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FORTEO™ teriparatide (rDNA origin) injection 750 mcg/3 mL

WARNING

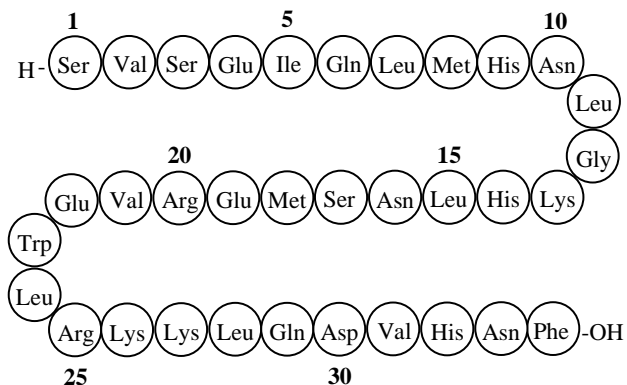
In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because 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*).

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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:



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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 prefilled delivery device is filled with 3.3 mL to deliver 3 mL. Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.10 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3.0 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

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24 Mechanism of Action

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

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

42 Human Pharmacokinetics

43 Teriparatide is extensively absorbed after subcutaneous injection; the absolute bioavailability is
44 approximately 95% based on pooled data from 20-, 40-, and 80-mcg doses. The rates of
45 absorption and elimination are rapid. The peptide reaches peak serum concentrations about
46 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable
47 concentrations within 3 hours.

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

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

60 Special Populations

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

62 Geriatric — No age-related differences in teriparatide pharmacokinetics were detected (range
63 31 to 85 years).

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

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

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

71 AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum
72 concentration of teriparatide was not increased. No studies have been performed in patients
73 undergoing dialysis for chronic renal failure (*see* PRECAUTIONS).

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

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

80 **Drug Interactions**

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

86 Furosemide — In a study of 9 healthy people and 17 patients with mild, moderate, or severe
87 renal insufficiency (CrCl 13 to 72 mL/min), coadministration of intravenous furosemide (20 to
88 100 mg) with teriparatide 40 mcg resulted in small increases in the serum calcium (2%) and
89 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically
90 important.

91 **Human Pharmacodynamics**

92 **Effects on mineral metabolism**

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

95 *Serum calcium concentrations*

96 When teriparatide 20 mcg is administered once daily, the serum calcium concentration
97 increases transiently, beginning approximately 2 hours after dosing and reaching a maximum
98 concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium
99 concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16
100 to 24 hours after each dose.

101 In a clinical study of postmenopausal women with osteoporosis, the median peak serum
102 calcium concentration measured 4 to 6 hours after dosing with FORTEO (teriparatide 20 mcg)
103 was 2.42 mmol/L (9.68 mg/dL) at 12 months. The peak serum calcium remained below
104 2.76 mmol/L (11.0 mg/dL) in >99% of women at each visit. Sustained hypercalcemia was not
105 observed.

106 In this study, 11.1% of women treated with FORTEO had at least 1 serum calcium value above
107 the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with 1.5% of women treated
108 with placebo. The percentage of women treated with FORTEO whose serum calcium was above
109 the upper limit of normal on consecutive 4- to 6-hour post-dose measurements was 3.0%
110 compared with 0.2% of women treated with placebo. In these women, calcium supplements
111 and/or FORTEO doses were reduced. The timing of these dose reductions was at the discretion
112 of the investigator. FORTEO dose adjustments were made at varying intervals after the first
113 observation of increased serum calcium (median 21 weeks). During these intervals, there was no
114 evidence of progressive increases in serum calcium.

115 In a clinical study of men with either primary or hypogonadal osteoporosis, the effects on
116 serum calcium were similar to those observed in postmenopausal women. The median peak
117 serum calcium concentration measured 4 to 6 hours after dosing with FORTEO was 2.35 mmol/L

118 (9.44 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL)
119 in 98% of men at each visit. Sustained hypercalcemia was not observed.

120 In this study, 6.0% of men treated with FORTEO daily had at least 1 serum calcium value
121 above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with none of the men
122 treated with placebo. The percentage of men treated with FORTEO whose serum calcium was
123 above the upper limit of normal on consecutive measurements was 1.3% (2 men) compared with
124 none of the men treated with placebo. Although calcium supplements and/or FORTEO doses
125 could have been reduced in these men, only calcium supplementation was reduced (*see*
126 PRECAUTIONS and ADVERSE EVENTS).

127 In a clinical study of women previously treated for 18 to 39 months with raloxifene (n=26) or
128 alendronate (n=33), mean serum calcium >12 hours after FORTEO injection was increased by
129 0.09 to 0.14 mmol/L (0.36 to 0.56 mg/dL), after 1 to 6 months of FORTEO treatment compared
130 with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium
131 >2.76 mmol/L (11.0 mg/dL), and of those pretreated with alendronate, 3 (9.1%) had a serum
132 calcium >2.76 mmol/L (11.0 mg/dL). The highest serum calcium reported was
133 3.12 mmol/L (12.5 mg/dL). None of the women had symptoms of hypercalcemia. There were no
134 placebo controls in this study.

