initiation. This case had biopsy confirmed calciphylaxis, but there was a conflicting statement that also stated the biopsy "looked like" cutaneous polyarteritis nodosa. Cutaneous polyarteritis nodosa is a different diagnosis from calciphylaxis that is thought to be immune-complex mediated, where immunoglobulin M and C3 deposits are detectable in lesional biopsies.[24] Therefore, this case was assessed as possible due to the conflicting biopsy statements. We tried to reach the reporter for clarification regarding the biopsy results; however, we were unable to obtain additional information because the reporting physician has retired (MedWatch report submitted in 2003).
‖ Periodic report not submitted to FAERS
Abbreviations: COPD = chronic obstructive pulmonary disease, CKD = chronic kidney disease, CREST = calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia, CT = computed tomography, D/C = discontinuation, ESRD = end-stage renal disease, POVD = peripheral occlusive vascular disease, NR = not reported

3.1.3 Key Point Summary (N=15)

- Majority of cases involved multiple risk factors including co-existing autoimmune disease or other inflammatory disorder (13), female sex (13), and/or concomitant medications known to be independently associated with cutaneous calcification (14)
- 15 cases were assessed as probable (6) or possible (9)
- Of the 6 probable cases, 2 had no confounding medications
- 14 cases reported confirmatory biopsy and/or imaging
- 14 cases with intervention outcome reported improved or stable lesions following treatment (9), worsening or no recovery (4), and death due to progression of calciphylaxis (1) o 4 of the 9 cases that had improvement or stable lesions occurred following discontinuation of teriparatide ± calcium/vitamin D only
- 12 cases had new onset calciphylaxis and 3 cases had worsening pre-existing cutaneous calcification (2) and dystrophic calcification (1) that were stable prior to teriparatide initiation
- 12 cases reported a time to onset and the median was 3 months (range 1 to 20)
- 7 cases reported concomitant warfarin therapy; however, 3 cases reported "chronic" use by an HCP
- Only 2 cases had CKD, a major risk factor for calciphylaxis o Both cases described patients who had stable CKD (see **Table** 7), including 1 patient with ESRD who was on dialysis for 25 years
- No cases had known metabolic abnormalities such as hypercalcemia, hyperphosphatemia, or hyperparathyroidism that may have predisposed patients to calciphylaxis

3.2 REPRESENTATIVE CASES

Cases for the events of calciphylaxis (2), unspecified cutaneous calcification (2), and dystrophic calcification (1) are summarized below. For the two cases of calciphylaxis, we selected the best probable case based on the case details provided and the fatal case related to the progression of calciphylaxis. Since there were only three cases describing the worsening of pre-existing

unspecified cutaneous calcification or dystrophic calcification, we summarized all of them as they contained sufficient evidence to support a drug-event association.

3.2.1 Calciphylaxis

Spanakis et al, 2014; Case ID 10084142; Expedited; U.S.[18]

A literature case report described an 86-year-old Caucasian female patient with a history of polymyalgia rheumatica (PMR), recurrent deep vein thrombosis (DVT), and low bone density of femoral neck (T-score -2.5) and lumbar spine (T-score -2.3). The patient had been on chronic warfarin therapy for several years because of recurrent DVT. She also chronically took prednisone 5 mg daily, calcium, and unspecified vitamin D. The patient was initiated on teriparatide 20 mcg daily subcutaneously due to a decrease in bone density at the femoral neck despite calcitonin use. Within two months after initiating teriparatide, the patient "developed painful erythematous nodular lesions on her calves bilaterally." Initially, the patient was treated with antibiotics for presumed cellulitis; however, the lesion on the left calf progressed and became ulcerated. Lower extremity magnetic resonance imaging (MRI) showed "circumferential subcutaneous edema," consistent with cellulitis. However, a biopsy was performed due to the lack of clinical improvement, and findings were consistent with calciphylaxis: calcification of the subcutaneous fat and fat necrosis as well as medial calcification of small vessels. Reported labs at the time of referral included calcium of 9.4 mg/dL (reference 8.5-10 mg/dL), ionized calcium 5.4 mg/dL (4.8-5.6 mg/dL), phosphorus 3.5 mg/dL (2.5-4.6 mg/dL), and iPTH 47 pg/mL (12-65 pg/mL). Management of the calciphylaxis included discontinuation of teriparatide and warfarin and aggressive wound care. However, warfarin was resumed as the patient was at high risk for recurrent DVTs. Zoledronic acid was initiated three months after discontinuation of teriparatide. The time to resolution of the patient's lesions was eight months.

*Reviewer's comments: This case represents a **probable** causal association due to the temporal relationship between teriparatide initiation and development of biopsy-proven calciphylaxis (time to onset of 2 months), and positive dechallenge. The patient had risk factors for calciphylaxis such as female sex, Caucasian, PMR, and concomitant medications (prednisone, warfarin, calcium). However, it was reported that the patient was on chronic prednisone, warfarin, and calcium, which would make these drugs less likely to trigger the acute onset of calciphylaxis. It was only after teriparatide was initiated that the patient developed calciphylaxis. Furthermore, the patient's lesions improved after discontinuation of teriparatide despite continuation of prednisone and reinitiation of warfarin. All reported labs were within normal limits and excluded metabolic abnormalities as contributing factors.*

Dominguez et al, 2014; Case ID 10008893; Expedited; U.S.; Fatal[17]

A literature case report described a 66-year-old female patient with a history of obesity, pulmonary emboli, osteoporosis, and a 20-year history of well-controlled rheumatoid arthritis. Concomitant medications included leflunomide, prednisone 2 mg daily, and warfarin. Two months following initiation of teriparatide, the patient developed painful lower extremity nodules. On physical examination, "a 10 x 3 cm indurated subcutaneous plaque with livedoid erythema and retiform purpura" were noted bilaterally on the thighs and scattered indurated

subcutaneous nodules bilaterally on the lower extremities. Two months prior to this presentation, an outside facility performed a biopsy on the lateral thigh and it showed thrombotic vasculopathy with no changes consistent with early calciphylaxis. "Normal" renal function, PTH, and calcium phosphate product were reported. Warfarin and teriparatide were discontinued due to the patient's multiple risk factors and clinically suspected calciphylaxis. Due to lesion progression, another biopsy was performed that showed intramural calcium deposits in subcutaneous arterioles with intimal hyperplasia and ischemic changes of the surrounding tissue, consistent with calciphylaxis. The patient was treated with intravenous sodium thiosulfate as the patient was not a candidate for surgical debridement. The patient's lesions progressed further causing intractable pain; she was transitioned to hospice care and died shortly after.

*Reviewer's comments: This case represents a **possible** causal association due to the temporal relationship between teriparatide initiation and development of biopsy-proven calciphylaxis. However, the patient was also on warfarin with an unknown temporal association that may have contributed to the onset of calciphylaxis. As warfarin and teriparatide were both discontinued, and the patient had a negative dechallenge despite treatment with sodium thiosulfate, we are unable to determine if one or both drugs were the offending agent. It is possible that the patient did not respond to sodium thiosulfate due to a delay in accurate diagnosis that resulted in severe calciphylaxis that would have required surgical debridement, for which she was not a candidate.*

3.2.2 Worsening of Pre-existing Cutaneous Calcification

Echeverri et al, 2016; Case IDs 12215941 and 12215948; Expedited; Foreign[19] A literature case report described two patients who had worsening of previously stable "calcinosis cutis" following teriparatide treatment.

Case ID 12215941 involved a 54-year-old female with a 16-year history of dermatomyositis who achieved disease remission with azathioprine 100 mg daily, prednisolone 5 mg daily, and chloroquine 250 mg daily. She had pre-existing "calcinosis cutis" on the left buttock due to DM. Renal function, serum PTH, and calcium phosphate product were reported as "normal." Teriparatide was initiated for severe osteoporosis secondary to glucocorticoids. Nine months following teriparatide initiation, the patient had significant worsening of calcinosis cutis on the left buttock and new lesions on the right buttock, all confirmed by pelvis radiography. Management of "calcinosis cutis" included discontinuation of teriparatide and initiation of aluminum hydroxide and alendronate. Following treatment, it was reported that the patient had stable lesions without further progression.

