

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **21-318**

FINAL PRINTED LABELING

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 are 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

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