135 *Urinary calcium excretion*

136 In a clinical study of postmenopausal women with osteoporosis who received 1000 mg of
137 supplemental calcium and at least 400 IU of vitamin D, daily FORTEO increased urinary calcium
138 excretion. The median urinary excretion of calcium was 4.8 mmol/day (190 mg/day) at 6 months
139 and 4.2 mmol/day (170 mg/day) at 12 months. These levels were 0.76 mmol/day (30 mg/day) and
140 0.30 mmol/day (12 mg/day) higher, respectively, than in women treated with placebo. The
141 incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the women treated
142 with FORTEO or placebo.

143 In a clinical study of men with either primary or hypogonadal osteoporosis who received
144 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily FORTEO had
145 inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was
146 5.6 mmol/day (220 mg/day) at 1 month and 5.3 mmol/day (210 mg/day) at 6 months. These
147 levels were 0.50 mmol/day (20 mg/day) higher and 0.20 mmol/day (8.0 mg/day) lower,
148 respectively, than in men treated with placebo. The incidence of hypercalciuria (>7.5 mmol
149 Ca/day or 300 mg/day) was similar in the men treated with FORTEO or placebo.

150 *Phosphorus and vitamin D*

151 In single-dose studies, teriparatide produced transient phosphaturia and mild transient
152 reductions in serum phosphorus concentration. However, hypophosphatemia (<0.74 mmol/L or
153 2.4 mg/dL) was not observed in clinical trials with FORTEO.

154 In clinical trials of daily FORTEO, the median serum concentration of
155 1,25-dihydroxyvitamin D was increased at 12 months by 19% in women and 14% in men,
156 compared with baseline. In the placebo group, this concentration decreased by 2% in women and
157 increased by 5% in men. The median serum 25-hydroxyvitamin D concentration at 12 months
158 was decreased by 19% in women and 10% in men compared with baseline. In the placebo group,
159 this concentration was unchanged in women and increased by 1% in men.

160 *Effects on markers of bone turnover*

161 Daily administration of FORTEO to men and postmenopausal women with osteoporosis in
162 clinical studies stimulated bone formation, as shown by increases in the formation markers serum
163 bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide
164 (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of
165 treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above
166 baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations

167 increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months.
 168 The maximum increases of BSAP were 45% above baseline in women and 23% in men. After
 169 discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in
 170 formation markers were accompanied by secondary increases in the markers of bone resorption:
 171 urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the
 172 physiological coupling of bone formation and resorption in skeletal remodeling. Changes in
 173 BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic
 174 exposure to teriparatide in men.

175

CLINICAL STUDIES

176 Treatment of Osteoporosis in Postmenopausal Women

177 The safety and efficacy of once-daily FORTEO, median exposure of 19 months, were
 178 examined in a double-blind, placebo-controlled clinical study of 1637 postmenopausal women
 179 with osteoporosis (FORTEO 20 mcg, n=541).

180 This multicenter study was performed in the US and 16 other countries. All women received
 181 1000 mg of calcium per day and at least 400 IU of vitamin D per day. Baseline and endpoint
 182 spinal radiographs were evaluated using the semiquantitative scoring method of Genant et al
 183 [*J Bone Miner Res* 1993;8(9):1137-48]. Ninety percent of the women in the study had 1 or more
 184 radiographically diagnosed vertebral fractures at baseline. The primary efficacy endpoint was the
 185 occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height
 186 of previously undeformed vertebrae. Such fractures are not necessarily symptomatic.

187 Effect on fracture incidence

188 New vertebral fractures — FORTEO, when taken with calcium and vitamin D and compared
 189 with calcium and vitamin D alone, reduced the risk of 1 or more new vertebral fractures from
 190 14.3% of women in the placebo group to 5.0% in the FORTEO group. This difference was
 191 statistically significant ($p<0.001$); the absolute reduction in risk was 9.3% and the relative
 192 reduction was 65%. FORTEO was effective in reducing the risk for vertebral fractures regardless
 193 of age, baseline rate of bone turnover, or baseline BMD.

194

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		

195 ^a $p\leq 0.001$ compared with placebo.

196

197 New nonvertebral osteoporotic fractures — Table 2 shows the effect of FORTEO on the risk of
 198 nonvertebral fractures. FORTEO significantly reduced the risk of any nonvertebral fracture from
 199 5.5% in the placebo group to 2.6% in the FORTEO group ($p<0.05$). The absolute reduction in
 200 risk was 2.9% and the relative reduction was 53%.

201

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.

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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).