*Reviewer's comments: The first case **(Case ID 12215941)** represents a **probable** causal association due to the temporal relationship between teriparatide initiation and worsening of previously stable calcinosis cutis (i.e., unspecified cutaneous calcification), radiographic imaging confirming diagnosis, the lack of other significant contributory factors (i.e., renal function, serum PTH and calcium phosphate product reported as "normal"), and positive dechallenge. Although the patient had dermatomyositis, it is unlikely that this contributed to the worsening of calcinosis cutis as it was reported that the patient had achieved disease remission.*

Case ID 12215948 involved a 66-year-old female with limited systemic calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia (CREST syndrome) and osteoporosis. Concomitant medications included methotrexate 10 mg weekly and colchicine 0.5 mg daily. The patient had limited mobility and pre-existing calcinosis cutis in the right knee (3 cm) and multiple indurated subcutaneous plaques with erythema on the scalp, buttock, and elbows due to CREST syndrome. The patient was initiated on teriparatide due to intolerance to bisphosphonates and within six months developed increasingly limited mobility and worsening calcinosis in her right knee. An X-ray of the right knee confirmed increased and extensive calcification in the soft tissues. Calcium phosphate product was reported as "normal." Teriparatide was discontinued and at a six-month follow-up, the patient had clinical signs of stable "calcinosis cutis."

*Reviewer's comments: The second case **(Case ID 12215948)** represents a **possible** causal association due to the temporal relationship between teriparatide initiation and worsening of previously stable calcinosis cutis (i.e., unspecified cutaneous calcification) and radiographic imaging confirming diagnosis. The patient had a positive dechallenge; however, she had additional risk factors such as CREST syndrome and concomitant methotrexate that may explain the worsening of her pre-existing calcinosis cutis. It was not reported whether the patient's CREST syndrome was in remission. Prior to initiation of teriparatide the patient already had significant immobility. Other than the patient's calcium phosphate product being reported as "normal," it was unknown if she had normal renal function and serum PTH.*

3.2.3 Worsening of Pre-existing Dystrophic Calcification

Htet et al, 2018; Case ID 14355163; Expedited; Foreign[1]

A literature case report described a 74-year-old Caucasian male patient with a history of osteoporosis, Parkinson's disease, heavy alcohol use, Barrett's esophagus, and "restless legs." Concomitant medications included benserazide, calcium citrate, carbidopa, cholecalciferol, clonazepam, esomeprazole, levodopa, and sotalol. The patient had pre-existing calcific lesions in the right buttock since childhood secondary to an intramuscular injection. On a previous computer tomography (CT) scan of the abdomen (5 years earlier), dystrophic calcification was observed on both ischial tuberosities, measuring 30.2 x 16.8 mm (right) and 24.2 x 13 mm (left). Three months following teriparatide initiation, the patient developed right buttock pain and eight months after initiation, pain in the left buttock. On physical examination, the patient had tender, palpable irregular nodules with bone-like consistency over the ischial tuberosities; however, no skin changes were noted. On a pelvic CT, no change in the size of the lesions were observed. Also, an ultrasound did not show signs of inflammation or necrosis, and a bone scan showed no uptake in the lesions. Nevertheless, he was diagnosed with symptomatic worsening of dystrophic calcification. "Normal" corrected serum calcium, phosphate, PTH, renal function, and inflammatory markers were reported. Teriparatide and calcium citrate were discontinued, and the patient had complete resolution of his pain one week later.

*Reviewer's comments: This case represents a **probable** causal association due to the temporal relationship between teriparatide initiation and symptomatic worsening of dystrophic calcification, absence of other significant contributory factors, and rapid resolution of his pain*

following discontinuation of teriparatide (dechallenge). Although the patient was on calcium citrate, it is unlikely to have contributed as his corrected serum calcium was reported as normal.

3.3 LITERATURE SEARCH

DPV did not identify additional literature cases, other than the eight literature cases also reported to FAERS, of cutaneous calcification associated with teriparatide, abaloparatide, or parathyroid hormone.

3.4 ADDITIONAL SAFETY DATA FROM EMA AND IPMS

DPV reached out to EMA and IPMS for additional safety data regarding cutaneous calcification, including calciphylaxis. Of the 46 cases reviewed, two additional cases met our case definition that were not included in our case series. Refer to **Appendix E** for DPV's detailed assessment of the written responses from EMA and IPMS.

The following summarizes the two additional cases we identified from EMA:

- PT *Calciphylaxis: One case **(Manufacturer Control # ES-AEMPS-370342)**[28] described a female patient (age redacted) classified in the ICSR as "elderly" who developed infected ulcers in both lower extremities eight months following teriparatide exposure and was initially treated with IV antibiotics. She was diagnosed with possible microscopic polyarteritis nodosa. However, due to slow improvement in the ulcers without systemic involvement and recent exposure to teriparatide, she was treated with IV sodium thiosulfate for possible calcification disorder. Concomitant medications included a glucocorticoid (deflazacort), but the time course of use was not described. Reported laboratory values included PTH 50 pg/mL (no reference range provided) and calcium 8 (no units or reference range provided). Skin biopsy of left foot showed vessels in the deep dermis with recanalized thrombus, vessels with calcifications in the wall and focal chronic inflammatory infiltrate suggestive of early stage vasculitis. A dermatologist reported a differential diagnosis of either dystrophic calcification or calciphylaxis without significant metabolic changes in calcium/phosphorus.*
    - *This case represents a **possible** causal association due to the temporal association between teriparatide exposure and development of either dystrophic calcification or calciphylaxis without significant metabolic changes as reported by an HCP. However, the case is limited by the unknown temporal association of glucocorticoid use, lack of details regarding possible polyarteritis nodosa, and outcome following treatment with IV sodium thiosulfate and withdrawal of teriparatide.*
- PT *Calcification of muscle: One case **(Manufacturer Control # US201007007247)** described a female patient (age redacted) with a relevant past medical history of DVT,*

[28] This case was translated from Spanish to English by our medical officer using https://www.proz.com/search/ for medical translation and https://translate.google.com/ for general term translation.

sarcoid, and primary hyperparathyroidism. The patient reportedly tolerated teriparatide during the first year of exposure; however, during the second year of treatment she developed three painful lesions of indurated subcutaneous tissue over her lower thighs at the injection sites. Four months later, she developed another painful lesion on the anterior thigh. The patient had surgical excision of the indurated tissue from the left hip/buttock and lateral thigh. Surgical pathology showed dystrophic subcutaneous tissue, dense sclerosis, largely hyalinized with large areas of dystrophic stromal calcification. One month later, the patient had another surgical excision of both thighs and the pathology showed fibrosis with calcification of soft tissue from right upper thigh excision, and calcified fat necrosis of soft tissue from left inner thigh excision. The patient continued to have complications following the surgical excisions including delayed lesion healing and subsequent hospitalizations for possible infections. Teriparatide was not discontinued until three to four months later. According to the reporting physician, these events were related to the use of teriparatide. o *This case represents a* ***possible*** *causal association due to the temporal association with the development of dystrophic stromal calcification and exposure to teriparatide. However, the patient had underlying risk factors such as sarcoid (unknown status), primary hyperparathyroidism (unknown status), and concomitant calcium (unknown if chronic). Discontinuation of teriparatide occurred several months following the development of the dystrophic calcification and information regarding dechallenge was not reported.*

4 DISCUSSION

DPV identified 15 cases from FAERS (N=14) and the teriparatide periodic safety report (N=1) with probable (6) or possible (9) causal association between teriparatide and cutaneous calcification, an unlabeled adverse event. New onset calciphylaxis (12) was the most commonly reported adverse event followed by three cases of worsening pre-existing unspecified cutaneous calcification (2) and dystrophic calcification (1) that were stable prior to teriparatide initiation. We did not identify any cases related to abaloparatide or parathyroid hormone, which may be due to the longer marketing status of teriparatide (2002) compared to parathyroid hormone (2015) and abaloparatide (2017).

