CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-318/S-016

Trade Name: Forteo 3ml Cartridge

Generic Name: teriparatide

Sponsor: Eli Lilly and Company

Approval Date: June 25, 2008

Purpose: Provides for a new pre-filled pen-injector for use with teriparatide cartridges manufactured with a lower nominal fill volume at the currently approved facility in Fegersheim, France

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APPLICATION NUMBER:

21-318/S-016

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-318/S-016

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-318/S-016

Eli Lilly and Company
Attention: Jean Wright, DVM
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

SUPPLEMENT APPROVAL

Dear Dr. Wright:

Please refer to your supplemental new drug application dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Forteo (teriparatide) 3ml Cartridge.

We acknowledge receipt of your submissions dated February 12, March 28, and June 20, 2008.

This supplemental new drug application provides for a new pre-filled pen-injector for use with teriparatide cartridges manufactured with a lower nominal fill volume at the currently approved facility in Fegersheim, France.

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 text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-318/S016**."

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 20, 2008, submission containing final printed carton and container labels.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100

5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

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

If you have any questions, call Oluchi Elekwachi, PharmD, MPH, Regulatory Project Manager, at (301) 796-1207.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Approved Labeling for Forteo PI, Medguide, User Manual, Carton and Container

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks

6/25/2008 05:19:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-318/S-016

LABELING

3.0ANL 9400 FSAMP

FORTEO®

teriparatide (rDNA origin) injection

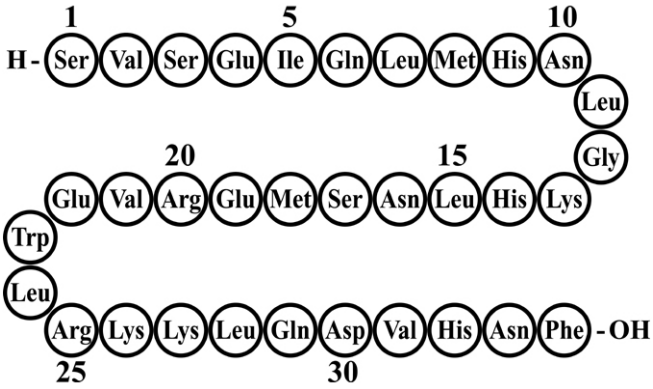
WARNING

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) (*see* WARNINGS *and* PRECAUTIONS, Carcinogenesis).

DESCRIPTION

FORTEO® [teriparatide (rDNA origin) injection] contains recombinant human parathyroid hormone (1-34), [rhPTH(1-34)], which has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



Teriparatide (rDNA origin) is manufactured by Eli Lilly and Company 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 disposable pen device for subcutaneous injection. Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg 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.

Each cartridge pre-assembled into a pen device delivers 20 mcg of teriparatide per dose each day for up to 28 days.

See accompanying User Manual: Instructions for Use.

CLINICAL PHARMACOLOGY

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.

Human Pharmacokinetics

Teriparatide is extensively absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80-mcg doses. The rates of absorption and elimination are rapid. 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.

Systemic clearance of teriparatide (approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25% to 50%. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer half-life following subcutaneous administration reflects the time required for absorption from the injection site.

No metabolism or excretion studies have been performed with teriparatide. However, the mechanisms of metabolism and elimination of PTH(1-34) and intact PTH have been extensively described in published literature. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

Special Populations

Pediatric — Pharmacokinetic data in pediatric patients are not available (*see* WARNINGS).

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

Gender — Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than women, the recommended dose for both genders is 20 mcg/day.

Race — The populations included in the pharmacokinetic analyses were 98.5% Caucasian. The influence of race has not been determined.

Renal insufficiency — No pharmacokinetic differences were identified in 11 patients with mild or moderate renal insufficiency [creatinine clearance (CrCl) 30 to 72 mL/min] administered a single dose of teriparatide. In 5 patients with severe renal insufficiency (CrCl<30 mL/min), 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 (*see* PRECAUTIONS).

Heart failure — No clinically relevant pharmacokinetic, blood pressure, or pulse rate differences were identified in 13 patients with stable New York Heart Association Class I to III heart failure after the administration of two 20-mcg doses of teriparatide.

Hepatic insufficiency — 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. No studies have been performed in patients with hepatic impairment.

Drug Interactions

Hydrochlorothiazide — In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 mcg. 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 teriparatide on serum calcium levels has not been studied.

Furosemide — In a study of 9 healthy people and 17 patients with mild, moderate, or severe renal insufficiency (CrCl 13 to 72 mL/min), coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important.

Human Pharmacodynamics

Effects on mineral metabolism

Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (eg, increases serum calcium and decreases serum phosphorus).

Serum calcium concentrations

When teriparatide 20 mcg is administered once daily, the serum calcium concentration increases 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 begins to decline approximately 6 hours after dosing and returns 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 (teriparatide 20 mcg) was 2.42 mmol/L (9.68 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 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 [2.64 mmol/L (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 upper limit of normal on consecutive 4- to 6-hour post-dose measurements was 3.0% 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 2.35 mmol/L (9.44 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6.0% of men treated with FORTEO daily had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (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 upper limit of normal on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Although calcium supplements and/or FORTEO doses could have been reduced in these men, only calcium supplementation was reduced (*see* PRECAUTIONS *and* ADVERSE EVENTS).

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 injection was increased by 0.09 to 0.14 mmol/L (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 >2.76 mmol/L (11.0 mg/dL), and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >2.76 mmol/L (11.0 mg/dL). The highest serum calcium reported was 3.12 mmol/L (12.5 mg/dL). None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

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 4.8 mmol/day (190 mg/day) at 6 months and 4.2 mmol/day (170 mg/day) at 12 months. These levels were 0.76 mmol/day (30 mg/day) and 0.30 mmol/day (12 mg/day) higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 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 5.6 mmol/day (220 mg/day) at 1 month and 5.3 mmol/day (210 mg/day) at 6 months. These levels were 0.50 mmol/day (20 mg/day) higher and 0.20 mmol/day (8.0 mg/day) lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 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 (<0.74 mmol/L or 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.

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.

CLINICAL STUDIES

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, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis (FORTEO 20 mcg, n=541).

This multicenter study was performed in the US and 16 other countries. All women received 1000 mg of calcium per day and at least 400 IU of vitamin D per day. Baseline and endpoint spinal radiographs were evaluated using the semiquantitative scoring method of Genant et al [*J Bone Miner Res* 1993;8(9):1137-48]. 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. 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.

Table 1. 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 — Table 2 shows the effect of FORTEO on the risk of nonvertebral 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%.

Table 2. Effects of FORTEO on Risk of New Nonvertebral Fractures in Postmenopausal Women with Osteoporosis

	FORTEO[a] N=541	**Placebo[a]** N=544
Skeletal site		
Wrist	2 (0.4%)	7 (1.3%)
Ribs	3 (0.6%)	5 (0.9%)
Hip	1 (0.2%)	4 (0.7%)
Ankle/Foot	1 (0.2%)	4 (0.7%)
Humerus	2 (0.4%)	2 (0.4%)
Pelvis	0	3 (0.6%)
Other	6 (1.1%)	8 (1.5%)
Total	14 (2.6%)[b]	30 (5.5%)

[a] Data shown as number (%) of women with fractures.
[b] p<0.05 compared with placebo.

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).

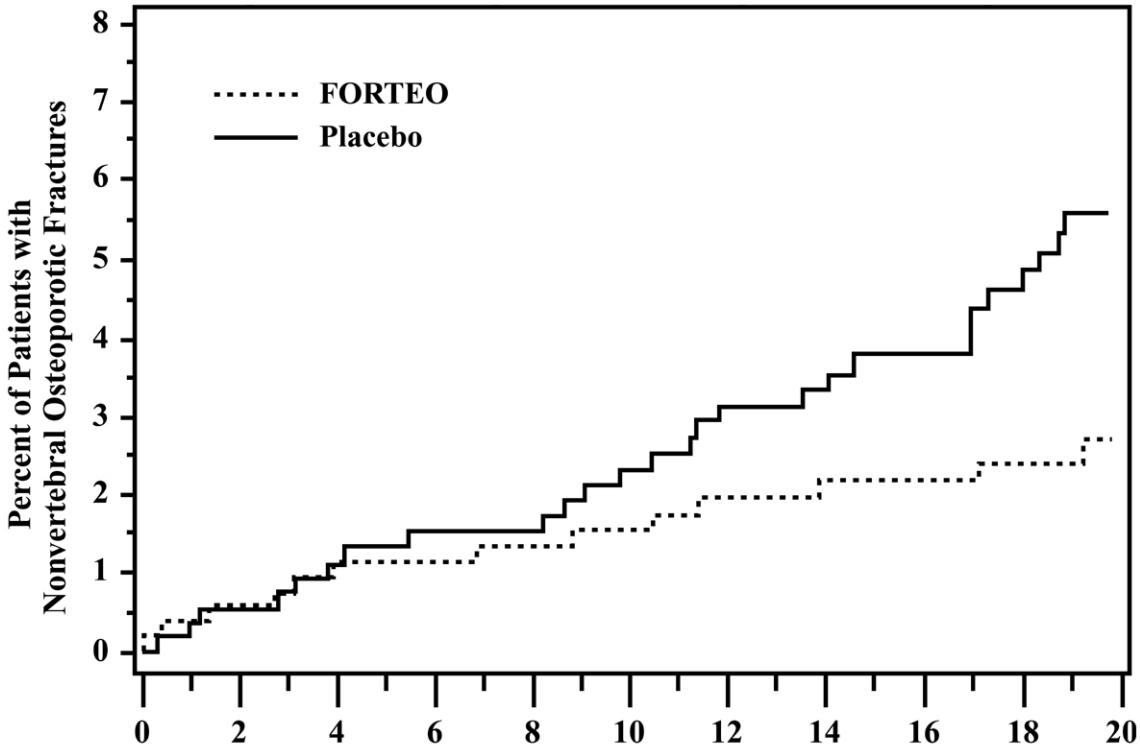


Figure 1. Cumulative percentage of postmenopausal women with osteoporosis sustaining new nonvertebral osteoporotic fractures.*

* This graph includes all fractures listed above in Table 2.