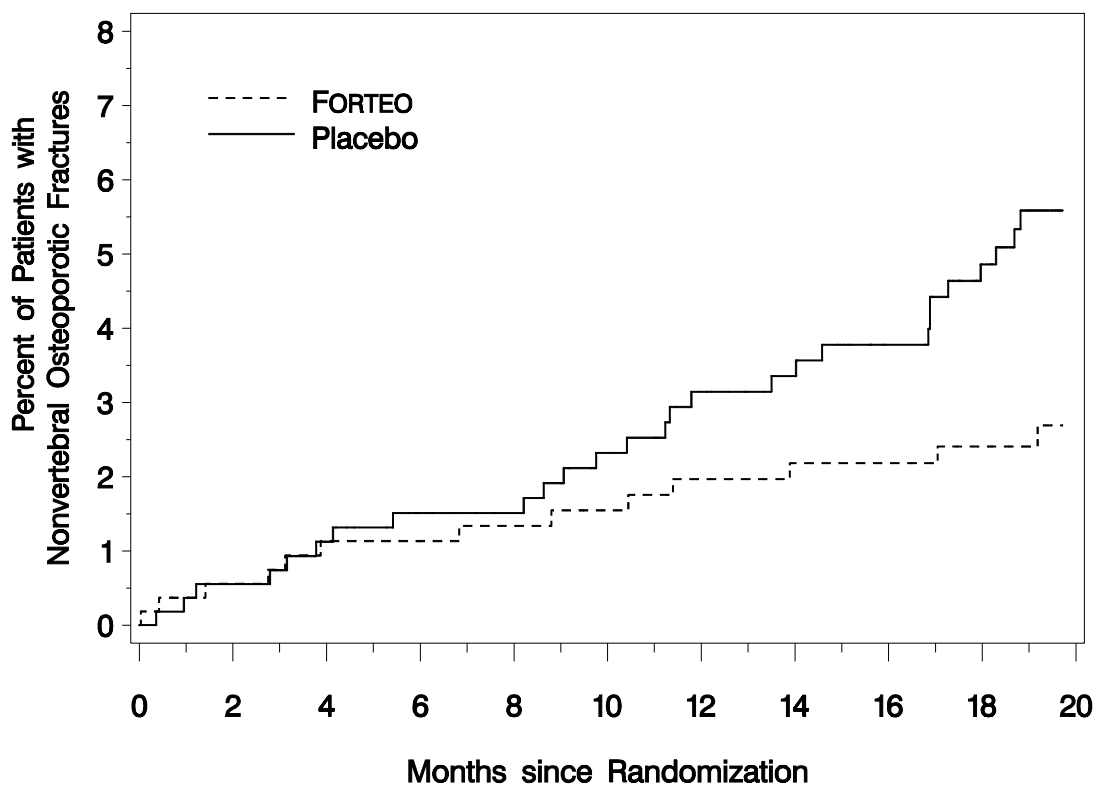


Figure 1. Cumulative percentage of postmenopausal women with osteoporosis sustaining new nonvertebral osteoporotic fractures.*

209 * This graph includes all fractures listed above in Table 2.
 210

211 Effect on bone mineral density (BMD)

212 FORTEO increased lumbar spine BMD in postmenopausal women with osteoporosis.

213 Statistically significant increases were seen at 3 months and continued throughout the treatment

214 period, as shown in Figure 2.

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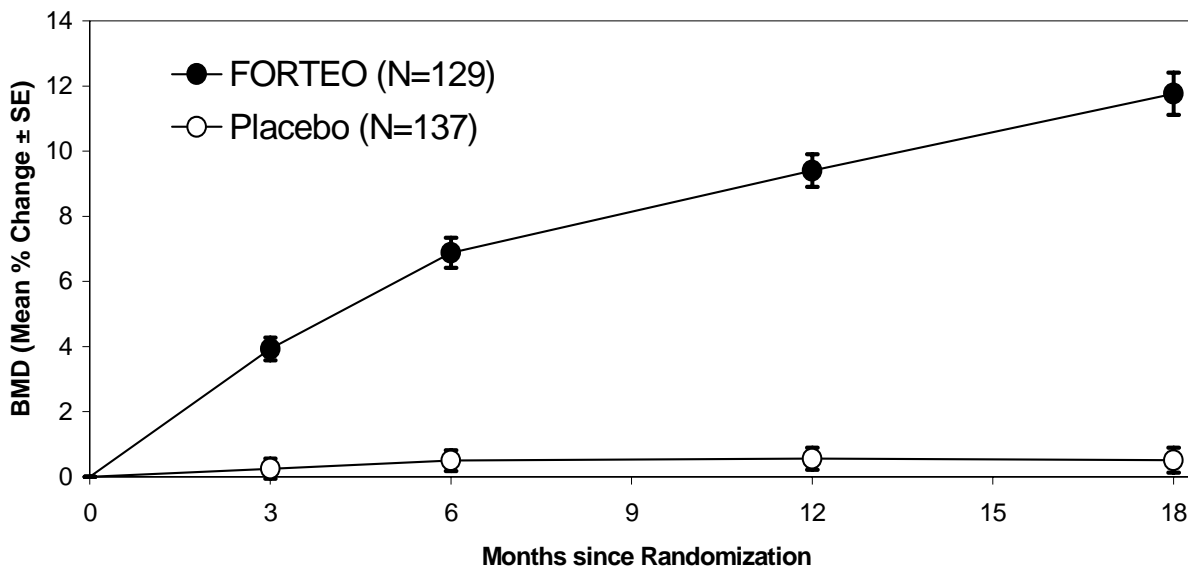