All probable and possible cases were diagnosed by an HCP and the majority had a biopsy and/or imaging that confirmed the diagnosis. While all the cases had underlying risk factors for cutaneous calcification, we differentiated our six probable cases from possible based on the following criteria: unlikely to be attributed to CKD (as assessed by either reported metabolic parameters or CKD reported to be stable), less likely to be attributed to co-existing confounding disease because it is in remission, and less likely to be attributed to confounding concomitant

medication (i.e., warfarin, systemic corticosteroids, calcium[29], active vitamin D, methotrexate) because of stable chronic use.

One case (**ID 7275323**) did not clearly meet the probable criteria as the information provided did not indicate that the patient was on chronic prednisone or that her underlying PMR was in remission. However, we designated it as a probable case due to the relatively quick time to onset of calciphylaxis (2 months) following teriparatide initiation and the rapid improvement (3 weeks) after only discontinuing teriparatide.[10] Although the patient died six months later due to progressive congestive heart failure, it was reported at the time of her death that the skin lesions had completely resolved.[10] The remaining nine possible cases had evidence to support a drugevent association based on the temporal relationship between teriparatide initiation and either development of calciphylaxis or worsening of pre-existing cutaneous calcification.

There is biologic plausibility to support teriparatide as a cause of these adverse events since it is a recombinant human PTH analog (1-34)[30] and exhibits similar activities as endogenous PTH. Leis-Dosil et al[10], based on the theory proposed by Weenig[12], hypothesized that teriparatide may cause an imbalance in NFκB signaling, leading to calciphylaxis. Vascular endothelial cells, osteoblasts, osteoclasts, and VSMCs express the receptor activator of NFκB (RANK) and its ligand (RANKL). PTH activates RANK resulting in increased activity of transcription factor, NFκB. Following increases in NFκB activity, calcium is deposited in the vessels and may result in calcifications and subsequent thrombosis leading to calciphylaxis.[7,10] Also, PTH decreases osteoprotegerin, a soluble RANKL antagonist, which further increases the activity of NFκB. Interestingly, estrogen may have a protective effect against cutaneous calcifications as it increases the expression of osteoprotegerin; however, this protective effect may be lost after menopause.[10] An additional consideration is that teriparatide requires daily subcutaneous injections, and the injection itself (break in the skin) could possibly act as a trigger for calciphylaxis either alone or synergistically with the pharmacologic effects of the drug.

Although the median time to onset in our case series was relatively short at 3 months (range 1 to 20 months), the expected time to onset of cutaneous calcification following teriparatide use remains unclear. Prompt diagnosis and a multi-disciplinary and multi-interventional approach to treatment is imperative because calciphylaxis is associated with significant morbidity such as painful ulcers, nonhealing skin lesions, superimposed infections, and high mortality rate due to sepsis.[2,4]

To our knowledge, of all the confounding medications associated with calciphylaxis, we are only aware of the inclusion of calciphylaxis in the Coumadin® (warfarin) product label under *Warnings and Precautions* (5.3) in September 2016 based on observational studies submitted by

[29] Calcium supplementation has been associated with calciphylaxis; however, only calcium gluconate is labeled for tissue necrosis and calcinosis under *Warnings and Precautions* (5.3).
[30] 1-34 is the active fragment of the amino-acid sequence of PTH. It is the identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid endogenous PTH.[8]

Bristol-Myers Squibb. The Division of Hematology Products consulted the Division of Epidemiology (DEPI) to review these observational studies. DEPI concluded that *"these studies support that either risk factors or comorbid conditions (i.e., warfarin indication) or warfarin itself has a positive association with development of calciphylaxis in the predisposed population. The effect of warfarin cannot be disentangled from its underlying indication using available epidemiological data."*[25]

Yu et al,[26] suggested that the time to onset of calciphylaxis secondary to warfarin was delayed (mean of 32 months, range 1 to 168 months), which may affect how we interpret the chronicity of warfarin as a confounding factor.[31] However, two cases reported concomitant teriparatide and warfarin use, and the contributory role of teriparatide in causing calciphylaxis was not considered even though both medications were discontinued. In our case series we included both warfarin/teriparatide cases described by Yu et al, which correlate to **case IDs 10084142 (probable) and 10008893 (possible)**.[17,18] We assessed **case ID 10084142**[18] as a probable case because the onset of calciphylaxis was more temporally associated with teriparatide initiation (after 2 months) compared to chronic warfarin (duration of 48 months prior), and despite reinitiation of warfarin, the patient's lesions did not recur. Therefore, we interpreted warfarin's role to be less likely than teriparatide in causing calciphylaxis. We assessed **case ID 10008893** as a possible case because of the unknown temporal association between warfarin and calciphylaxis onset. The patient's lesions progressed, and she died shortly after despite discontinuation of both warfarin and teriparatide and treatment with sodium thiosulfate. We were unable to determine if one or both drugs were the offending agent in this case.

We believe the data presented in this review supports a clinically serious adverse event of calciphylaxis (12/15 cases) and worsening of pre-existing cutaneous calcifications (3/15) that warrants consideration as an addition to the labeling of teriparatide under section 5, *Warnings and Precautions*. Given the rarity of the outcome and inherent difficulty to study, our case series provides sufficient evidence to support teriparatide use as a contributory factor in the outcome of cutaneous calcification based on the temporal relationship between teriparatide initiation and the onset of calciphylaxis or worsening of cutaneous calcification, biological plausibility, and positive dechallenge. Additional risk factors (e.g., autoimmune disease, concomitant warfarin or systemic corticosteroids, ESRD, obesity) should be listed to advise HCPs regarding patients who may be predisposed to calciphylaxis. HCPs should be aware of the possibility of calciphylaxis in patients with multiple risk factors including teriparatide exposure to expedite diagnosis and management, since untreated calciphylaxis may be life-threatening.

[31] Yu et al, described a retrospective case series of 18 patients who developed calciphylaxis following chronic warfarin. There are some limitations to consider that may affect the validity of the study results. Firstly, due to the wide reported range of 1 to 168 months, median duration would have been a more accurate calculation to describe the nonparametric data. With the durations of warfarin provided (14/18 cases), we estimated a median value of 16.5 months, which is a shorter time to onset than reported (mean of 32 months). Secondly, several of the cases had concomitant risk factors, such as obesity, autoimmune disease, and concomitant medications, that may have contributed to the development of calciphylaxis rather than warfarin alone being the inciting factor, and these were not adequately addressed by the investigators (i.e., status of disease state and temporal association with concomitant medications).

Based on the mechanism of action of both abaloparatide and parathyroid hormone, we believe that patients could be predisposed to calciphylaxis or worsening of cutaneous calcification. Given our lack of cases for abaloparatide, the risk is theoretical but worth consideration of labeling given the common mechanism of action. However, because parathyroid hormone is used in a different patient population, we do not recommend labeling at this time and will continue routine surveillance for parathyroid hormone.

5 CONCLUSION

In conclusion, we find an association between teriparatide and cutaneous calcification, including calciphylaxis. We believe it is reasonable to consider adding calciphylaxis to the teriparatide and potentially abaloparatide labels given the significant morbidity and potential life-threatening outcome associated with the adverse event. Evidence of worsening of previously stable cutaneous calcification was observed in a few cases and adding this adverse event should also be taken into consideration.