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, as shown in Figure 2.

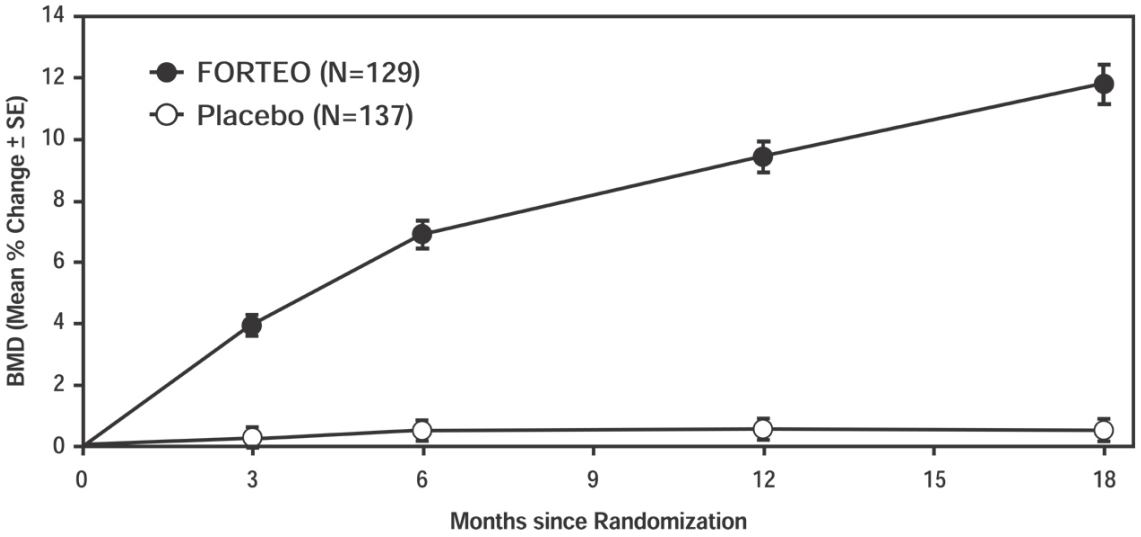


Figure 2. Time course of change in lumbar spine BMD in postmenopausal women with osteoporosis treated with FORTEO vs placebo* (women with data available at all time points).

* p<0.001 for FORTEO compared with placebo at each post-baseline time point

Postmenopausal women with osteoporosis who were treated with FORTEO also had statistically significant increases in BMD at the femoral neck, total hip, and total body (*see* Table 3).

Table 3. Mean Percent Change in BMD from Baseline to Endpoint* in Postmenopausal Women with Osteoporosis, Treated with FORTEO or Placebo

	FORTEO N=541	**Placebo** N=544
Lumbar spine BMD	9.7[a]	1.1
Femoral neck BMD	2.8[b]	-0.7
Total hip BMD	2.6[b]	-1.0
Trochanter BMD	3.5[b]	-0.2
Intertrochanter BMD	2.6[b]	-1.3
Ward's triangle BMD	4.2[b]	-0.8
Total body BMD	0.6[b]	-0.5
Distal 1/3 radius BMD	-2.1	-1.3
Ultradistal radius BMD	-0.1	-1.6

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

Figure 3 shows the cumulative distribution of the percentage change from baseline of lumbar spine BMD for the FORTEO and placebo groups. FORTEO treatment increased lumbar spine BMD from baseline in 96% of postmenopausal women treated (*see* Figure 3). Seventy-two percent of patients treated with FORTEO achieved at least a 5% increase in spine BMD, and 44% gained 10% or more.

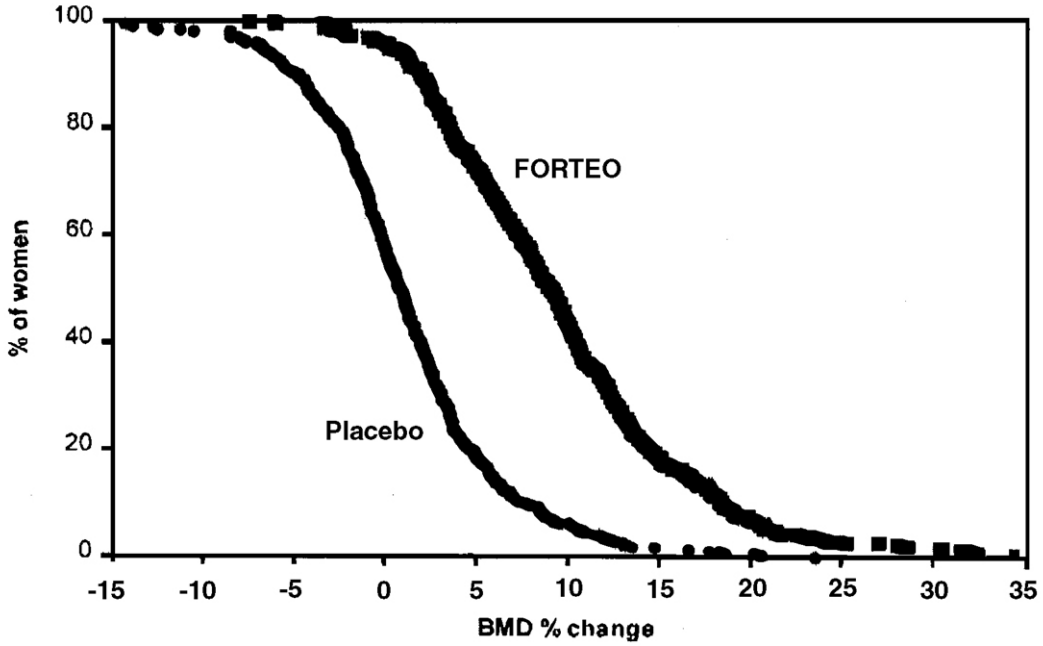


Figure 3. Percent of postmenopausal women with osteoporosis attaining a lumbar spine BMD percent change from baseline at least as great as the value on the x-axis (median duration of treatment 19 months).

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 teriparatide 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 teriparatide 20 or 40 mcg/day. Normal mineralization was observed with no evidence of cellular toxicity. The new bone formed with teriparatide was of normal quality (as evidenced by the absence of woven bone and marrow fibrosis).

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, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis (FORTEO 20 mcg, n=151). This multicenter efficacy study was performed in the US and 10 other countries. All men received 1000 mg of calcium per day 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.

Table 4. Mean Percent Change in BMD from Baseline to Endpoint* 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[a]	0.5
Femoral neck BMD	1.5[b]	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

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

Figure 4 shows the cumulative distribution of the percentage change from baseline of lumbar spine BMD for the FORTEO and placebo groups. 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.

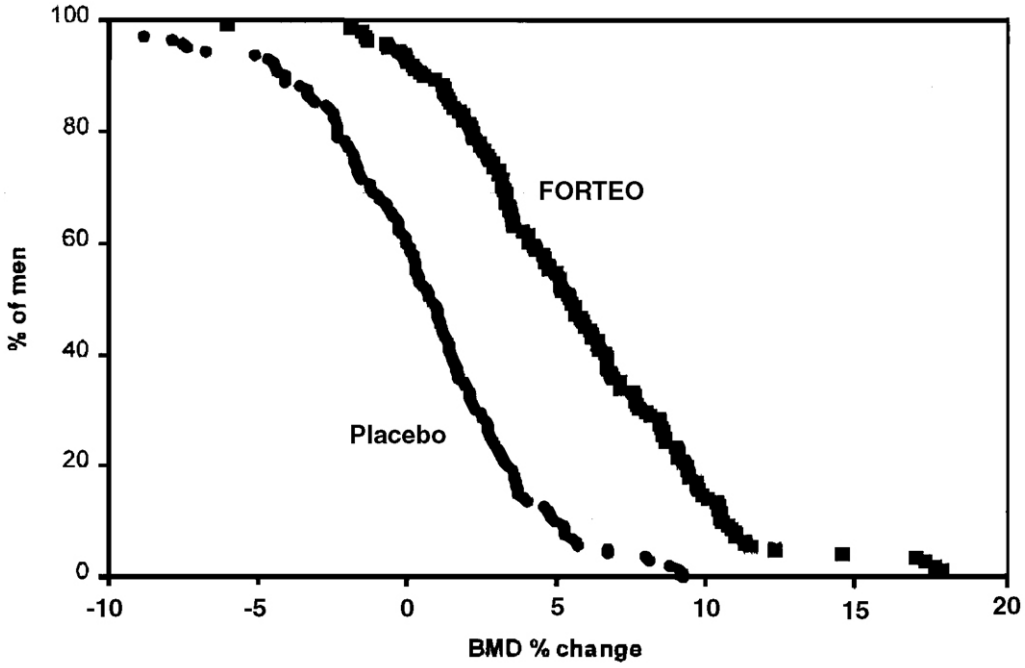


Figure 4. Percent of men with primary or hypogonadal osteoporosis attaining a lumbar spine BMD percent change from baseline at least as great as the value on the x-axis (median duration of treatment 10 months).