Figure 2. Time course of change in lumbar spine BMD in postmenopausal women with osteoporosis treated with FORTEO vs placebo (women with data available at all time points).

($p < 0.001$ for FORTEO compared with placebo at each post-baseline time point)

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

220

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

221 * Intent-to-treat analysis, last observation carried forward.

222 ^a $p < 0.001$ compared with placebo.

223 ^b $p < 0.05$ compared with placebo.

224

225 Figure 3 shows the cumulative distribution of the percentage change from baseline of lumbar
226 spine BMD for the FORTEO and placebo groups. FORTEO treatment increased lumbar spine
227 BMD from baseline in 96% of postmenopausal women treated (*see* Figure 3).

228 Seventy-two percent of patients treated with FORTEO achieved at least a 5% increase in spine
 229 BMD, and 44% gained 10% or more.
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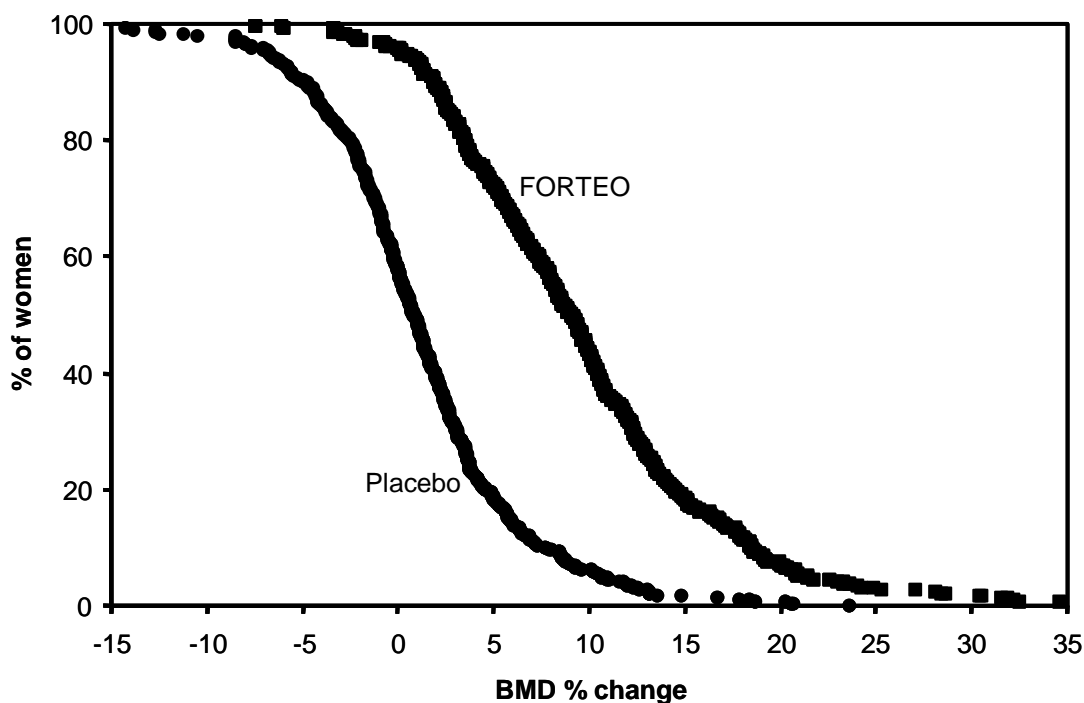


Figure 3. Percent of postmenopausal women with osteoporosis attaining a lumbar spine BMD percent change from baseline at least as great as the value on the x-axis (median duration of treatment 19 months).

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

234 Bone histology — The effects of teriparatide on bone histology were evaluated in iliac crest
 235 biopsies of 35 postmenopausal women treated for 12 to 24 months with calcium and vitamin D
 236 and teriparatide 20 or 40 mcg/day. Normal mineralization was observed with no evidence of
 237 cellular toxicity. The new bone formed with teriparatide was of normal quality (as evidenced by
 238 the absence of woven bone and marrow fibrosis).