6 RECOMMENDATIONS

Based on this review, DPV recommends the following:

- Add to the *Warnings and Precautions* (5) of the teriparatide label the adverse event of calciphylaxis and worsening of pre-existing cutaneous calcifications, including a list of risk factors that could work synergistically with teriparatide to predispose patients to calciphylaxis (e.g., autoimmune disease, concomitant warfarin or systemic corticosteroids, end-stage renal disease, obesity)
- Consider adding a similar *Warnings and Precautions* to the abaloparatide label

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8 APPENDICES

8.1 APPENDIX A. ADAPTED FROM JIMENEZ-GALLO D ET AL. (2015), DESCRIPTION OF THE

FIVE SUBTYPES OF CALCINOSIS CUTIS[3]

Subtype of calcinosis cutis	Pathogenesis	Associated diseases	Serum calcium and/or phosphorus levels
Calciphylaxis	Calcification of the small vessel walls in the dermis and subcutaneous cell tissue with subsequent ischemia	• Chronic kidney disease • Other non-uremic causes	Abnormalities can be observed
Dystrophic calcification	Secondary to tissue damage	• Autoimmune diseases • Skin neoplasms • Collagen or elastic fiber diseases • Infections • Trauma • Porphyria cutanea tarda • Pancreatic panniculitis	Normal
Iatrogenic calcification	Adverse effect of medical treatment	• Intravenous calcium-containing solutions • Venipuncture sites	Normal
Idiopathic calcification	Unknown; no previous damage to skin or metabolic disturbances	• Tumoral calcinosis • Calcified subepidermal nodules (nodular calcinosis of Winer) • Scrotal calcinosis	Normal
Metastatic calcification	Calcium precipitation in the skin	• Chronic kidney failure • Hyperparathyroidism • Hypervitaminosis D • Sarcoidosis • Milk-alkali syndrome • Malignant neoplasms	Abnormal

8.2 APPENDIX B. RELEVANT PRODUCT LABELING INFORMATION FOR TERIPARATIDE,

ABALOPARATIDE, AND PARATHYROID HORMONE

Product Name	Applicable Sections of the Current Product Labeling

Forteo (teriparatide)	***5 WARNINGS AND PRECAUTIONS*** **5.4 Metabolic Bone Diseases** Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO. **5.5 Hypercalcemia and Hypercalcemic Disorders** FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO. ***6 ADVERSE REACTIONS*** **Laboratory Findings** Serum Calcium — FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men. **6.2 Postmarketing Experience** **Hypercalcemia:** Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. ***17 PATIENT COUNSELING INFORMATION*** **17.3 Hypercalcemia** Although symptomatic hypercalcemia was not observed in clinical trials, physicians should instruct patients taking FORTEO to contact a health care provider if they develop persistent symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness).
Tymlos (abaloparatide)	***5 WARNINGS AND PRECAUTIONS*** **5.3 Hypercalcemia** TYMLOS may cause hypercalcemia. TYMLOS is not recommended in patients with preexisting hypercalcemia or in patients who have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, because of the possibility of exacerbating hypercalcemia [see Adverse Reactions (6.1)]. ***6 ADVERSE REACTIONS*** The following adverse reactions are described in greater detail in other sections: Hypercalcemia [see Warnings and Precautions (5.3)] **Laboratory Abnormalities** Hypercalcemia In the clinical trial of women with postmenopausal osteoporosis, TYMLOS caused increases in serum calcium concentrations [see Warnings and Precautions (5.3)]. The incidence of hypercalcemia, defined as albumin-corrected serum calcium ≥ 10.7 mg/dL at 4 hours following injection at any visit was 3% in TYMLOS-treated patients and 0.1% with placebo. Pre-dose serum calcium was similar to baseline in both groups. There were 2 (0.2%) TYMLOS-treated patients and no placebo-treated patients who discontinued from the study due to hypercalcemia. The incidence of hypercalcemia with TYMLOS was higher in patients with mild or moderate renal impairment (4%) compared to patients with normal renal function (1%). ***10 OVERDOSAGE***

Product Name	Applicable Sections of the Current Product Labeling
	In a clinical study, accidental overdose was reported in a patient who received 400 mcg in one day (5 times the recommended clinical dose); dosing was temporarily interrupted. The patient experienced asthenia, headache, nausea, and vertigo. Serum calcium was not assessed on the day of the overdose, but on the following day the patient's serum calcium was within the normal range. The effects of overdose may include hypercalcemia, nausea, vomiting, dizziness, tachycardia, orthostatic hypotension, and headache. ***17 PATIENT COUNSELING INFORMATION*** **Hypercalcemia** Advise patients that TYMLOS may cause hypercalcemia and discuss the symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness) [see Warnings and Precautions (5.3)]. Instruct patients to promptly report signs and symptoms of hypercalcemia.
Natpara (parathyroid hormone)	***5 WARNINGS AND PRECAUTIONS*** **5.3 Hypercalcemia** Severe hypercalcemia has been reported with NATPARA. In the pivotal trial, 3 patients randomized to NATPARA required administration of IV fluids to correct hypercalcemia during treatment with NATPARA. The risk is highest when starting or increasing the dose of NATPARA, but can occur at any time. Monitor serum calcium and patients for signs and symptoms of hypercalcemia. Treat hypercalcemia per standard practice and consider holding and/or lowering the dose of NATPARA if severe hypercalcemia occurs [see Dosage and Administration (2), Adverse Reactions (6.1)]. ***6 ADVERSE REACTIONS*** The following serious adverse reactions are described in greater detail in other sections of the label: • Hypercalcemia [see Warnings and Precautions (5.3)] **Hypercalcemia** In the overall pivotal trial a greater proportion of patients on NATPARA had albumin-corrected serum calcium above the normal range (8.4 to 10.6 mg/dL). During the entire trial duration 3 patients on NATPARA and 1 patient on placebo had a calcium level above 12 mg/dL. Table 2 displays the number of subjects who had albumin-corrected serum calcium levels above the normal range (8.4 to 10.6 mg/dL) by study treatment period in the placebo-controlled study based on routine monitoring at each trial visit. More patients randomized to NATPARA had hypercalcemia in both phases of the study (note: all trial participants underwent a 50% reduction in active vitamin D dose at randomization). ***17 PATIENT COUNSELING INFORMATION*** **17.3 Severe Hypercalcemia** [see Warnings and Precautions (5.3)] Instruct patients that severe hypercalcemia can occur when starting or adjusting NATPARA dose and/or when making changes to co-administered drugs known to raise serum calcium. Instruct patients to: report symptoms of hypercalcemia promptly, report any changes to co-administered drug(s) known to influence calcium levels and follow recommended serum calcium monitoring.

8.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.4 APPENDIX D. FAERS LINE LISTING OF CUTANEOUS CALCIFICATION INCLUDING CALCIPHYLAXIS ASSOCIATED WITH TERIPARATIDE CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	3/13/2014	10008893†	1	PHHY2014US027031	Expedited (15Day)	66	Female	USA	DE,HO
2	4/17/2014	10084142†	1	US-TARO PHARMACEUTICALS U.S.A., INC-2014SUN00825	Expedited (15Day)	86	Female	USA	OT
3	11/4/2015	11698775†	2	US-ELI_LILLY_AND_COMPANYUS201510008882	Expedited (15Day)	82.661	Female	USA	OT
4	3/28/2016	12215941†	1	CO-ELI_LILLY_AND_COMPANYUS201603008083	Expedited (15Day)	54	Female	COL	OT
5	3/28/2016	12215948†	1	CO-ELI_LILLY_AND_COMPANYCO201603009631	Expedited (15Day)	66	Female	COL	OT
6	10/4/2016	12808058†	1	IL-ELI_LILLY_AND_COMPANYIL201609011813	Expedited (15Day)	84	Female	ISR	HO
7	4/4/2017	13400991	1	ES-PFIZER INC-2017139724	Expedited (15Day)	51	Female	ESP	OT
8	1/5/2018	14355163	1	AU-ELI_LILLY_AND_COMPANYAU201801000815	Expedited (15Day)	74	Male	AUS	OT
9	3/26/2003	3931407	2	US_030292219	Expedited (15Day)	47	Male	USA	DE,HO
10	11/2/2006	6160764†	7	US-ELI_LILLY_AND_COMPANYUS200610003102	Expedited (15Day)	81.35	Female	USA	OT
11	2/10/2010	7275323†	2	ES-ELI_LILLY_AND_COMPANYES201001005831	Expedited (15Day)	80	Female	ESP	OT
12	1/18/2012	8349167	1		Direct	86	Female	USA	DE,OT
13	3/1/2012 ‡	8436345	1	US-ELI_LILLY_AND_COMPANYUS201112004685	Expedited (15Day)	87	Female	USA	OT
14	2/2/2012	8384826	1		Direct	86	Female	USA	LT,RI
15	4/30/2012	8537234†	3	FI-ELI_LILLY_AND_COMPANYFI201203006381	Expedited (15Day)	67	Female	FIN	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
† Case also in EudraVigilance database.
‡ This case is a duplicate of case ID 8349167.
Abbreviations: DE = Death, HO = Hospitalization, LT = Life-threatening, OT = Other medically significant, RI = Required intervention

8.5 APPENDIX E. EMA AND IPMS WRITTEN RESPONSES AND ASSESSMENT

Following an internal discussion with DBRUP regarding this safety signal, DPV sent a request to EMA and IPMS on June 18, 2019 for a written response to the following questions:

FDA is reviewing postmarketing reports regarding a potential safety signal of cutaneous calcification, including calciphylaxis, associated with teriparatide exposure. Please provide a written response by June 28, 2019.