INDICATIONS AND USAGE

FORTEO is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment (*see* BLACK BOX WARNING). In postmenopausal women with osteoporosis, FORTEO increases BMD and reduces the risk of vertebral and nonvertebral fractures.

FORTEO is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment (*see* BLACK BOX WARNING). In men with primary or hypogonadal osteoporosis, FORTEO increases BMD. The effects of FORTEO on risk for fracture in men have not been studied.

- FORTEO reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.
- FORTEO reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
- FORTEO increases vertebral and femoral neck BMD in postmenopausal women with osteoporosis and in men with primary or hypogonadal osteoporosis.
- The effects of FORTEO on fracture risk have not been studied in men.

CONTRAINDICATIONS

FORTEO should not be given to patients with hypersensitivity to teriparatide or to any of its excipients.

WARNINGS

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration (*see* BLACK BOX WARNING *and* PRECAUTIONS; Carcinogenesis).

The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with FORTEO:

- Paget's disease of bone. FORTEO should not be given to patients with Paget's disease of bone. Unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone.
- Pediatric populations. FORTEO has not been studied in pediatric populations. FORTEO should not be used in pediatric patients or young adults with open epiphyses.
- Prior external beam or implant radiation therapy involving the skeleton. FORTEO should not be given to such patients.

Patients with bone metastases or a history of skeletal malignancies should be excluded from treatment with FORTEO.

Patients with metabolic bone diseases other than osteoporosis should be excluded from treatment with FORTEO.

FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should be excluded from treatment with FORTEO because of the possibility of exacerbating hypercalcemia.

PRECAUTIONS

General

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years is not recommended.

In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Hypotension

In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed infrequently. Typically, an event began within 4 hours of dosing and spontaneously resolved 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.

Concomitant treatment with digitalis

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). However, sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, FORTEO should be used with caution in patients taking digitalis.

Hepatic, renal, and cardiac

Limited information is available to evaluate safety in patients with hepatic, renal, and cardiac disease.

Information for Patients

For safe and effective use of FORTEO, the physician should inform patients about the following:

General

Patients should read the *Medication Guide* and *User Manual* provided with the delivery device (pen) before starting therapy with FORTEO and re-read them each time the prescription is renewed.

Osteosarcomas in rats

Patients should be made aware that FORTEO caused osteosarcomas in rats and that the clinical relevance of these findings is unknown.

Orthostatic hypotension

FORTEO should be administered initially under circumstances where the patient can immediately sit or lie down if symptoms occur. Patients should be instructed that if they feel lightheaded or have palpitations after the injection, they should sit or lie down until the symptoms resolve. If symptoms persist or worsen, patients should be instructed to consult a physician before continuing treatment (*see* PRECAUTIONS, General).

Hypercalcemia

Although symptomatic hypercalcemia was not observed in clinical trials, physicians should instruct patients to contact a health care provider if they develop persistent symptoms of hypercalcemia (ie, nausea, vomiting, constipation, lethargy, muscle weakness).

Use of the delivery device (pen)

Patients should be instructed on how to properly use the delivery device (refer to *User Manual*), properly dispose of needles, and be advised not to share their pens with other patients.

Other osteoporosis treatments

Patients should be informed regarding the roles of supplemental calcium and/or vitamin D, weight-bearing exercise, and modification of certain behavioral factors such as cigarette smoking and/or alcohol consumption.

Laboratory Tests

Serum calcium — FORTEO transiently increases serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. By 16 hours post-dose, serum calcium generally has returned to or near baseline. These effects should be kept in mind because serum calcium concentrations observed within 16 hours after a dose may reflect the pharmacologic effect of teriparatide. Persistent hypercalcemia was not observed in clinical trials with FORTEO. If persistent hypercalcemia is detected, treatment with FORTEO should be discontinued pending further evaluation of the cause of hypercalcemia.

Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO (*see* WARNINGS).

Urinary calcium — FORTEO increases urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo (*see* CLINICAL PHARMACOLOGY, Human Pharmacodynamics).

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. Long-term evaluation of patients with severe renal insufficiency, patients undergoing acute or chronic dialysis, or patients who have functioning renal transplants has not been performed.

Serum uric acid — FORTEO increases serum uric acid concentrations. In clinical trials, 2.8% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 0.7% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

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 systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans 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 doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day 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.

The relevance of these rat findings to humans is uncertain.

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).

Pregnancy

Pregnancy Category C — In pregnant rats given subcutaneous teriparatide doses up to 1000 mcg/kg/day, there were no findings. In pregnant mice given subcutaneous doses of 225 or 1000 mcg/kg/day (≥60 times the human dose based on surface area, mcg/m^2) from gestation Day 6 through 15, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib).

Developmental effects in a perinatal/postnatal study in pregnant rats given subcutaneous doses of teriparatide from gestation Day 6 through postpartum Day 20 included mild growth retardation in female offspring at doses ≥225 mcg/kg/day (≥120 times the human dose based on surface area, mcg/m^2), and in male offspring at 1000 mcg/kg/day (540 times the human dose based on surface area, mcg/m^2). There was also reduced motor activity in both male and female offspring at 1000 mcg/kg/day. There were no developmental or reproductive effects in mice or rats at a dose of 30 mcg/kg (8 or 16 times the human dose based on surface area, mcg/m^2). The effect of teriparatide treatment on human fetal development has not been studied. FORTEO is not indicated for use in pregnancy.

Nursing Mothers

Because FORTEO is indicated for the treatment of osteoporosis in postmenopausal women, it should not be administered to women who are nursing their children. There have been no clinical studies to determine if teriparatide is secreted into breast milk.

Pediatric Use

The safety and efficacy of FORTEO have not been established in pediatric populations. FORTEO is not indicated for use in pediatric patients (*see* WARNINGS).

Geriatric Use

Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No significant differences in bone response or adverse reactions were seen in geriatric patients receiving FORTEO as compared with younger patients. Nonetheless, as with many medications, elderly patients may have greater sensitivity to the adverse effects of FORTEO.

ADVERSE EVENTS

The safety of teriparatide has been evaluated in 24 clinical trials that enrolled over 2800 women and men. Four long-term Phase 3 clinical trials included 1 large placebo-controlled, double-blind, multinational trial with 1637 postmenopausal women; 1 placebo-controlled, double-blind, multinational trial with 437 men; and 2 active-controlled trials including 393 postmenopausal women. Teriparatide doses ranged from 5 to 100 mcg/day in short-term trials and 20 to 40 mcg/day in the other trials. A total of 1943 of the patients studied received teriparatide, including 815 patients at 20 mcg/day and 1107 patients at 40 mcg/day. In the clinical trials, a total of 1432 patients were treated with teriparatide for 3 months to 2 years, of whom 1137 were treated for greater than 1 year (500 at 20 mcg/day and 637 at 40 mcg/day). The maximum duration of treatment was 2 years. Adverse events associated with FORTEO usually were mild and generally did not require discontinuation of therapy.

In the two Phase 3 placebo-controlled clinical trials in men and postmenopausal women, early discontinuation due to adverse events occurred in 5.6% of patients assigned to placebo and 7.1% of patients assigned to FORTEO. Reported adverse events that appeared to be increased by FORTEO treatment were dizziness and leg cramps.

Table 5 lists adverse events that occurred in the two Phase 3 placebo-controlled clinical trials in men and postmenopausal women at a frequency ≥2.0% in the FORTEO groups and in more FORTEO-treated patients than in placebo-treated patients, without attribution of causality.

Table 5. 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

Serum calcium — FORTEO transiently increases 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 1.5% of women and none of the men treated with placebo to 11.1% of women and 6.0% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3.0% of women and 1.3% of men.

Immunogenicity — In a large clinical trial, antibodies that cross-reacted with teriparatide were detected in 2.8% of women receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions, allergic reactions, effects on serum calcium, or effects on BMD response.

Postmarketing Reports

Since market introduction, adverse events reported have included:

- Possible allergic events soon after injection: acute dyspnea, oro/facial edema, generalized urticaria, chest pain (less than 1 in 1000 patients treated).

- Hypercalcemia greater than 2.76 mmol/L (11 mg/dL) (less than 1 in 100 patients treated); hypercalcemia greater than 3.25 mmol/L (13 mg/dL) (less than 1 in 1000 patients treated).
- Injection site and injection technique events including pain, swelling, erythema, localized bruising, pruritus and minor bleeding at the injection site (less than 1 in 30 patients treated). These usually have been mild and transient.
- Muscle spasms, such as of the leg or back, are reported commonly (between 1 and 10 patients per 100 patients treated), sometimes shortly after the first dose. Serious back spasms have been reported very rarely (less than 1 in 10,000 patients treated).

OVERDOSAGE

Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur.

In postmarketing spontaneous reports, there have been cases of medication error in which the entire contents (up to 800 mcg) of the FORTEO delivery device have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

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).

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

DOSAGE AND ADMINISTRATION

FORTEO should be administered as a subcutaneous injection into the thigh or abdominal wall. The recommended dosage is 20 mcg once a day.

FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (*see* PRECAUTIONS, Information for the Patient).

FORTEO is a clear and colorless liquid. Do not use if solid particles appear or if the solution is cloudy or colored. The delivery device (pen) used to administer FORTEO should not be used past the stated expiration date.

No data are available on the safety or efficacy of intravenous or intramuscular injection of FORTEO.

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years is not recommended.

INSTRUCTIONS FOR PEN USE

Patients and caregivers who administer FORTEO should receive appropriate training and instruction on the proper use of the FORTEO delivery device from a qualified health professional. It is important to read, understand, and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing. Each FORTEO delivery device can be used for up to 28 days, including the first injection from the pen. After the 28-day use period, discard the FORTEO delivery device, even if it still contains some unused solution. Never share a FORTEO delivery device.