239 Treatment to increase bone mass in men with primary or hypogonadal osteoporosis — The
 240 safety and efficacy of once-daily FORTEO, median exposure of 10 months, were examined in a
 241 double-blind, placebo-controlled clinical study of 437 men with either primary (idiopathic) or
 242 hypogonadal osteoporosis (FORTEO 20 mcg, n=151). This multicenter efficacy study was
 243 performed in the US and 10 other countries. All men received 1000 mg of calcium per day and at
 244 least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine
 245 BMD.

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

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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.

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256 Figure 4 shows the cumulative distribution of the percentage change from baseline of lumbar
257 spine BMD for the FORTEO and placebo groups. FORTEO treatment for a median of 10 months
258 increased lumbar spine BMD from baseline in 94% of men treated. Fifty-three percent of patients
259 treated with FORTEO achieved at least a 5% increase in spine BMD, and 14% gained 10% or
260 more.

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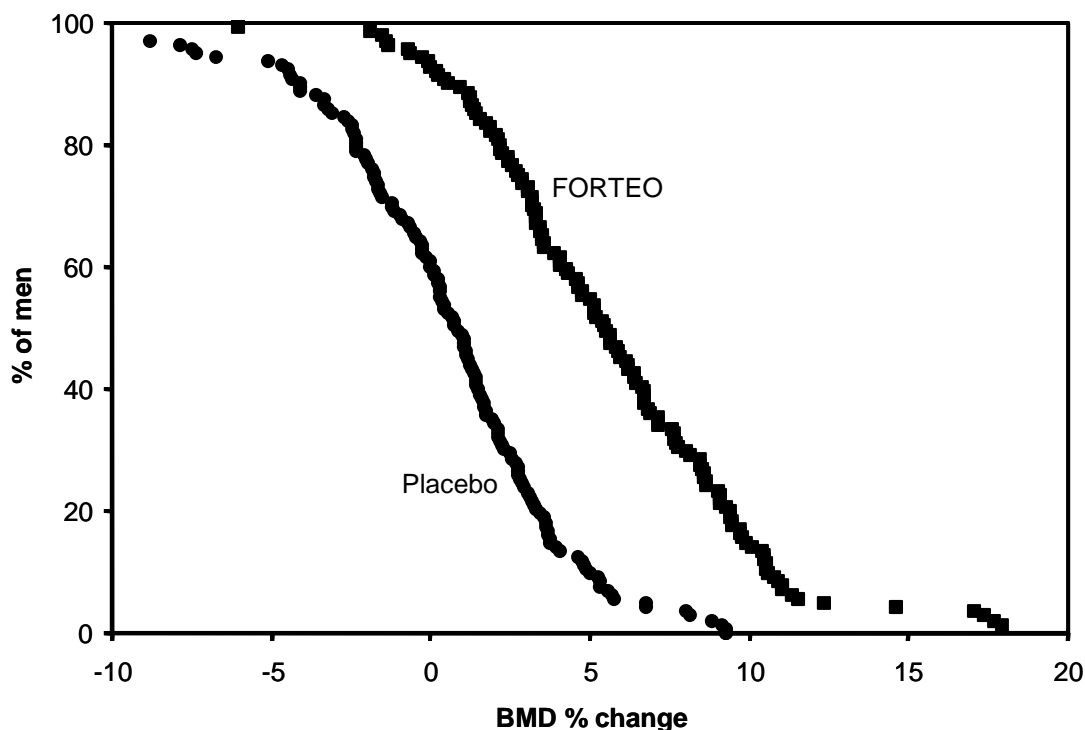


Figure 4. Percent of men with primary or hypogonadal osteoporosis attaining a lumbar spine BMD percent change from baseline at least as great as the value on the x-axis (median duration of treatment 10 months).

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INDICATIONS AND USAGE

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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.

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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.

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- 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.

283

CONTRAINDICATIONS

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285

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

WARNINGS

286
287 **In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma**
288 **(a malignant bone tumor) that was dependent on dose and treatment duration** (*see* BLACK
289 BOX WARNING *and* PRECAUTIONS; Carcinogenesis).

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

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

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

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

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

PRECAUTIONS

306 General

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

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

314 Hypotension

315 In short-term clinical pharmacology studies with teriparatide, transient episodes of
316 symptomatic orthostatic hypotension were observed infrequently. Typically, an event began
317 within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When
318 transient orthostatic hypotension occurred, it happened within the first several doses, it was
319 relieved by placing the person in a reclining position, and it did not preclude continued treatment.

320 Concomitant treatment with digitalis

321 In a study of 15 healthy people administered digoxin daily to steady state, a single FORTEO
322 dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic
323 Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect).
324 However, sporadic case reports have suggested that hypercalcemia may predispose patients to
325 digitalis toxicity. Because FORTEO transiently increases serum calcium, FORTEO should be
326 used with caution in patients taking digitalis.

327 Hepatic, renal, and cardiac

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

330 Information for Patients

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

333 General

334 Patients should read the *Medication Guide* and pen *User Manual* before starting therapy with
335 FORTEO and re-read them each time the prescription is renewed.