1. *Have EMA or IPMS reviewed postmarketing reports of teriparatide and this safety signal?*
2. *If so, would they be willing to share any spontaneous reports they have and their assessment?*

EMA Response

On June 25, 2019, EMA responded with the following information:

- *EMA identified the safety signal July 2014 based on nine cases of PT Calciphylaxis associated with teriparatide and recommended the MAH to evaluate the cumulative cases of calciphylaxis and other calcification disorders with a view of updating the product information and propose risk minimization activities as appropriate by November 2014.*
- *"The MAH provided a review of spontaneous reports (noting complex medical histories and aetiological/predisposing factors for NUC), the literature (including nonclinical studies suggesting preventive effects in vascular calcification) and the lack of histologic evidence of vascular mineralization or other changes in toxicology studies with teriparatide."*
- *On January 2015, according to the Pharmacovigilance Risk Assessment Committee (PRAC) of EMA assessment, "Given that evidence of causality of calciphylaxis by teriparatide is weak on analysis of individual cases, and that the disproportionality analysis is confounded by corticosteroid-related osteoporosis, overall it is the opinion of the Rapporteur that the current evidence is not strong enough to support updating of the teriparatide product information to include calciphylaxis as an adverse event."* o *Additionally, PRAC stated, "Even if all cases involving corticosteroids are excluded, there still remain from 3 – 6 cases of calciphylaxis in which corticosteroids do not play a role. This is still a relatively high number of cases for this rare event and it remains possible that teriparatide may be a risk factor which in rare cases can trigger the onset of calciphylaxis in the presence of other risk factors, either disease states or concomitant medications."*
    - *PRAC recommended to closely monitor calciphylaxis through routine pharmacovigilance, and non-uraemic calciphylaxis be added to the teriparatide risk management plan as an important potential risk.*
- On June 20, 2019, EMA conducted an updated search of the EudraVigilance database to update case numbers and retrieved the following 44 cases:

- 27 cases of PT *Calciphylaxis* o 9 cases of PT *Vascular calcification* o 6 cases of PT *Calcification of muscle* o 2 cases of PT *Cutaneous calcification*

Reviewer's comments: We reviewed the 44 cases provided by EMA and identified the following:

- *Of the 27 cases of PT Calciphylaxis, we already reviewed 26 of which 8 were included in our case series* ***(FAERS Case IDs 10008893, 8537234, 7275323, 6160764, 10084142, 11698775, 12808058 and periodic report Manufacturer Control # FI201312000913).*** *The remaining case (****Manufacturer Control # ES-AEMPS-370342)*** *was assessed as a possible case.*
- *Of the 9 cases of PT Vascular calcification, 7 did not meet our case definition of cutaneous calcification diagnosed or reported by an HCP, 1 did not have enough case details for assessment, and 1 was a duplicate case that also contained PT Calciphylaxis that we already included* ***(FAERS Case ID 10084142).***
- *Of the 6 cases of PT Calcification of muscle, 4 did not meet our case definition of cutaneous calcification diagnosed or reported by an HCP and 1 was a duplicate. The remaining case (****Manufacturer Control # US201007007247)*** *was assessed as a possible case.*
  - *DPV ran an updated FAERS search through July 1, 2019 for reports associated with teriparatide and PT Calcification of muscle and did not retrieve additional reports.*
- *Of the 2 cases of PT Cutaneous calcification, we already included both in our case series* ***(FAERS Case IDs 12215941, 12215948).***

IPMS Response

On July 3-5, 2019, IPMS responded with the following information:

- **Health Canada:** *Has not reviewed this safety signal and received a single report of PT Calciphylaxis.*
  - This was a duplicate report of **FAERS Case ID 6692877**, which was excluded from our case series due to insufficient case details.
- **Health Singapore:** *Has not reviewed this safety signal and we have not received any reports associated with cutaneous calcification.*
- **Medicines and Healthcare products Regulatory Agency (United Kingdom):** *"Nonuraemic calciphylaxis has been included as an important potential risk in the teriparatide Risk Management Plan since 2016. The most recent review of this potential risk was considered during the European assessment of the Periodic Safety Update Reports for teriparatide in May 2019. No further action was taken regarding non-uraemic calciphylaxis and*

teriparatide following this review. The MHRA have received no UK spontaneous cases of cutaneous calcification, including calciphylaxis that is associated with teriparatide use."

- **Medsafe (New Zealand):** *Has not reviewed this safety signal; 8 reports reported teriparatide as the suspect medicine, but none described cutaneous calcification.*
- **Swissmedic:** *Has received no reports of cutaneous calcification among 809 individual case safety report received so far associated with teriparatide exposure.*
- **Therapeutic Goods Administration (Australia):** *"As of June 24, 2019, the TGA has received one report of teriparatide exposure and dystrophic calcification from the sponsor of teriparatide. We have not yet reviewed the issue as a potential safety signal."* o This was a duplicate report of **FAERS Case ID 14355163**, which was included in our case series.

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/s/

JENNY J KIM
02/05/2020 11:23:20 AM

KAREN E KONKEL
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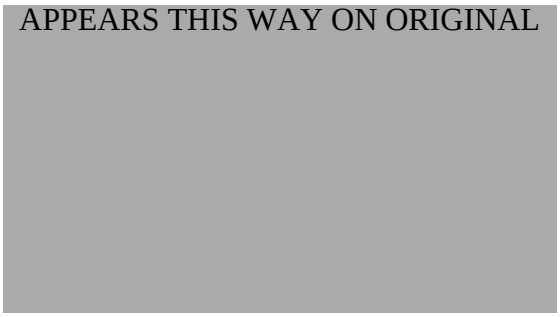
LYNDA V MCCULLEY
02/06/2020 03:36:20 PM

STEVEN C JONES
02/07/2020 09:38:09 AM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OLIVIA J EASLEY
11/15/2020 09:03:32 PM

THERESA E KEHOE
11/16/2020 07:23:07 AM

Medical Officer Memorandum to File

NDA 21318

Drug product: Forteo (teriparatide)

Re: Post-marketing reports of cutaneous calcification including calciphylaxis

On February 12, 2019, the Division of Pharmacovigilance II (DPV II) received an email literature alert from Embase of a citation entitled, *Worsening of soft tissue dystrophic calcification in an osteoporotic patient treated with teriparatide*.[1] The article by Htet et. al. described a 74-year-old male patient who experienced symptomatic worsening of previously stable dystrophic calcification four months after teriparatide initiation. Following discontinuation of teriparatide, the patient's symptoms resolved within one week.

DPV II evaluated this potential safety signal by searching the following sources for reports of cutaneous calcification associated with parathyroid hormone (PTH) agonists [Forteo (teriparatide) and Tymlos (abaloparatide)] and PTH product [Natpara (parathyroid hormone)]:

- Periodic safety reports submitted to FDA from September 13, 2015 through September 12, 2018
- FDA Adverse Event Reporting System (FAERS) reports and the medical literature through February 12, 2019.

DPV II also requested information from the European Medicines Agency and International Post Market Surveillance about their investigation of this potential safety signal.

According to a memorandum filed to DARRTS on February 7, 2020, DPV identified 15 cases with sufficient evidence to support teriparatide use as a contributory factor in development of new, or exacerbation of existing, cutaneous calcification. DPV II believes that teriparatide in concert with an underlying risk factor for cutaneous calcification (e.g., autoimmune disease or concomitant medications) can trigger this adverse event. Given the presence also of biologic plausibility, DPV II concludes that there is an association between teriparatide use and cutaneous calcification and recommends adding this safety signal to the Warnings and Precautions section of teriparatide product labeling.

Conclusion: DGE concurs with DPV II's recommendation.