STORAGE

The FORTEO delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. Recap the pen 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.

HOW SUPPLIED

The FORTEO delivery device is available in the following:

- 3 mL prefilled pen delivery device NDC 0002-8971-01 (MS8971)
- 2.4 mL prefilled pen delivery device NDC 0002-8400-01 (MS8400).

Literature revised Month dd, yyyy

Manufactured by Lilly France - F-67640 Fegersheim, France for Eli Lilly and Company - Indianapolis, IN 46285, USA

www.forteo.com

3.0ANL 9400 FSAMP

2.0 ANL 9410 FSAMP

Medication Guide

FORTEO® (for-TAY-o)

teriparatide (rDNA origin) injection

Read this Medication Guide carefully before you start taking FORTEO and each time you get a refill. The information may have changed. 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. Ask your healthcare provider if there is something you do not understand or if you want to learn more about the benefits and risks of FORTEO.

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

As part of drug testing, teriparatide, the active ingredient in FORTEO, was given to rats for a significant part of their lifetime. **In these studies, teriparatide caused some rats to develop osteosarcoma, a bone cancer.** Osteosarcoma in humans is a serious but very rare cancer. Osteosarcoma occurs in about 4 out of every million older adults each year. **It is not known if humans treated with FORTEO also have a higher chance of getting osteosarcoma.**

What is FORTEO?

FORTEO is a prescription medicine that contains teriparatide, a man-made medicine that is like the natural hormone called parathyroid hormone or PTH. PTH is produced by the body. FORTEO forms new bone, increases bone mineral density and bone strength. This lowers the chance of getting a fracture. In postmenopausal (after the “change of life”) women with osteoporosis, FORTEO can lessen the number of fractures of the spine and other bones. The effect on fractures has not been studied in men.

FORTEO is used in both men and postmenopausal women with osteoporosis who are at high risk for having fractures. FORTEO can be used by people who have had a fracture related to osteoporosis, or who have multiple risk factors for fracture, or who cannot use other osteoporosis treatments.

FORTEO has not been studied in children.

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.
- have Paget’s disease of bone.
- have unexplained high levels of alkaline phosphatase in your blood, which means you might have Paget’s disease of bone. If you are not sure, ask your doctor.
- are a child or growing adult.
- have ever been diagnosed with bone cancer or other cancers that have spread (metastasized) to your bones.

- have had radiation therapy involving your bones.
- have certain bone diseases. If you have a bone disease, tell your doctor.
- have too much calcium in your blood (hypercalcemia).

FORTEO should not be used to prevent osteoporosis. FORTEO should be used to treat patients who are considered to be at high risk for fracture.

What should I tell my healthcare provider before taking FORTEO?

Tell your healthcare provider about all of your medical conditions, including if you:

- have one of the conditions listed in the section "Who should not use FORTEO?"
- have trouble injecting yourself and do not have someone who can help you.
- have or have had kidney stones.
- are pregnant or thinking about becoming pregnant. It is not known if FORTEO will harm your unborn baby.
- are breast-feeding or thinking about breast-feeding. It is not known if FORTEO passes into breast milk. You should not breast-feed while taking FORTEO.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Your healthcare provider needs this information to help keep you from taking FORTEO with other medicines that may harm you.

- Especially tell your doctor if you take medicines that contain digoxin (for example, Digoxin, Lanoxicaps, Lanoxin).

How should I use FORTEO?

- Use FORTEO one time each day. Your healthcare provider should teach you how to use the FORTEO delivery device (see the User Manual).
- The use of FORTEO for more than 2 years is not recommended.
- The FORTEO delivery device has enough medicine for 28 days. It is set to give a 20 microgram dose of medicine each day (see User Manual). Do not inject all the medicine in the FORTEO delivery device at any one time.
- Do not transfer the contents of the FORTEO delivery device to a syringe. This can result in taking the wrong dose of FORTEO. If you do not have pen needles available to use with your FORTEO delivery device, talk with your healthcare provider.
- Inject FORTEO one time each day in your thigh or abdomen (lower stomach area). Talk to your healthcare provider about how to rotate injection sites.
- 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 (see the User Manual).
- You can take FORTEO with or without food or drink.

- You can take FORTEO at any time of the day. To help you remember to take FORTEO, take it at about the same time each day.
- If you forget or are unable to take FORTEO at your usual time, take it as soon as you can on that day. Do not take more than one injection in the same day.

Follow your healthcare provider's instructions about other ways you can help your osteoporosis, such as exercise, diet, and reducing or stopping your use of tobacco and alcohol. 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?

Most side effects are mild and include:

- nausea.
- dizziness or fast heartbeat. Some people get dizzy or get a fast heartbeat right after the first few doses. This usually happens within 4 hours of taking FORTEO and goes away within a few hours. For the first few doses, take 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, stop taking FORTEO and call your healthcare provider.
- leg cramps.
- joint aches.
- increased calcium in your blood. Tell your healthcare provider if you have continuing nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs there is too much calcium in your blood.
- injection site reactions including redness, swelling, pain, itching, a few drops of blood, and bruising.

Your healthcare provider may take samples of blood and urine during treatment to check your response to FORTEO. Also, your healthcare provider may ask you to have follow-up tests of bone mineral density. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of FORTEO. 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?

- Keep your FORTEO delivery device in the refrigerator at 36° to 46°F (2° to 8°C).
- Do not freeze the FORTEO delivery device. Do not use FORTEO if it has been frozen.
- Do not use FORTEO after the expiration date printed on the delivery device and packaging.
- Throw away the FORTEO delivery device after 28 days even if it has medicine in it (see the User Manual).

General information about 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 condition you have.

This Medication Guide summarizes the most important information about FORTEO. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about FORTEO that is written for healthcare professionals. For more information, go to www.FORTEO.com or call Lilly toll free at 1-866-4FORTEO (1-866-436-7836).

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.

What is Osteoporosis?

Osteoporosis is a disease in which the bones become thin and weak, increasing the chance of having a broken bone. Osteoporosis usually causes no symptoms until a fracture happens. The most common fractures are in the spine (backbone). They can shorten height, even without causing pain. Over time, the spine can become curved or deformed and the body bent over. Fractures from osteoporosis can also happen in almost any bone in the body, for example, the wrist, rib, or hip. Once you have had a fracture, the chance for more fractures greatly increases.

The following risk factors increase your chance of getting fractures from osteoporosis:

- past broken bones from osteoporosis.
- very low bone mineral density (BMD).
- frequent falls.
- limited movement, such as using a wheelchair.
- medical conditions likely to cause bone loss, such as some kinds of arthritis.
- medicines that may cause bone loss, for example: seizure medicines (such as phenytoin), blood thinners (such as heparin), steroids, high doses of vitamin A.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised Month XX, YYYY

Manufactured by Lilly France - F-67640 Fegersheim, France
for Eli Lilly and Company - Indianapolis, IN 46285, USA

FORTEO® (for-TAY-o)
teriparatide (rDNA origin) injection

User Manual

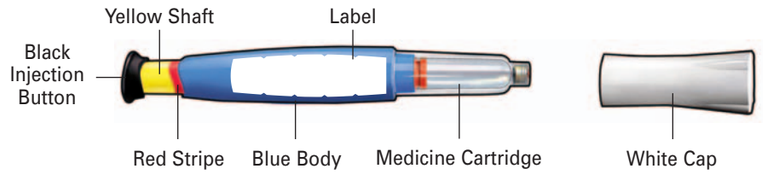
Important: First read the Medication Guide that comes inside your FORTEO carton.

Before you use your new FORTEO delivery device, please read the entire front and back of this User Manual completely. Follow the directions carefully when using the FORTEO delivery device.

The FORTEO delivery device contains 28 days of medicine. Throw away the FORTEO delivery device after 28 days, even if it is not completely empty. Do not inject more than one dose of FORTEO in the same day.

Do not transfer FORTEO to a syringe.

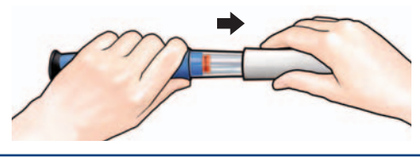
FORTEO Delivery Device Parts*



***Needles not included.** Becton, Dickinson and Company pen needles from 29 to 31 gauge are recommended for use with this device.

Wash your hands before every injection. Prepare the injection site as your healthcare provider instructed.

1 Pull off white cap

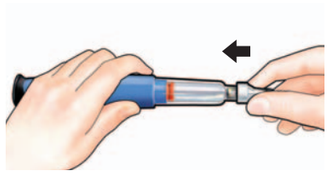


Check the FORTEO delivery device label to make sure you have the right medicine and that it has not expired.

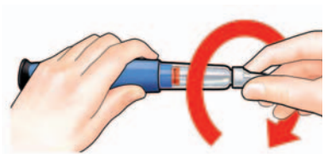
Do not use if the FORTEO delivery device looks damaged, if the medicine in the cartridge is not clear and colorless, or if it has particles in it.

2 Attach new needle

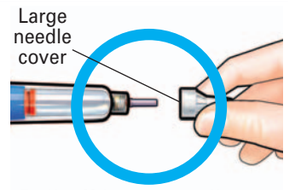
Pull off paper tab.



Push needle **straight** onto medicine cartridge.



Screw on needle until firmly attached.