336 Osteosarcomas in rats

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

339 Orthostatic hypotension

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

345 Hypercalcemia

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

349 Use of the pen

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

352 Other osteoporosis treatments

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

356 Laboratory Tests

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

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

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

369 Renal function — No clinically important adverse renal effects were observed in clinical
370 studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN),
371 creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine
372 sediment. Long-term evaluation of patients with severe renal insufficiency, patients undergoing
373 acute or chronic dialysis, or patients who have functioning renal transplants has not been
374 performed.

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

379 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

380 **Carcinogenesis**

381 Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and
382 female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 mcg/kg/day for
383 24 months from 2 months of age. These doses resulted in systemic exposures that were,
384 respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans
385 following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment
386 resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant
387 bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the
388 incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related
389 increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or
390 osteomas were observed in untreated control rats. The bone tumors in rats occurred in association
391 with a large increase in bone mass and focal osteoblast hyperplasia.

392 The second 2-year study was carried out in order to determine the effect of treatment duration
393 and animal age on the development of bone tumors. Female rats were treated for different periods
394 between 2 and 26 months of age with subcutaneous doses of 5 and 30 mcg/kg (equivalent to
395 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study
396 showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon
397 dose and duration of exposure. Bone tumors were observed when immature 2-month old rats
398 were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone
399 tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for
400 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with
401 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to
402 bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

403 The relevance of these rat findings to humans is uncertain.

404 **Mutagenesis**

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

409 **Impairment of fertility**

410 No effects on fertility were observed in male and female rats given subcutaneous teriparatide
411 doses of 30, 100, or 300 mcg/kg/day prior to mating and in females continuing through gestation
412 Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m²).

413 **Pregnancy**

414 Pregnancy Category C — In pregnant rats given subcutaneous teriparatide doses up to
415 1000 mcg/kg/day, there were no findings. In pregnant mice given subcutaneous doses of 225 or
416 1000 mcg/kg/day (≥60 times the human dose based on surface area, mcg/m²) from gestation
417 Day 6 through 15, the fetuses showed an increased incidence of skeletal deviations or variations
418 (interrupted rib, extra vertebra or rib).

419 Developmental effects in a perinatal/postnatal study in pregnant rats given subcutaneous doses
420 of teriparatide from gestation Day 6 through postpartum Day 20 included mild growth retardation
421 in female offspring at doses ≥225 mcg/kg/day (≥120 times the human dose based on surface area,
422 mcg/m²), and in male offspring at 1000 mcg/kg/day (540 times the human dose based on surface
423 area, mcg/m²). There was also reduced motor activity in both male and female offspring at
424 1000 mcg/kg/day. There were no developmental or reproductive effects in mice or rats at a dose
425 of 30 mcg/kg (8 or 16 times the human dose based on surface area, mcg/m²). The effect of
426 teriparatide treatment on human fetal development has not been studied. FORTEO is not
427 indicated for use in pregnancy.

428 **Nursing Mothers**

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

432 **Pediatric Use**

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

435 **Geriatric Use**

436 Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women,
437 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients
438 receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and
439 13% were 75 years of age and over. No significant differences in bone response or adverse
440 reactions were seen in geriatric patients receiving FORTEO as compared with younger patients.
441 Nonetheless, as with many medications, elderly patients may have greater sensitivity to the
442 adverse effects of FORTEO.

ADVERSE EVENTS

443 The safety of teriparatide has been evaluated in 24 clinical trials that enrolled over
444 2800 women and men. Four long-term Phase 3 clinical trials included 1 large placebo-controlled,
445 double-blind, multinational trial with 1637 postmenopausal women; 1 placebo-controlled,
446 double-blind, multinational trial with 437 men; and 2 active-controlled trials including
447 393 postmenopausal women. Teriparatide doses ranged from 5 to 100 mcg/day in short-term
448 trials and 20 to 40 mcg/day in the other trials. A total of 1943 of the patients studied received
449 teriparatide, including 815 patients at 20 mcg/day and 1107 patients at 40 mcg/day. In the clinical
450 trials, a total of 1432 patients were treated with teriparatide for 3 months to 2 years, of whom
451 1137 were treated for greater than 1 year (500 at 20 mcg/day and 637 at 40 mcg/day). The
452 maximum duration of treatment was 2 years. Adverse events associated with FORTEO usually
453 were mild and generally did not require discontinuation of therapy.

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

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

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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

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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.

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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.

477 **Postmarketing Reports**

478 Since market introduction, adverse events reported have included:

- 479 • Possible allergic events soon after injection: acute dyspnea, oro/facial edema, generalized
- 480 urticaria, chest pain. (less than 1 in 1000 patients treated).
- 481 • Hypercalcemia greater than 2.76 mmol/L (11 mg/dL) (less than 1 in 100 patients treated);
- 482 hypercalcemia greater than 3.25 mmol/L (13 mg/dL) (less than 1 in 1000 patients treated).
- 483 • Injection site and injection technique events including pain, swelling, erythema, localized
- 484 bruising, pruritus and minor bleeding at the injection site (less than 1 in 30 patients treated).
- 485 These usually have been mild and transient.

