Forteo Monograph

Brand Name: Forteo®
Generic Name: teriparatide (rDNA origin)
Manufacturer: Eli Lilly
Year introduced: 2002

Mechanisms of Action: [1-2]

Teriparatide is a recombinant amino terminal fragment of parathyroid hormone (PTH), comprised of the first 34 amino acids of PTH, which produce most of its biologic effects. Endogenous parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in the bone and kidney. Teriparatide's anabolic effects manifest as an increase in skeletal mass, an increase in the number of osteoblasts and osteoclasts (allowing for an increase in bone remodeling), and an increase in bone strength. Depending on the level of exposure, PTH and teriparatide may also decrease bone mass.

FDA approved indications:[1-2]

Forteo® is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for vertebral or nonvertebral fracture (failed or intolerant of previous osteoporosis therapy, history of osteoporotic fracture, or multiple risk factors for fracture). Additionally, Forteo® is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture (history of osteoporotic fracture, multiple risk factors for fracture, failed or intolerant of previous osteoporosis therapy). Forteo® is also indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

Contraindications:[1-2]

- Hypersensitivity to teriparatide or any of its excipients

Pharmacokinetics:[1-2]

Bioavailability: 95%
Metabolism: Hepatic
Elimination: Renal
Half-life: 5 minutes IV; 1 hour SQ

Adverse Effects:[1-2]

Adverse reaction	Forteo N=691 (%)	Placebo N=691 (%)
Body as a Whole		

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

Drug Interactions:[1-2]

Precipitant drug	Object drug	Description

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Teriparatide	Digoxin	↑	Teriparatide increases serum calcium and may predispose patients to digoxin toxicity.

Precaution/ Warnings:[1-2]

- **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 following categories of patients have increased baseline risk of osteosarcoma and should not be administered Forteo:
  - -Patients with Paget's disease of bone
  - -Pediatric patients or young adults with open epiphyses
  - -Patients with a prior history of radiation therapy involving the skeleton

- Patients with bone metastases or history of skeletal malignancies should be excluded from treatment with Forteo.
- Patients with metabolic bone diseases other than osteoporosis should not be treated with Forteo.
- The safety and efficacy of Forteo have not been evaluated beyond 2 years of treatment; use for greater than 2 years is not recommended.
- Transient episodes of symptomatic orthostatic hypotension have been observed following the administration of Forteo.
- Limited information is available concerning the use of Forteo in patients with hepatic, renal and cardiac disease. Forteo should be used with caution in these populations.
- Teriparatide transiently increases serum calcium, with a maximal effect seen approximately 4 to 6 hours following administration. Do not treat patients known to have an underlying hypercalcemic disorder, such as primary hyperthyroidism, with teriparatide.
- Muscle spasms of the leg and back have been reported during postmarketing experience with use of teriparatide.

Pregnancy/Lactation:[1-2] Teriparatide belongs to pregnancy category C, and it should not be given to nursing mothers.

Usual Dosage:[1-2] The recommended dosage is 20mcg SQ once daily. Forteo is available as a 600mcg/2.4 ml and 750mcg/3 ml pen device.

Patent/Exclusivity Expiration Date:[3] 11/26/2005

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Clinical Studies:

Title & Author	Study design	Results
A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis – Body J et al. [4] (2002)	In this randomized double-blind study, 146 postmenopausal women were assigned to receive once daily subcutaneous injections of teriparatide 40mcg plus oral placebo (n=73) or oral alendronate 10mg plus placebo injection (n=73) for a median of 14 months. *Inclusion Criteria* • 30-85 years of age • Ambulatory • 5 years post menopause • Lumbar spine or femoral neck bone mineral density (BMD) at least 2.5 SD below the mean for young adult women	***Primary endpoint:*** • Nonvertebral fracture incidence • Bone turnover ***Efficacy: teriparatide ≥ alendronate*** • At 3 months, teriparatide increased lumbar spine BMD more than did alendronate (P<0.001). • Lumbar spine-BMD increased by 12.2% in the teriparatide group and 5.6% in the alendronate group (P<0.001). • Teriparatide increased femoral neck BMD and total body BMD significantly more than did alendronate, but BMD at the one-third distal radius decreased compared with alendronate (P≤0.05). • Nonvertebral fracture incidence was lower in the teriparatide group (4.1%) than in the alendronate group (13.7%, P=0.042). (The time from baseline for each fracture revealed that 5 fractures occurred within the first 6 months of treatment in the alendronate group, and 5 fractures were reported after more than 6 months of treatment. In the teriparatide group, 1 fracture occurred within 6 months of treatment and 2 fractures occurred after more than 6 months of treatment.) • Mean height did not change between baseline and endpoint in either group. • There was an increase in serum 1,25-dihydroxyvitamin D_3, and a decrease in serum intact PTH (1-84) and 25-hydroxyvitamin D at the 12-month visit in the teriparatide group, compared with the alendronate group. ***Safety: teriparatide ≈ alendronate*** • A total of 21 women, 7 in the alendronate group (10%) and 14 in the teriparatide group (19%), withdrew because of adverse events (P=0.099). • Fewer patients reported new or worsened back pain in the teriparatide group (5.5%) than in the alendronate group (19.2%,