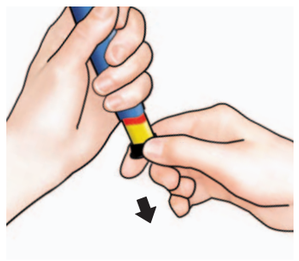


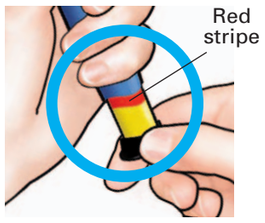
Pull off large needle cover and **save it.**

3 Set dose

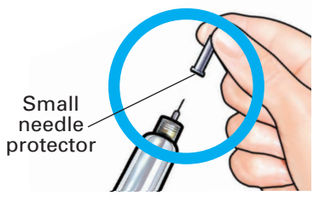
Pull out black injection button **until it stops.**

If you cannot pull out the black injection button see *Troubleshooting, Problem E,* on back page.



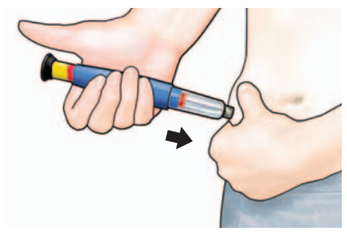


Check to make sure red stripe shows.

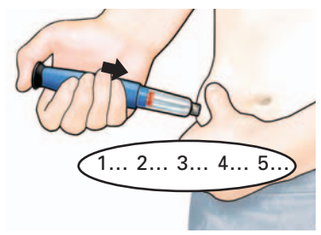


Pull off small needle protector and throw away.

4 Inject dose



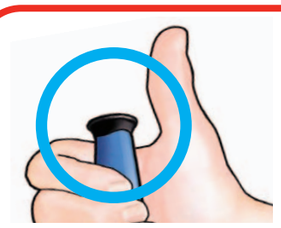
Gently hold a fold of skin on your thigh or abdomen and insert needle straight into skin.



Push in black injection button until it stops. Hold it in and **count to 5 slowly. You must wait until the count of 5 to make sure you receive the correct dose.** Then pull the needle from skin.

5 Confirm dose

IMPORTANT

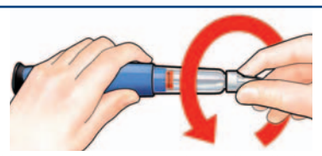


After completing the injection:
Once the needle is removed from the skin, take your thumb off the black injection button. **Check** to make sure the black injection button is all the way in. If the yellow shaft does not show, you have finished the injection steps the right way.

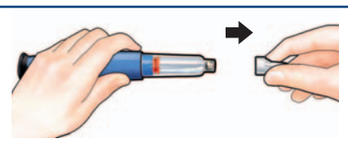
You should **NOT** see any of the yellow shaft. If you do and have already injected the medicine, do not inject yourself a second time on the same day. Instead, **you MUST reset the FORTEO** delivery device (see *Troubleshooting, Problem A,* on back page).

6 Remove needle

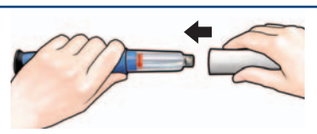
Put large needle cover on needle. Do not try to put the needle cover back on with your hands.



Unscrew the covered needle all the way by giving the large needle cover 3 to 5 counter-clockwise turns.



Pull off needle and throw away in a puncture-resistant container.



Push white cap back on.
Right after use, place FORTEO delivery device in the refrigerator.

For more information, or if you have any questions, turn to the back of this page.

PA MAQ015 AM

Lilly

FORTEO® (for-TAY-o)
teriparatide (rDNA origin) injection

Troubleshooting

Problem	Solution
A. The yellow shaft is still showing after I push in the black injection button. How do I reset my FORTEO delivery device? 	To reset the FORTEO delivery device, follow the steps below. 1) **If you have already injected, DO NOT inject yourself a second time on the same day.** 2) Remove the needle. 3) Attach a new needle, pull off the large needle cover and save it. 4) Pull out the black injection button until it stops. Check to make sure the red stripe shows. 5) Pull off the small needle protector and throw away. 6) Point the needle down into an empty container. Push in the black injection button until it stops. Hold it in and **slowly count to five.** You may see a small stream or drop of fluid. **When you have finished, the black injection button should be all the way in.** 7) If you still see the yellow shaft showing, contact Eli Lilly and Company (see *Contact Information* below) or your healthcare provider. 8) Put the large needle cover on needle. Unscrew the needle all the way by giving the needle cover 3 to 5 counter-clockwise turns. Pull off the covered needle and throw away as instructed by your healthcare provider. Push the white cap back on, and put your FORTEO delivery device in the refrigerator. You can prevent this problem by **always using a NEW needle for each injection, and by pushing the black injection button all the way in and slowly counting to five.**
B. How can I tell if my FORTEO delivery device works?	The black injection button should be all the way in to show that the full dose of medicine has been injected from the FORTEO delivery device. Use a new needle every time you inject to be sure your FORTEO delivery device will work properly.
C. I see an air bubble in my FORTEO delivery device.	A small air bubble will not affect your dose and it will not harm you. You can continue to take your dose as usual.
D. I cannot get the needle off.	1) Put the large needle cover on the needle. 2) Use the large needle cover to unscrew the needle. 3) Unscrew the needle all the way by giving the large needle cover 3 to 5 counter-clockwise turns. 4) If you still cannot get the needle off, ask someone to help you.
E. What should I do if I have difficulty pulling out the black injection button?	**Change to a new FORTEO delivery device to take your dose as instructed by your healthcare provider.** When the black injection becomes hard to pull out, this means there is not enough medicine in your FORTEO delivery device for another dose. You may still see some medicine left in the cartridge.

Cleaning and Storage

Cleaning Your FORTEO Delivery Device
- Wipe the outside of the FORTEO delivery device with a damp cloth.
- Do not place the FORTEO delivery device in water, or wash or clean it with any liquid.

Storing Your FORTEO Delivery Device
- After each use, refrigerate the FORTEO delivery device right away. Read and follow the instructions in the Medication Guide section "How should I store FORTEO?".
- Do not store the FORTEO delivery device with a needle attached. Doing this may cause air bubbles to form in the medicine cartridge.
- Store the FORTEO delivery device with the white cap on.
- Do not freeze FORTEO. If the FORTEO delivery device has been frozen, throw the device away and use a new FORTEO delivery device.
- If the FORTEO delivery device has been left out of the refrigerator, do not throw the delivery device away. Place the delivery device back in the refrigerator and call Eli Lilly and Company at 1-866-4FORTEO (1-866-436-7836).

Other Important Notes

- The FORTEO delivery device contains 28 days of medicine.
- Do not transfer FORTEO to a syringe. This may result in you taking the wrong dose of medicine.
- Read and follow the instructions in the User Manual so that you use your FORTEO delivery device the right way.
- Check the FORTEO delivery device label to make sure you have the right medicine and that it has not expired.
- Do not use the FORTEO delivery device if it looks damaged. Look at the FORTEO medicine in the cartridge. If the medicine is not clear and colorless, or if it has particles, do not use it. Call Eli Lilly and Company if you notice any of these (see *Contact Information*).
- Use a new needle for each injection.
- Do not share your FORTEO delivery device or needles with anyone.
- During injection, you may hear one or more clicks – this is normal.
- The FORTEO delivery device is not recommended for use by the blind or by those who have vision problems without help from a person trained in the proper use of the device.
- Keep your FORTEO delivery device and needles out of the reach of children.

Disposal of Pen Needles and Delivery Device

Disposal of Pen Needles and the FORTEO Delivery Device
- Before throwing away the FORTEO delivery device, be sure to remove the pen needle.
- Throw away your FORTEO delivery device and used needles as instructed by your healthcare provider, local or state laws, or institutional policies.

Dispose of the FORTEO delivery device 28 days after first use.

1st use date _____ / _____ / _____

Throw away after _____ / _____ / _____

Contact Information

If you have questions or need help with your FORTEO delivery device, contact Eli Lilly and Company at 1-866-4FORTEO (1-866-436-7836) or your healthcare provider.

For more information about FORTEO, go to www.FORTEO.com

Manufactured by Lilly France, F-67640 Fegersheim, France for Eli Lilly and Company.

Literature issued XXX xx, 2008

PA MAQ015 AM

Read User Manual BEFORE Injecting

Preset dose: 20 mcg teriparatide once daily.
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.

Manufactured by Lilly France, F-67640 Fegersheim, France
For Eli Lilly and Company, Indianapolis, IN 46285, USA

FORTEO® is a trademark of Eli Lilly and Company.

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 0002-8400-01 2

Lilly

SH MAQ 017AM

FORTEO®
teriparatide (rDNA origin) injection

20 mcg per dose

MS8400

Lilly

1"

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

NDC 0002-**8400**-01
MS8400

FORTEO®

To open, lift here and pull.

Lilly

FORTEO®
teriparatide (rDNA origin) injection
20 mcg per dose

Each prefilled pen will deliver 28 subcutaneous doses, 20 mcg per dose
600 mcg / 2.4 mL

Same FORTEO, new pen. Please read the enclosed User Manual for new injection instructions.