Recommended Regulatory Action: The following comment should be conveyed to the applicant as an information request for NDA 021318 s054:

The Division has become aware of a potential association between teriparatide use and adverse events of cutaneous calcification, including calciphylaxis, in the setting of underlying risk factors for cutaneous calcification. The association is biologically plausible given teriparatide's mechanism of action.

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[1] Htet TD, Eisman JA, Elder GJ, et al. Worsening of soft tissue dystrophic calcification in an osteoporotic patient treated with teriparatide. *Osteoporos Int* 2018;29:517-8.

Add “Calciphylaxis” to section 5 of the FORTEO package insert submitted to Prior Approval Labeling Supplement 54. We suggest the following language:

Calciphylaxis
FORTEO has been associated with serious adverse event reports of calciphylaxis and worsening of previously stable cutaneous calcification in the post-marketing setting. All affected patients had underlying risk factors for development of calciphylaxis (e.g. underlying auto-immune disease, end stage renal disease, concomitant warfarin or systemic corticosteroid use). Discontinue FORTEO in patients who develop calciphylaxis or worsening of previously stable cutaneous calcification during treatment with FORTEO.

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/s/

OLIVIA J EASLEY
03/27/2020 04:27:30 PM

THERESA E KEHOE
03/30/2020 02:00:12 PM

NDA 21318 eCTD Seq 384 SD 1684
Prior Approval Labeling Supplement – Safety Labeling Change

Medical Officer's 45-Day Filing Memorandum

Application Letter Date: January 16, 2020

Prescription Drug User Fee Act (PDUFA) Goal Date: November 16, 2020

Product, route, dose: Forteo® (teriparatide), subcutaneous injection, 20 mcg daily

Background: FORTEO [teriparatide (rDNA origin) injection] is a recombinant human parathyroid hormone analogue that is approved for the following indications:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

In pre-license, non-clinical studies, teriparatide showed a higher incidence of osteosarcoma in rats (but not in monkeys) at a higher systemic exposure than in humans; and the risk appeared to be dose- and treatment duration-dependent. Since the bone metabolism in rats differs from that in humans, the relevance of the animal finding to humans is uncertain. There were no human cases of osteosarcoma identified in the pre-license clinical trials

Still, because of these findings in rats, product labeling included a boxed warning for the potential risk for osteosarcoma and a recommendation to limit lifetime use of Forteo® to two years or less since clinical safety and efficacy beyond that time had not been demonstrated. In addition, the Agency required that the sponsor examine the clinical risk of osteosarcoma with teriparatide use in post-marketing.

Since approval, Lilly has completed five post-marketing observational studies to fulfill this requirement:

(1) a case-series study in Europe, (study GHBX [1])
(2) a case-series study in the US, (study GHBX [b])
(3) a prospective patient registry in the U.S. (study GHBX 2.1)
(4) two claims based retrospective cohort studies in Medicare D and IQVIA Longitudinal Prescription Database (GHBX 2.2 and 2.3)

The Division of Epidemiology II (DEpi II) reviewed the results of these post-marketing studies in a memorandum dated May 3, 2019, and concluded and recommended the following:

- The two case series studies (GHBX[1] and GHBX[b]) did not identify a safety concern for osteosarcoma.
- The results of the case series studies should be added to the Adverse Reaction Section of labeling.

- The patient registry [GHBX 2.1], which enrolled 71,417 teriparatide users, identified no incident and do not suggest a risk for osteosarcoma. The registry is unlikely to meet its target sample size (of 1.7 million patient years) so the sponsor should be released from the registry requirement.

DBRUP and DEpi presented the findings from the post-marketing studies to the FDA Medical Policy and Program Review Council (MPPRC) on April 10, 2019. The MPRCC agreed that a boxed warning regarding risk of osteosarcoma was no longer necessary based on available data.

A type C meeting between Lilly and FDA occurred on July 26, 2019, to discuss changes to Forteo® labeling based on the GHBX program results. FDA advised the following:

- Discontinuation of study GHBX (2.1) is acceptable
- Lilly may submit a labeling supplement to remove the GHBX (2.1) registry information from labeling.
- removal of the boxed warning regarding risk of osteosarcoma is appropriate based on the additional post-marketing data
- (b) (5)
- FDA would consider modifying the 2-year limitation of use if adequate data showed continued benefit beyond two years in the desired population. BMD response after bisphosphonate use and BMD response after discontinuation of teriparatide should be shown. In addition, timing of BMD return to baseline after discontinuation of Forteo should be addressed. (b) (4)

Lilly submitted a prior approval labeling supplement request to remove references to the Forteo® Patient registry on November 25, 2019 (sequence 372/supporting document 1670/Supplement 53). That submission also contained the final GHBX (2.1) study report.

The current prior approval safety labeling supplement calls for the following major changes to the Forteo® US prescribing information (USPI):

1. Removal of the Boxed Warning regarding Osteosarcoma.
2. Modify the 2-year limitation of use to allow for longer duration of treatment in patients at high risk for fracture.
3. Modify the Warning regarding Osteosarcoma (b) (4) (b) (4) (b) (4)
4. Revise *Section 6.2 Post-marketing experience* to reflect the current status of the long-term osteosarcoma surveillance studies.

Data sources submitted in support of removal of the Boxed Warning are shown in Table 1.

Table 1. Studies Submitted in Support of Removal of Boxed Warning regarding Osteosarcoma

Study ID	Design	Status
Labeling Change 1: Removal of Boxed warning		
Post-marketing observational studies		
B3D-MC-GHBX(b)	US Case series initiated following 2002 approval of Forteo, identified cases of osteosarcoma among men and women ≥ 40 years of age and determined if any had a history of teriparatide treatment	Complete
B3D-MC-GHBX(1)	Initiated in Europe in 2004. 10-year surveillance study evaluated potential association between Forteo and osteosarcoma in adults using medical records	Complete Final study report submitted (Seq 316 on 10/12/18).
B3D-MC-GHBX(2.1)	Post-marketing requirement following approval of the glucocorticoid-induced osteoporosis indication n 2009. This was a voluntary registry of adult Forteo users in the US during a 10-year enrollment period.	Complete Final study report submitted (Seq 372 on 11/25/19).
B3D-MC-GHBX(2.2)	initiated in 2015 to compare the incidence of osteosarcoma among Forteo users and non-Forteo users by linking Medicare Part D and state cancer registry data.	Complete Final report submitted (seq 316 on 10/12/18)
B3D-MC-GHBX(2.3[b])	Initiated in 2015 to compare the incidence of osteosarcoma among Forteo users and non-users by linking state cancer registry data to large national pharmacy database data.	Complete Final report submitted (Seq 316 on 10/12/18).

Data to support the modification of the 2-year limitation of use are summarized in Table 2.

Table 2. Data Submitted to Support the Modification of the Two-Year Limitation of Use

Clinical Studies	Design	Status	Rationale for inclusion in this NDA submission
BMD response after teriparatide discontinuation			
B3D-MC-GHBJ	Multicenter, multinational, observational study to assess safety and effect of teriparatide after treatment discontinuation. Patients were included if they had participated in one of the following clinical studies of teriparatide: B3D-MC-GHAC, B3D-MC-GHAF, B3D-MCGHAH, B3D-MC-GHAJ, B3D-MC-GHAL, B3D-MC-GHAU, and B3D-MC-GHAV. A total of 1930 patients enrolled.	Complete Initially submitted to IND 48633 10/20/04, but re-submitted at DBRUP request to NDA 21318 Seq 388 on 2/18/20 Datasets submitted 2/26/20	The Applicant states that the study shows that lumbar spine BMD decreases in men and women after teriparatide discontinuation, but total hip BMD is maintained.
BMD effect after 2 years of continuous use			
B3D-EW-GHCA (EUROFORS)	Multi-center, prospective, open-label Phase 3-4 trial with two sub-studies in 868 post-menopausal women with severe osteoporosis. The objective was to compare the effect of 24 months of treatment with teriparatide with the effect of 12 months of teriparatide followed by 12 months of no active treatment on change in lumbar spine BMD	Complete Submitted to NDA 21318 Seq 371, PSUR 26	The Applicant states that this study supports absence of a plateau in BMD effect at 24 months of continuous teriparatide therapy
Efficacy and safety beyond 2 years of use			
B3D-US-GHBZ	Global, multicenter, randomized, double-blind, double-dummy, active comparator-controlled study with three study periods. The primary objective was to determine whether the increase from baseline to 18 months in lumbar spine BMD induced by teriparatide statistically significantly exceeded that with alendronate in men and women who had taken glucocorticoids for $\geq$3 months.	Complete Submitted to NDA 21318 Supplement 12 SD 191 on 5/29/08	Evaluation of BMD at 24 and 36 months were secondary objectives. The Applicant believes that this study supports continued efficacy of teriparatide beyond two years of use.
Lindsey, et. al. (1997)[1]	3-year randomized, controlled trial of the effect of teriparatide in post-menopausal women with osteoporosis taking hormone replacement therapy. Women were assigned to teriparatide	Published	The Applicant believes that this study supports continued efficacy of teriparatide beyond two years of use.