486 **OVERDOSAGE**

487 Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been
 488 administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for
 489 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect
 490 and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur.

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

496 In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was
 497 seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area,
 498 mcg/m²) or in mice given 10,000 mcg/kg (2700 times the human dose based on surface area,
 499 mcg/m²).

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

503 **DOSAGE AND ADMINISTRATION**

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

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

509 FORTEO is a clear and colorless liquid. Do not use if solid particles appear or if the solution is
 510 cloudy or colored. The FORTEO pen should not be used past the stated expiration date.

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

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

515 **INSTRUCTIONS FOR PEN USE**

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

523 **STORAGE**

524 The FORTEO pen should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times.
525 Recap the pen when not in use to protect the cartridge from physical damage and light. During
526 the use period, time out of the refrigerator should be minimized; the dose may be delivered
527 immediately following removal from the refrigerator.

528 Do not freeze. Do not use FORTEO if it has been frozen.

529 **HOW SUPPLIED**

530 The FORTEO pen is available in the following package size: One 3 mL prefilled pen delivery
531 device NDC 0002-8971-01 (MS8971)

532

533 Literature revised February 16, 2004

www.forteo.com

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535 Manufactured by Lilly France S.A.S., - F-67640 Fegersheim, France for Eli Lilly and
536 Company - Indianapolis, IN 46285, USA

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539 **Medication Guide**

540 **FORTEO™**

541 **Generic name: teriparatide (rDNA origin) injection**

542 Read this information carefully before you start taking FORTEO (for-TAY-o) to learn about the
543 benefits and risks of FORTEO. Before beginning therapy, read the FORTEO pen User Manual
544 for information on how to use the pen to inject your medicine. Read the information you get with
545 FORTEO each time you get a refill, in case something has changed. Talk with your health care
546 provider if there is something you do not understand or if you want to learn more about
547 FORTEO.

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

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

554 FORTEO is approved for use in both men and postmenopausal (after the “change of life”)
555 women with osteoporosis who are at high risk for having broken bones (fractures) from
556 osteoporosis.

557 Before starting treatment, talk with your doctor about the possible benefits and risks of FORTEO
558 so you can decide if it is right for you.

559 **What is osteoporosis?**

560 Osteoporosis is a disease in which the bones become thin and weak, increasing the chance of
561 having a broken bone. Osteoporosis usually causes no symptoms until a fracture happens. The
562 most common fractures are in the spine (backbone). They can shorten height, even without
563 causing pain. Over time, the spine can become curved or deformed and the body bent over.

564 Fractures from osteoporosis can also happen in almost any bone in the body, for example, the
565 wrist, rib, or hip. Once you have had a fracture, the chance for more fractures greatly increases.

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

- 567 • past broken bones from osteoporosis.
- 568 • very low bone mineral density (BMD).
- 569 • frequent falls.
- 570 • limited movement, such as using a wheelchair.
- 571 • medical conditions likely to cause bone loss, such as some kinds of arthritis.
- 572 • medicines that may cause bone loss, for example: seizure medicines (such as phenytoin),
573 blood thinners (such as heparin), steroids (such as prednisone), high doses of vitamins A
574 or D.

575 **What is FORTEO?**

576 FORTEO is a prescription medicine used to treat osteoporosis by forming new bone. FORTEO is
577 the brand name for teriparatide, which is the same as the active part of a natural hormone called
578 parathyroid hormone or “PTH.” FORTEO forms new bone, increases bone mineral density and
579 bone strength, and as a result, reduces the chance of getting a fracture. In a study of
580 postmenopausal (after the “change of life”) women with osteoporosis, FORTEO reduced the
581 number of fractures of the spine and other bones. The effect on fractures has not been studied in
582 men.

583 FORTEO is approved for use in both men and postmenopausal women with osteoporosis who
584 are at high risk for having fractures. FORTEO can be used by people who have had a fracture
585 related to osteoporosis, or who have multiple risk factors for fracture (See “What is
586 osteoporosis?”), or who cannot use other osteoporosis treatments.

587 **Who should not use FORTEO?**

588 **Do not use FORTEO if you:**

- 589 • have Paget’s disease of the bone.
- 590 • have unexplained high levels of alkaline phosphatase in your blood, which means you
591 might have Paget’s disease. If you are not sure, ask your doctor.
- 592 • are a child or growing adult.
- 593 • have ever been diagnosed with bone cancer or other cancers that have spread
594 (metastasized) to your bones.
- 595 • have had radiation therapy involving your bones.
- 596 • have certain bone diseases. If you have a bone disease, tell your doctor.
- 597 • have too much calcium in your blood (hypercalcemia).
- 598 • are pregnant or nursing.
- 599 • have had an allergic reaction to FORTEO or one of its ingredients (See the ingredients
600 section at the end of this Medication Guide).
- 601 • have trouble injecting yourself and do not have someone who can help you.