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

Needles not included
Becton, Dickinson and Company pen needles from 29 to 31 gauge are recommended for use with this device

www.forteo.com

Lilly

Control No.:

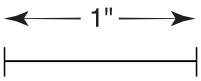
Exp. Date:

Lilly

20 mcg per dose

FORTEO®
teriparatide (rDNA origin) injection

MS8400



FORTEO®
teriparatide (rDNA origin) injection
20 mcg per dose
Do NOT transfer contents to a syringe. Read User Manual BEFORE Injecting.
Each prefilled pen will deliver 28 subcutaneous doses, 20 mcg per dose
600 mcg / 2.4 mL
Throw away 28 days after first use
REFRIGERATE – DO NOT FREEZE

MS8400
NDC 0002-8400-01
(01) 1 0 3 0002 8400 0 1 8

Manufactured by: Lilly France
F-67640 Fegersheim, France for Eli Lilly and Co., Indianapolis, IN 46285, USA

Control No. / Exp. Date:

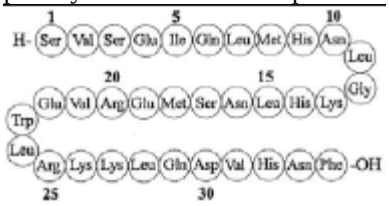
YL MAQ014 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-318/S-016

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION ONDQA	2. NDA NUMBER 21-318
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 Tel: (317) 276-2000, Fax: (317) 276-1652		
		5. SUPPLEMENT(S) NUMBER(S) & DATES(S) SCS-016(10/30/07)
6. NAME OF DRUG Forteo®	7. NONPROPRIETARY NAME teriparatide (rDNA origin) injection	
8. SUPPLEMENT PROVIDES FOR: a new pre-filled pen injector for use with teriparatide cartridges manufactured with a lower nominal fill volume at the currently approved facility in Fegersheim, France.		
9. PHARMACOLOGICAL CATEGORY Parathyroid Hormone/Treatment of osteoporosis in postmenopausal women and in men	10. HOW DISPENSED RX X OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Subcutaneous Injection	13.POTENCY 3 ml cartridge (20 microgram dose)	
14.CHEMICAL NAME AND STRUCTURE FORTEO® [teriparatide (rDNA origin) injection] contains recombinant human parathyroid hormone (1-34), [rhPTH (1-34)], which has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. Teriparatide has a molecular weight of 4117.8 daltons  		15. RECORDS AND REPORTS CURRENT YES___NO REVIEWED YES___NO
16. COMMENTS: The Forteo (b) (4) requires fewer steps to set and deliver a dose and less effort to push the injection button down as compared to the currently approved Forteo Pen. These modifications are intended to make the device easier for the target population to operate. The new Forteo (b) (4) is much improved version of the current Forteo Pen.		
17. CONCLUSIONS AND RECOMMENDATIONS Chemist recommends approval of this supplement.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE	DATE COMPLETED February 19, 2008

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/s/

Chong-Ho Kim
2/25/2008 05:36:50 AM
CHEMIST

Jim Vidra
2/25/2008 09:04:50 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-318/S-016

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

19 December 2007

NDA: 21-318/SCS-016

Drug Product Name
Proprietary: Forteo
Non-proprietary: teriparatide (rDNA origin) injection.
Drug Product Priority Classification:

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
30 OCT 2007	31 OCT 2007	14 NOV 2007	15 NOV 2007

Applicant/Sponsor
Name: Eli Lilly and Co.
Address: Lilly Corporate Center
Indianapolis, IN 46285
Representative: LeeAnn Chambers
Telephone: 317-277-1813

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommended for approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval CMC Supplement.

2. SUBMISSION PROVIDES FOR: A new pre-filled pen-injector (Forteo [redacted] (b) (4) for use with teriparatide cartridges manufactured with a lower nominal fill volume.

3. MANUFACTURING SITE:
Eli Lilly France S.A.
rue du Colonel Lilly
67640 Fegersheim, France.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Solution in 3 mL cartridge for autoinjector/pen.
- Subcutaneous injection.
- 20 µg.

5. METHOD(S) OF STERILIZATION: [redacted] (b) (4)

6. PHARMACOLOGICAL CATEGORY: Indicated for treatment of osteoporosis in postmenopausal women and in men.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:
The subject supplemental application was submitted electronically in the CTD format.

The proposed (Forteo [redacted] (b) (4) device will use the same 3 mL container closure components that are approved with the current (Forteo PEN) device. The fill volume will be less (2.4 mL instead of 3.0 mL). The Forteo cartridges with the proposed fill volume will be filled on the current filling lines at the currently approved (Fegersheim, France) manufacturing facility using the same manufacturing controls as the current process and stored at the currently approved conditions prior to assembly.

File Name: N021318S016R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 21-318/SCS-016 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The subject drug product is (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block_____
Bryan Riley, Ph.D.

C. CC Block
N/A

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/s/

John Metcalfe
1/2/2008 09:55:20 AM
MICROBIOLOGIST

Bryan Riley
1/2/2008 10:17:21 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-318/S-016

OTHER REVIEW(S)

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

Date:	April 15, 2008
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrinology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Education and Labeling Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling (Medication Guide)
Drug Name(s):	Forteo (teriparatide (rDNA origin) injection
Application Type/Number:	NDA 21-318
Submission Number:	S-016
Applicant/sponsor:	Eli Lilly & Company
OSE RCM #:	2008-89

1 INTRODUCTION

Eli Lilly & Co. submitted a Prior Approval Control Supplement (SCS), Supplemental New Drug Application, sNDA21-318/S-016 on October 30, 2007. This supplement proposes a new pre-filled pen-injector (Fortec[(b) (4)] for use with teriparatide cartridges manufactured with a lower nominal fill volume at the currently approved facility in Fegersheim, France. The sponsor states in their cover letter that "The [(b) (4)] is designed to achieve greater ease of patient use through simplification of the steps required to operate the pen, lowering the force required for injection, and improving patient feedback during the injection process." This supplemental NDA submission includes the following labeling pieces: Professional Information, Medication Guide, pen label, pen carton, and the delivery device user manual. The review division subsequently notified the sponsor to submit the Professional Information in the old labeling format. The sponsor submitted an Amendment to the Pending Supplement on March 28, 2008, incorporating agreed upon changes based on email communications with the review division PO non March 13 and 14, 2008. The sponsor did not submit a revised Medication Guide at this time.

DMETS completed a review of the submitted labeling and labels for this supplement on March 14, 2008. DMETS recommends that the [(b) (4)] qualifier be removed from all labels and labeling.

2 MATERIAL REVIEWED

- FORTEO Medication Guide (MG) submitted October 30, 2007
- FORTEO User Manual submitted March 28, 2008
- FORTEO Professional Information (PI) submitted March 28, 2008

3 DISCUSSION

The purpose of Medication Guides is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 9.1. Our revised MG has a Flesch Kinkaid grade level of 8.6.. In our review of the MG, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- removed unnecessary or redundant information
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

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/s/

Sharon Mills
4/15/2008 06:18:41 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/15/2008 07:55:42 PM
CSO

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

Date:	March 14, 2008
To:	Mary Parks, MD, Director Division of Metabolic and Endocrinology Products
Thru:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention
From:	Kristina Arnwine, PharmD, Acting Team Leader Kellie Taylor, PharmD, MPH, Team Leader Division of Medication Error Prevention
Subject:	Label and Labeling Review
Drug Name(s):	Forteo [Teriperatide (rDNA origin)] Injection
Submission Number:	S-016
Application Type/Number:	NDA 21-318
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2008-89

CONTENTS

EXECUTIVE SUMMARY

Our analysis of the introduction of the new pen determined the pen and its proposed labels and labeling are not likely to exacerbate the medication errors identified in our postmarketing error analysis (OSE 04-0319). Some sources of error identified in our postmarketing analysis have been addressed by the new pen design. Other sources of error identified may be improved upon revision of the labels and labeling. Thus, we noted areas of vulnerability in which improvements should be made to the container label, carton labeling, and Instructions for Use labeling to increase the prominence of warnings and to reduce the clutter of information presented therein. Such improvements include revision of the dosage statements on the container label and carton labeling, increasing the prominence of the "Do NOT transfer contents to a syringe" statement on the container label and carton labeling, and more specific instruction with regard to attaching and removing the needle from the pen in the Instructions for Use.

For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Metabolism and Endocrinology Products (DMEP) to evaluate the container label, carton labeling, and Instructions for Use for Forteo (b) (4) [Teriperatide (rDNA origin)] Injection, 20 mcg.

1.2 REGULATORY HISTORY

Forteo was approved November 26, 2002. On October 30, 2007, Eli Lilly and Company submitted a prior approval supplement for a new pre-filled pen-injector.

Subsequently, the Applicant has submitted revised container labels, carton labeling, and Instructions for Use for the new pen. With this submission, Lilly included a Market Transition Plan to minimize the potential for confusion between the currently marketed Forteo Pen and the new Forteo Pen.

In the "Market Transition Plan" the Applicant describes plans to quickly phase out the currently marketed Forteo Pen upon the launch of the new Forteo Pen. The Applicant proposes to (b) (4)

The Applicant states that the transition plan will not affect how a physician writes a prescription for Forteo (b) (4) To supplement the plan the Applicant proposes a (b) (4) s to ensure they understand how and why the upcoming transition from the Forteo Pen to Forteo (b) (4) will occur.

The applicant also proposes labeling elements to augment the market transition plan and minimize the potential for confusion.

1.3 PRODUCT INFORMATION

Forteo is indicated for the treatment of osteoporosis in postmenopausal women and in men with primary or hypogonadal osteoporosis; to increase bone mass in patients who are at risk for fracture, or who have failed or are intolerant to previous osteoporosis therapy. The recommended dose is 20 mcg once daily as a subcutaneous injection into the thigh or abdominal wall for up to two years. Forteo is supplied in a pre-filled disposable pen device which delivers 20 mcg of teriparitide per dose, for 28 doses.

2 METHODS AND MATERIALS

This section describes the methods and materials used by our medication error staff to conduct a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including the proprietary and established name, strength, form, container quantity, expiration date, and so on. The insert labeling is intended to communicate to practitioners all the information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program (MERP) may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

We analyze reported misuse of drugs and are able to use their experience to identify potential errors with all packaged, labeled and/or prescribed medications. We also use failure mode and effects analysis (FMEA) and human factor principles to identify potential sources of error with the proposed product labels and insert labeling. We then provide recommendations that aim at reducing the risk of medication errors.