[1] Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, Dempster D, Cosman F. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet.* 1997;350(9077):550-555.

	25 mcg daily or placebo in addition to HRT for 3 years (n=34).		
Efficacy of Re-Treatment with Teriparatide			
Cosman, et. al. (2009)[2]	This was a follow-on study to an original study in which 126 women who had been taking alendronate for >1 year were randomized to continue alendronate alone or receive alendronate PLUS daily teriparatide or cyclic teriparatide (3-month cycles) for 15 months. Of the 72 patients who completed this initial study, 49 complete 12 months of follow-up on alendronate alone. At the conclusion of the first study, 32 patients, who remained at high risk of future fracture, were recruited into a re-treatment protocol. In the re-treatment protocol, subjects received a 15- month course of teriparatide 25 mcg/day along with continued alendronate therapy.	Published	The Applicant believes that this study supports that re-treatment with teriparatide has similar efficacy with respect to BMD increase as initial teriparatide treatment.
Finkelstein, et. al. (2009)[3]	Subjects previously participated in a 30-month randomized trial comparing the effects of alendronate (group 1), teriparatide (group 2), or both (group 3) on BMD and bone turnover in men and women with low BMD (phase 1). Subjects who completed phase 1 on their assigned therapy entered phase 2 (months 30–42), during which teriparatide was stopped in groups 2 and 3. Teriparatide was administered to all subjects during months 42 to 54 (phase 3). Patients were not required to be high risk for fracture.	Published	The Applicant notes that the skeletal response to teriparatide was attenuated during re-treatment. However, the enrolled subjects were not high-risk for fracture (T-score $\leq$-1) which the Applicant believes supports the premise for re-treatment only in high-risk patients.
Mana et. al. (2017)[4]	This study evaluated the BMD response to a second cycle of teriparatide in three patients with severe osteoporosis.	Published	

[2] Cosman F., Nieves JW, et. al. Retreatment with Teriparatide One Year after the first Teriparatide Course in patients on Continued long-term alendronate. J Bone Miner Res 2009;24:1110–1115.

[3] Finkelstein JS, Wyland JJ, Leder BZ, Burnett-Bowie SM, Lee H, Jüppner H, Neer RM. Effects of Teriparatide Retreatment in Osteoporotic Men and Women. *J Clin Endocrinol Metab.* 2009;94(7):2495–2501.

[4] Mana DL, Zanchetta MB, Zanchetta JR. Retreatment with teriparatide: our experience in three patients with severe secondary osteoporosis. *Osteoporos Int.* 2017;28(4):1491–1494.

In addition to the study reports summarized in tables 1 and 2, the sponsor has included the following data to support the labeling changes:

- Review of cumulative post-marketing safety data to evaluate spontaneously reported cases of osteosarcoma
- Review of available published literature to address questions raised by FDA in support of the proposed modification to the 2 year limit of use.
- Review of relevant safety information pertaining to osteosarcoma derived from nonclinical studies, clinical trials, post-marketing pharmaco-epidemiological safety studies, published scientific literature, and spontaneously reported adverse events (AEs) from post-marketing experience cumulatively through 30 September 2019. It comprises specific data on the population previously exposed to external beam radiation therapy that used Forteo in an off-label indication.

The clinical filing checklist is found in Appendix 1.

Conclusion: The adequacy of the data to support the proposed labeling changes will be a review issue. Data supporting the efficacy of chronic treatment or re-treatment with teriparatide are limited by varying study designs and patient populations, and generally small sample sizes.

The application may be filed from a clinical standpoint. Additional data will be requested from the Applicant, but these do not preclude filing of the application.

Recommended Regulatory Action:

Send the following comments with the 74-day filing letter:

1. Submit datasets and narrative summaries for deaths for the second 18 month portion of Study GHBZ.
2. Submit financial disclosure information for studies GHBJ and GHBZ.

Appendix 1.

NDA/BLA Number: 21318 Supplement 54 | Applicant: Eli Lilly | Stamp Date: 01/16/2020

Drug Name: Forteo (teriparatide injection) | NDA/BLA Type: Prior Approval Labeling Supplement

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?			x	
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	

	Content Parameter	Yes	No	NA	Comment
10.	Has the applicant submitted a benefit-risk analysis for the product?	x			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			x	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			x	
14.	Describe the scientific bridge (e.g., BA/BE studies)			x	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)?			x	
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			x	
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	Efficacy studies submitted in support of modifying the two-year limitation of use are of variable design and their adequacy in support of the proposed change will be a review issue.
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	There were no previous agreements regarding efficacy endpoints.
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		Efficacy findings in support of modifying the two-year limitation of use include domestic and foreign data sources and this is acceptable

	Content Parameter	Yes	No	NA	Comment
					for the proposed changes.

SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[5]) been exposed at the dosage (or dosage range) believed to be efficacious?		x		The adequacy of exposure beyond 2 years of use will be a review issue.
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
25.	Has the applicant submitted the coding dictionary[6] used for mapping investigator verbatim terms to preferred terms?		x		This can be requested later if needed.
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			This submission includes a thorough assessment of osteosarcoma risk.
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		x		The sponsor should submit these for study GHBZ.
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			See medical officer filing memorandum for a complete list of studies submitted to

[5] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[6] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

					support the labeling changes.
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self-selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?			x	Forteo labeling is already compliant with PLLR format.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		The modification of the two-year limitation of use relies in part on clinical data obtained outside the U.S. which is acceptable.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		x		The sponsor should submit datasets for study GHBZ
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		x		

37.	Are all datasets to support the critical safety analyses available and complete?		x		
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		x		
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		x		CRFs were not submitted but they are not necessary and can be requested individually if needed.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?		x		Financial disclosure for study GHBJ and GHBZ cannot be located.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

Reviewing Medical Officer	Date
Clinical Team Leader	Date

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/s/

OLIVIA J EASLEY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021318Orig1s054

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 10, 2020
To:	Meghna Jairath Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, PharmD. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	FORTEO (teriparatide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 021318
Supplement Number:	S-054
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On January 16, 2020, Eli Lilly and Company submitted for the Agency's review a Prior Approval Supplement-Efficacy for Supplemental New Drug Application (sNDA) 021318/S-054 for FORTEO (teriparatide injection), for subcutaneous use. The purpose of this sNDA is to propose the removal of the Boxed Warning, the addition of observational study results, and the modification of the 2-year limit of use statement and the osteosarcoma warning.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of General Endocrinology (DGE) on February 12, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for FORTEO (teriparatide injection), for subcutaneous use.