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Title & Author	Study design	Results
		P=0.012). • Leg cramps were reported by 6 patients (8.2%) in the teriparatide group and none in the alendronate group (P=0.012). • Asymptomatic hypercalcemia occurred with teriparatide treatment (P<0.001). • Teriparatide increased median 24-h urinary calcium excretion by 38mg/d at the 1-month visit (P=0.001, compared with baseline and alendronate). • There were decreases in total alkaline phosphatase in the alendronate group and increases in the teriparatide group. • There was also an increase in serum uric acid in the teriparatide group.
The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis – Orwoll E, et al. [5] (2003)	In this randomized double-blind study, 437 men were assigned to receive placebo, teriparatide 20mcg or teriparatide 40mcg plus calcium and vitamin D for a median of 11 months. *Inclusion Criteria* • 30-85 years of age • Ambulatory • Lumbar spine or proximal femur bone mineral density (BMD) more than 2.0 SD below the mean for young adult men	***Primary endpoint:*** • Lumbar spine BMD (change from baseline) ***Secondary endpoints:*** • BMD of the total hip, femoral neck, intertrochanter, trochanter, radial, and whole body • Whole body bone mineral content ***Efficacy: teriparatide > placebo*** • Spine BMD was greater in the teriparatide group than placebo after 3 months of therapy. By the end of therapy, BMD increased by 5.9% in the 20mcg and 9.0% in the 40mcg group (P<0.001 vs. placebo for both comparisons). • Femoral neck BMD increased 1.5% (20mcg; P=0.029) and 2.9% (40mcg; P<0.001), and whole body bone mineral content increased 0.6% (20mcg; P=0.021) and 0.9% (40mcg; P=0.005) above baseline in the teriparatide group. • About 40% of patients in the placebo group had a net decrease in lumbar spine BMD at the end of the study, whereas lumbar spine BMD decreased in 7.1% of patients in the teriparatide 20ug group and 6.2% in the teriparatide 40ug group. ***Safety: teriparatide < placebo*** • 39 (8.9%) patients withdrew from the study

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Title & Author	Study design	Results
		due to an adverse event. • The most common drug related reason for withdrawal was nausea. • Headache occurred more frequently in the 40mcg group. • Mean serum calcium concentrations measured at 4-6 hours after injection of teriparatide were higher in the teriparatide groups at all time points (p<0.001 versus placebo). • Serum calcium levels were above the upper limit of normal in 6.2% of subjects receiving 20mcg of teriparatide (p=0.003 versus placebo) and in 16.8% receiving 40mcg of teriparatide (p<0.001 versus placebo). • Three patients in the 20mcg group and six patients in the 40mcg were withdrawn from the study because of elevated post injection serum calcium levels.

Conclusion:

Teriparatide effectively reduces the incidence of vertebral and nonvertebral fragility fractures in osteoporotic patients. In addition to reducing bone turnover, teriparatide stimulates the formation of new bone and increases bone mass. Teriparatide may be an alternative for the treatment of osteoporosis in patients who have failed other treatment modalities.[1-2] However, the dosage form requires a self-administered injection, which may limit utilization. The National Osteoporosis Foundation emphasizes the importance of evaluating patients at risk for developing fractures due to osteoporosis. Additionally, studies have shown that concurrent therapy with parathyroid hormone and alendronate is not beneficial in treating osteoporosis since alendronate impairs the ability of parathyroid hormone to increase bone mineral density. [6-7]

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