2.1 OSE POSTMARKETING ERROR ANALYSIS

We are conducting a post-marketing analysis of medication errors associated with the use of the currently marketed Forteo pen under separate cover (OSE 04-0319). For this review, we examined the types of errors identified in the aforementioned postmarketing analysis to determine if the issues identified have been resolved by the development of the new pen.

2.2 LABELS AND LABELING

For this product, the Sponsor submitted on October 30, 2007, the following container labels and carton labeling for our review (see Appendices A B for images) Additionally, for comparison, we reviewed the following labels and labeling submitted December 4, 2003 used Forteo (see Appendices C and D for images).

---

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

2.3 USER MANUAL

DMETS reviewed the proposed Patient Instructions for Use submitted on October 30, 2007)

2.4 MARKET TRANSITION PLAN

The Division of Medication Error Prevention reviewed the elements of the Applicant's "Market Transition Plan" and notes that the Applicant is planning to quickly phase out the currently marketed Forteo Pen upon the launch of the new Forteo Pen

3 RESULTS

3.1 POSTMARKETING ERROR ANALYSIS

In our review of medication errors associated with Forteo (OSE 04-0319), six types of medication errors were identified. They include:

- Transfer of pen contents to a syringe
- Pen priming problems
- Dose knob problems
- Pen jamming problems
- Confusion with diamond dose check
- Miscellaneous

3.2 CONTAINER LABEL AND CARTON LABELING

(b) (4)

(b) (4)

3.2 INSTRUCTIONS FOR USE

(b) (4)

3.3 MARKET TRANSITION PLAN

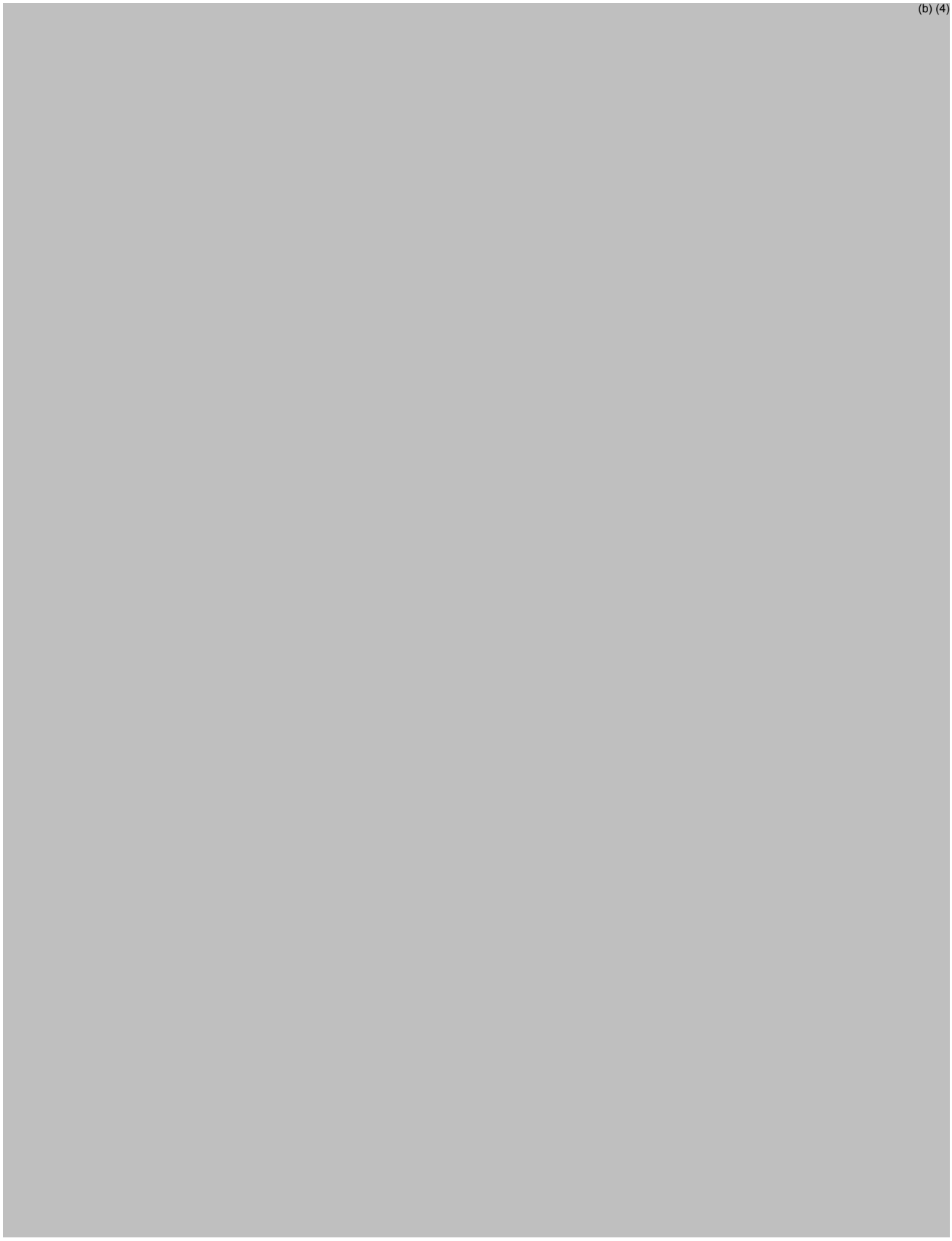
The applicant also proposes labeling to augment the Market Transition Plan and minimize the potential for confusion. Labeling components are described as follows:

1. The carton is clearly marked with a highlight to distinguish this product as a new pen and to notify the patient to carefully read the new user manual.
2. The user manual is clearly differentiated from the current Forteo Pen by heavy use of graphics and color rather than the black and white format of the current Forteo Pen.
3. Use of a qualifier – Forteo (b) (4) – to differentiate the new pen from the old.
4. The patient information leaflet is in the question and answer format recommended by the FDA and at an acceptable reading level.
5. The user manual contains a space for the customer to record the date the pen was put into use and when it should be discarded.
6. The Forteo (b) (4) label size has been maximized.

4 DISCUSSION

4.1 CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE LABELING

Our analysis of the container labels and carton labeling noted areas of vulnerability that could lead to medication errors. These areas include the lack of prominence regarding the presentation of the dose and important warning statements on the container label and carton labeling, the addition of a qualifier (b) (4) to the labels and labeling, and incomplete instructions in the Instructions for Use.


(b) (4)

4.2 POSTMARKETING ERROR ANALYSIS

In our review of medication errors associated with Forteo (OSE 04-0319), six types of medication errors were identified. We noted that the design of the new pen addresses many of the sources of error. Conversely, we noted some sources of error were not addressed by the new pen, however, we provide label and labeling recommendations in section 5.2 in an attempt to address the issues which were not addressed by the new pen. The medication error types identified in OSE 04-0319 and their respective interventions are as follows:

- Transfer of pen contents to a syringe – Not addressed by new pen design. See label and labeling recommendations in section 5.2
- Priming of the pen – Addressed by new pen design. Priming is not required with the new pen.
- Dose knob problems – Addressed by new pen design. The new pen does not include a dose knob. Instead, the pen utilizes a "black injection button" or plunger that is pulled out to set the dose, and pushed in to administer the dose.
- Pen jamming problems – Unknown if fully addressed by the new pen design. Jamming issues associated with priming of the old pen have been addressed by the new pen design as the new pen does not require priming. Jamming issues associated with needle replacement may be addressed by the associated label and labeling recommendations in section 5.2. However, the new pen may jam due to causes that may not be identified until the pen is marketed.
- Confusion with diamond dose check – Addressed by new pen design. The new pen no longer contains a dose check window. Instead, it contains a red stripe on the plunger which does not require manipulation (e.g. turning).
- Miscellaneous – Unknown if fully addressed by the new pen design. Some of the miscellaneous sources of error may be addressed by the label and labeling recommendations in section 5.2. However, the new pen may present new sources of error whose causes may not be identified until the pen is marketed.

4.3 MARKET TRANSITION PLAN

Overall, the Division of Medication Error Prevention believes the Applicant's Market Transition Plan should help to limit the potential for confusion that may occur with the concurrent marketing of the old and new Forteo Pens. However, DMETS believes that elements of the labeling component of the Plan could inadvertently introduce error. These risks are described in detail below.

4.3.1 USE OF THE (b) (4) QUALIFIER

The Division of Medication Error Prevention questions the overall usefulness of the (b) (4) qualifier given Lilly's plan to rapidly transition users from the old to the new Forteo Pen. The sponsor has proposed a number of measures, including market removal of the old pen and a change in the NDC codes that seem to be more effective measures in aiding the overall transition. Moreover, The Division of Medication Error Prevention is concerned that the use of the (b) (4) qualifier may cause confusion that leads to medication error. The Division of Medication Error Prevention has concern that the use of a qualifier may affect the way the prescribers write a prescription for the new Forteo Pen. The Division of Medication Error Prevention believes that healthcare practitioners would view the qualifier as a new proprietary name, "Forteo (b) (4) which could lead practitioners to communicate prescriptions and medication orders using the qualifier alone (e.g. " (b) (4) or the qualifier in conjunction with the proprietary name "Forteo (b) (4) From a medication errors perspective, The Division of Medication Error Prevention notes that the (b) (4) qualifier has orthographic similarity to the product Lidopen when scripted which could lead to the wrong drug being dispensed or administered if practitioners include the qualifier when communicating prescriptions and medication orders.