602
 603 FORTEO should not be used to prevent osteoporosis or to treat patients who are not considered
 604 to be at high risk for fracture.

605 **Tell your health care provider and pharmacist about all the medicines you are taking** when
 606 you start taking FORTEO, and if you start taking a new medicine after you start FORTEO
 607 treatment. Tell them about all medicines you get with prescriptions and without prescriptions, as
 608 well as herbal or natural remedies. Your doctor and pharmacist need this information to help
 609 keep you from taking a combination of products that may harm you.

610 **How should I take FORTEO?**

- 611 • Take FORTEO once a day for as long as your doctor prescribes it for you. Use of
 612 FORTEO for more than 2 years is not recommended. Your health care professional
 613 (doctor, nurse, or pharmacist) should teach you how to use the FORTEO pen (multidose
 614 prefilled delivery device). (See the User Manual for written instructions on how to use the
 615 FORTEO pen.)
- 616 • The FORTEO pen contains 28 daily doses. The daily dose is 20 micrograms (see the User
 617 Manual).
- 618 • Some patients get dizzy or get a fast heartbeat after the first few doses. For the first few
 619 doses, inject FORTEO where you can sit or lie down right away if you get dizzy.
- 620 • Inject FORTEO once each day in your thigh or abdomen (lower stomach area).
- 621 • You can take FORTEO with or without food or drink.
- 622 • You can take FORTEO at any time of the day. To help you remember to take FORTEO,
 623 take it at about the same time each day.
- 624 • Do not use FORTEO if it has solid particles in it, or if it is cloudy or colored. It should be
 625 clear and colorless.
- 626 • Do not use FORTEO after the expiration date printed on the pen and pen packaging.
- 627 • Do not transfer the contents of the FORTEO pen to a syringe.
- 628 • Throw away any FORTEO pen that you started using more than 28 days earlier, even if it
 629 still has medicine in it (See the User Manual).
- 630 • Inject FORTEO shortly after you take the pen out of the refrigerator. Recap the pen and
 631 put it back into the refrigerator right after use (See the User Manual).
- 632 • If you forget or are unable to take FORTEO at your usual time, take it as soon as possible
 633 on that day. Do not take more than one injection in the same day.
- 634 • Talk with your health care provider about other ways you can help your osteoporosis,
 635 such as exercise, diet, supplements, and reducing or stopping your use of tobacco and
 636 alcohol. If your health care provider recommends calcium and vitamin D supplements,
 637 you can take them at the same time as FORTEO.

638 **What are the possible side effects of FORTEO?**

639 Most side effects are mild and include dizziness and leg cramps. If you become lightheaded or
 640 have fast heartbeats after your injection, sit or lie down until you feel better. If you do not feel
 641 better, call your health care provider before continuing treatment.

642 Contact your health care provider if you have continuing nausea, vomiting, constipation, low
643 energy, or muscle weakness. These may be signs there is too much calcium in your blood.

644 Patients may experience 1 or more of the following at the site of the injection: redness, swelling,
645 pain, itching, a few drops of blood, and bruising. These are usually mild and last for a short time.

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

648 Your health care provider may take samples of blood and urine during treatment to check your
649 response to FORTEO. Also, your health care provider may ask you to have follow-up tests of
650 bone mineral density.

651 **How should I store FORTEO?**

- 652 • Keep your FORTEO pen in the refrigerator at 36° to 46°F (2° to 8°C).
- 653 • Do not freeze the pen. Do not use FORTEO if it has been frozen.
- 654 • You can use your FORTEO pen for up to 28 days including the first injection from the
655 pen.
- 656 • Throw away the pen properly (See the User Manual) after 28 days of use, even if it is not
657 completely empty.
- 658 • Recap the pen after each use (See the User Manual) to protect from physical damage.

659 **General information about using FORTEO safely and effectively**

660 Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides.
661 Do not use FORTEO for a condition for which it was not prescribed. Do not give FORTEO to
662 other people, even if they have the same condition you have.

663 This Medication Guide summarizes the most important information about FORTEO. If you
664 would like more information, talk with your doctor, nurse, or pharmacist. You can ask your
665 pharmacist or health care provider for information about FORTEO that is written for health care
666 professionals. You can also call Lilly toll free at 1-866-4FORTEO (1-866-436-7836).

667 **Ingredients**

668 In addition to the active ingredient teriparatide, inactive ingredients are glacial acetic acid,
669 sodium acetate (anhydrous), mannitol, Metacresol, and Water for Injection. In addition,
670 hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to
671 adjust product pH.

672 *This Medication Guide has been approved by the US Food and Drug Administration.*

673 Literature revised February 16, 2004

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