2 MATERIAL REVIEWED

- Draft FORTEO (teriparatide) MG received on January 16, 2020, and received by DMPP and OPDP on November 5, 2020.
- Draft FORTEO (teriparatide) Prescribing Information (PI) received on January 16, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 5, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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ELVY M VARGHESE
11/10/2020 08:18:13 AM

MARCIA B WILLIAMS
11/10/2020 08:22:03 AM

LASHAWN M GRIFFITHS
11/10/2020 08:39:33 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 9, 2020

To: Olivia J. Easley, M.D.
Division of General Endocrinology (DGE)

Meghna M. Jairath, PharmD.
Regulatory Project Manager, DGE

From: Elvy Varghese, PharmD.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD.
Team Leader, OPDP

Subject: OPDP Labeling Comments for FORTEO® (teriparatide injection) for subcutaneous use

NDA: 021318/ S-054

In response to DGE's consult request dated February 12, 2020, OPDP has reviewed the proposed product labeling (PI) for FORTEO® (teriparatide injection) for subcutaneous use (Forteo). This efficacy supplement (S-054) is intended to make updates to remove the Boxed Warning For Potential Risk of Osteosarcoma and W&P 5.2 Treatment Duration based on the review of postmarketing data. Updates were also made to labeling language and layout to be consistent with other osteoporosis products.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DGE (Meghna Jairath) on November 5, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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ELVY M VARGHESE
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 27, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 021318/S-54
Product Name and Strength:	Forteo (teriparatide) injection, 600 mcg/2.4 mL (250 mcg/ mL
Applicant/Sponsor Name:	Eli Lilly and Company
OSE RCM #:	2020-195-1
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 26, 2020 for Forteo. Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Forteo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that were request by the Office of Pharmaceutical Quality (OPQ) on October 6, 2020 and October 16, 2020.

2 CONCLUSION

The Applicant implemented all of the recommendations from OPQ and we do not have any additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 26, 2020

Container label

Carton labeling

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/s/

MELINA N FANARI
10/27/2020 11:07:35 AM

SEVAN H KOLEJIAN
10/27/2020 11:46:12 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 27, 2020
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 021318/S-54
Product Name and Strength:	Forteo (teriparatide) injection, 600 mcg/2.4 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	January 16, 2020
OSE RCM #:	2020-195
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

Eli Lilly and Company submitted an Efficacy supplement (S-54) for Forteo (teriparatide) injection to remove the Boxed Warning, add observational study results, and modify the 2-year limit of use and osteosarcoma warning in the Prescribing Information (PI) and Medication Guide. Subsequently, the Division of General Endocrinology (DGE) requested that we review the proposed revisions to the Forteo PI and Medication Guide for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On November 26, 2002, Forteo (teriparatide) injection was approved under NDA 021318 for osteoporosis with a post marketing study commitment to investigate any association between Forteo and osteosarcoma in humans. On July 22, 2009, Forteo (teriparatide) injection received approval for the Prior Approval Efficacy supplement (S-012) that expanded the indications, and the duration of the study was extended from 10 years to 15 years and the Agency converted the post marketing study commitment to a post marketing study requirement (PMR). Following the completion of the osteosarcoma post-marketing program, the Sponsor proposes to change the osteosarcoma-related warnings throughout the PI.

On July 26, 2019, Eli Lilly and Company, and the Agency held a Type C meeting to discuss the progress of the PMRs and potential labeling changes for Forteo. Thus, on January 16, 2020, Eli Lilly and Company submitted this supplement (S-54) with proposed labeling changes including the removal of the Boxed Warning, the addition of the GHBX observational study results, and modification of the 2-year limit of use and the osteosarcoma warning.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other: Cases found during routine post-marketing surveillance	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed revisions to the Forteo Prescribing Information (PI), and Medication Guide to identify risks that may lead to medication errors. Our review of Section 2 (Dosage and Administration) and Section 17 (Patient Counseling Information) of the PI, and the Medication Guide for Forteo notes that these sections have been updated appropriately to provide for the information proposed in this efficacy supplement and the proposed revisions are acceptable from a medication safety perspective.

We note there are no changes proposed to the content within Section 3 (Dosage Forms and Strength), and Section 16 (How Supplied/Storage and Handling) of the PI for Forteo.

As part of our review, we considered whether the changes proposed in this supplement would require revisions to the carton labeling, or container labels to ensure consistency and decrease risk of confusion and medication errors. We note no changes were proposed or required to the name, strength, or route of administration. As such, our evaluation did not identify any necessary revisions to the container label or carton labeling as a result of the changes proposed in this supplement.

During our routine post-marketing surveillance activities for Forteo, we identified medication error cases (n =3) that report patients who received the wrong needle size (See Appendix E). No contributing factors or outcomes were reported in any of the cases. One case (n = 1) reported that the "manufacturer recommends BD 31g 5mm needles." However, the patient was using "BD 32g 4 mm" needles. Another case (n = 1) reported a patient, who noticed her Forteo was disappearing quicker since starting to use the needle size 31 gauge 5 mm instead of the 32 gauge 4 mm pen needles she previously used; as a result, the patient thought she had not been receiving her full dose of Forteo when she used the 4 mm pen needles. The third case (n = 1), reported a patient is using nontraditional pen needles (4 mm) with her Forteo. We note that the Forteo labeling does not describe the recommended pen needle sizes (that is, diameter (gauge) and length (mm or inches)). Additionally, although the Medication Guide and carton labeling describe that pen needles are not provided, we note that the Forteo PI does not state that needles are not included, and therefore, does not alert prescribers that they need to write for a separate prescription for the pen needles. Our evaluation identified that revisions to the carton and PI labeling may help mitigate these error types. We communicated our post-market findings and concern about patients receiving the wrong needle size to the Division on May 21, 2020. (b) (5) [redacted]. We defer to the Division to determine whether labeling revisions are warranted.

5 CONCLUSION

Our evaluation of the proposed revisions to the Forteo PI and medication guide did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time. However, we defer to the Division to determine whether labeling revisions are needed, in response to postmarketing medication errors, to clarify the recommended needle size.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Forteo that Eli Lilly and Company submitted on January 16, 2020.

Table 2. Relevant Product Information for Forteo	
Initial Approval Date	November 26, 2002
Active Ingredient	teriparatide
Indication	• Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
Route of Administration	subcutaneously
Dosage Form	Injection
Strength	600 mcg/2.4 mL
Dose and Frequency	20 mcg once daily
How Supplied	The FORTEO delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 0002-8400-01
Storage	• The FORTEO delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. • Recap the delivery device when not in use to protect the cartridge from physical damage and light. • During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator. • Do not freeze. Do not use FORTEO if it has been frozen.
Container Closure	multi dose prefilled pen

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 13, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Forteo, teriparatide, NDA 021318, 21-318. Our search identified one previous review[a] and one open aims assignment, and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. Summary of Previous DMEPA Reviews for Forteo

OSE RCM #	Review Date	Summary of Recommendations
2008-89	March 14, 2008	We reviewed the proposed container label, carton labeling, and Instructions for Use for Forteo (b) (4) [Teriperatide (rDNA origin)] Injection, 20 mcg. We provided recommendations to the Sponsor.
(b) (4)	N/A (review in progress)	Recommendations are not available yet because this review is in progress.

[a] Arnwine K. Label and Labeling Review for Forteo (NDA 021318/S-016). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2008 MAR 14. RCM No.: 2008-89.

APPENDIX E. Line Listing of Wrong Technique Medication Errors with Forteo

Source	Case #	Report Year	Narrative	Root Cause	Adverse Event(s)	Suggested Mitigation
Direct report	16332744	2019	"Patient is using non traditional pen needles (4 mm) with her Forteo."	No root cause reported.	Not reported.	Not reported.
Direct report	16431398	2019	"Patient states that she noticed her Forteo medication is dissapearing quicker since beginning to use 31G 3/16in (5mm) pen needles rather than 32G 5/2 in (4mm) pen needles. The patient thinks that while she was using the 4mm pen needles, she wasn't getting her full dose of Forteo. Patient said she already discussed this with her doctor. Provided patient with manufacturer phone number."	No root cause reported.	Not reported.	Not reported.
Direct report	17164000	2019	"manufacturer recommends BD 31g 5mm needles to be used with Forteo, patient states she has been using BD 32g 4mm needles to inject for the last 6 months and has never cleared this with her doctor"	No root cause reported.	Not reported.	Not reported.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Forteo labels and labeling submitted by Eli Lilly and Company on January 16, 2020.

- Prescribing Information (image not shown), available from: \\cdsesub1\evsprod\nda021318\0384\m1\us\proposed-uspi.docx
- Medication Guide (image not shown), available from: \\cdsesub1\evsprod\nda021318\0384\m1\us\proposed-med-guide.docx

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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