5 CONCLUSIONS AND RECOMMENDATIONS

The introduction of a new Forteo pen, and the subsequent revised labels and labeling do not appear to exacerbate the medication errors identified in our postmarketing medication error analysis of the currently marketed Forteo pen. However, we recommend that the label and labeling recommendations regarding the container label, carton labeling, and Instructions for Use be implemented to address any sources for medication error not addressed by the design of the new pen.

5.1 COMMENTS TO THE DIVISION

The comments below should be forwarded to the applicant so that these recommendations can be implemented prior to approval of this supplement.

Based upon our assessment of the labeling, we have identified areas of needed improvement. We have provided recommendations in section 5.2 below and request this information be forwarded to the applicant.

5.2 COMMENTS TO THE APPLICANT

Overall, the Division of Medication Error Prevention believes the Applicant's Market Transition Plan should help to limit the potential for confusion that may occur with the concurrent marketing of the old and new Forteo Pens.

However, DMETS believes that elements of the labeling component of the Plan could inadvertently introduce error. Specifically, the Division of Medication Error Prevention questions the utility of the (b) (4) qualifier given Lilly's plan to rapidly transition users from the old to the new Forteo Pen. The sponsor has proposed a number of measures, including

market removal of the old pen and a change in the NDC codes that seem to be more effective measures in aiding the overall transition.

Moreover, The Division of Medication Error Prevention is concerned that the use of the (b) (4) qualifier may cause confusion that leads to medication error. The Division of Medication Error Prevention has concern that the use of a qualifier may affect the way the prescribers write a prescription for the new Forteo Pen. The Division of Medication Error Prevention believes that healthcare practitioners would view the qualifier as a new proprietary name, "Forteo (b) (4) which could lead practitioners to communicate prescriptions and medication orders using the qualifier alone (e.g. " (b) (4) or the qualifier in conjunction with the proprietary name "Forteo (b) (4) From a medication errors perspective, The Division of Medication Error Prevention notes that the (b) (4) qualifier has orthographic similarity to the product Lidopen when scripted which could lead to the wrong drug being dispensed or administered if practitioners include the qualifier when communicating prescriptions and medication orders.

As such, DMETS recommends that the (b) (4) qualifier be removed from all labels and labeling. DMETS also recommend that the label and labeling recommendations below regarding the container label, carton labeling, and Instructions for Use be to address additional sources for medication error relating to the container label, carton labeling, and user manual.

A. Container Label

1. Delete the word (b) (4)

2. Include the product strength "20 mcg" on the container label and ensure that it is presented prominently. Consider relocating the barcode to the bottom right corner of the label and presenting the "20 mcg" product strength where the barcode are currently presented.

3. Present the warnings "Do NOT transfer contents to a syringe. Read User Manual BEFORE Injecting" on the same line in bold red font.

4. Delete the (b) (4) . Add the statements "Each prefilled pen will deliver 28 subcutaneous doses, 20 mcg per dose" and "600 mcg/ 2.4 mL". The total content of the prefilled syringe ("600 mcg/ 2.4 mL) should have lesser prominence.

5. Remove the 'swoosh' graphic presented above the (b) (4)

B. Carton Labeling

1. Delete the word (b) (4)

2. Increase the prominence to the middle segment of the product NDC code (i.e. 0002-**8400**-01). This portion of the NDC code is most heavily relied by pharmacy staff to distinguish products within the same product line.

3. Include the product strength "20 mcg per dose" on the container label. Ensure that the strength is presented with more prominence than the total drug per total volume statement (i.e. 600 mcg/2.4 mL).

4. Include the statement “Each prefilled pen will deliver 28 subcutaneous doses, 20 mcg per dose” and ensure this statement is presented with more prominence than the total drug per total volume statement (i.e. 600 mcg/2.4 mL).

5. Remove the ‘swoosh’ graphic presented above the (b) (4) modifier.

6. Increase the prominence of the statement “Needles not included”.

7. Include the statement “Do NOT transfer contents to a syringe” statement on the principal display panel as well as the back panel.

C. Instructions for Use

1. Forteo (b) (4) Parts box - Increase the prominence of the “Needles not included” statement.

2. Step 2 “Attach new needle” – Revise the third step to read “Screw on needle clockwise until firmly attached”.

3. Step 4 “Inject Dose” – Append the statement “To ensure you got the correct dose, you **must wait until the count of 5** after the black injection stops before removing needle from the skin.

4. Step 4 “Inject Dose” – Remove the dashes in between the letters in the word “slowly” to improve readability of the word.

5. Step 5 “Confirm Dose” - Revise the first paragraph to read “Once the needle is removed from the skin, remove your thumb from the black injection button and check to make sure the black injection button is all the way in…”

6. Step 6 “Remove needle” – Revise the second step to read “Unscrew the needle all the way by giving the large needle cover 3 to 5 complete counter-clockwise turns”.

7. Troubleshooting Problem D – Revise step 3 to read “Unscrew the needle all the way by giving the large needle cover 3 to 5 complete counter-clockwise turns”.

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/s/

Kristina Arnwine
3/14/2008 01:50:57 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/14/2008 02:08:58 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/14/2008 04:45:21 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-318/S-016

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM OF TELECON

DATE: June 13, 2008

APPLICATION NUMBER: NDA 21-318/S-016

BETWEEN:

Name: Daniel Brady (substituting for Jean Wright)

Phone: (866) 682-7681
Representing: Eli Lilly and Co.

AND

Name: Division of Metabolism and Endocrinology Products
Oluchi Elekwachi, PharmD, MPH
Mary H. Parks, MD
Theresa Kehoe, MD
William Lubas, MD, PhD

Office of Surveillance and Epidemiology
Sharon Mills, RN (DRISK)
Kristina Arnwine, PharmD (DMEDP)

SUBJECT: Forteo (b) (4) User Manual

The purpose of this telecom was to discuss comments by DRISK regarding the User Manual and MedGuide for a new Forteo Pen delivery device. The discussions of this meeting were a follow to comments and sent to Lilly as well as their responses. These earlier comments and revisions are appended to this memo.

User Manual
Lilly: In response to DRISK's recommendation to add alcohol swabs and sharps container in the list of included items because this is not a universal recommendation. Market research is not typically submitted. Lilly is willing to discuss any clarification needed. The circle with diamond mentioned in the DRISK comments appear clearer on the actual User Guide.

FDA Comment: To the extent possible, add more white space and spread out the text on the User Manual.

Lilly – Stability or Forteo outside the refrigerator has a complex algorithm and this is the reason it is not included in the User Manual or PI.

- Bullet points under 'Other Important Information' will be moved up in the User Manual. As a separate paragraph.

- ‘Do not transfer would be move above the number steps in the User Manual.
- In step 1, 2 bullet points form the ‘Other Important Information’ would be added.

FDA Comment –
- Throughout the User Manual Change [redacted (b) (4)]’ to ‘medicine’
- Under ‘Disposal of Pen Needles and Delivery Device’ delete ‘[redacted (b) (4)]
- Delete ‘and’ or ‘or’ ‘and/or’ is confusing
- Include the Forteo Phone # under the storage and cleaning section.

- The User Manual is acceptable. We still believe that it is important to put the algorithm in the PI; however, FDA would like to see a proposal for this inclusion. This proposal will be consider under the review of complete response to S-012 (under review by Division of Reproductive and Urologic Products).

Lilly – We will submit a user manual updated with the points mentioned in this telecom.

MedGuide
FDA – We are in agreement on the MedGuide

_____
Oluchi Elekwachi, PharmD, MPH
Senior Regulatory Management Officer

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/s/

Oluchi Elekwachi
6/25/2008 10:56:08 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 6, 2008

To: Jean Wright, DVM	**From:** Oluchi Elekwachi, Pharm.D., M.P.H.
Company: Eli Lilly and Co.	Division of Metabolism and Endocrinology Products
Email: WRIGHT_JEAN_A@LILLY.COM	**Fax number:** 301-796-9712
Phone number: 317.276.2732	**Phone number:** 301-796-1207

Subject: NDA 21-318/S-016 Pre Meeting Comments for June 13, 2008 DRISK Meeting

Total no. of pages including cover: 8

Comments:

You have the option of canceling the meeting if these answers are clear to you. If you require further clarification, we will be prepared to clarify any questions you have regarding our responses, but be advised that any new information, data, or questions not contained in your meeting package and presented in response to these draft comments will not be considered for official comment at the scheduled meeting. Please feel free to contact to me if I may be of further assistance.

Document to be mailed: ❑ **YES** ☑ **NO**

FDA Comments to Lilly on Responses Summary of DRISK Comments to Forteo User Manual

(b) (4)

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/s/

Oluchi Elekwachi
6/6/2008 02:04:08 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-318/S-016 **PRIOR APPROVAL SUPPLEMENT**

Eli Lilly and Company
Attention: Jean Wright, DVM
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Wright:

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

Name of Drug Product:	Forteo (teriparatide) 3ml Cartridge
NDA Number:	21-318
Supplement number:	-016
Review Priority Classification:	Standard (S)
Date of supplement:	October 30, 2007
Date of receipt:	October 31, 2007

This supplemental application proposes the following change(s): "A new pre-filled pen-injector (Forteo (b) (4) for use with teriparatide cartridges manufactured with a lower nominal fill volume at the currently approved facility in Fegersheim, France."

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 30, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 29, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me, Regulatory Project Manager, at (301) 796-1207.

Sincerely,

{See appended electronic signature page}

Oluchi Elekwachi, PharmD, MPH
Senior Regulatory Management Officer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Oluchi Elekwachi

2/15/2008 09:52:45 AM