Clinical Imprints

Gemfrac

Prefilled Teriparatide Inj. 600 mcg/2.4ml

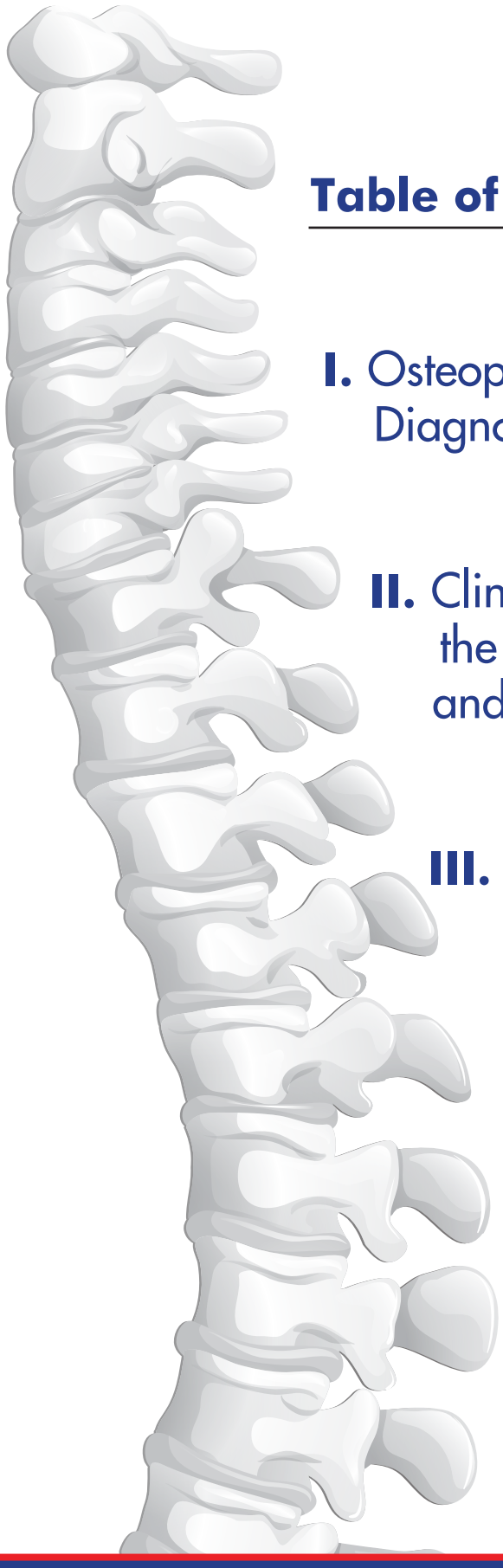


Table of Contents

I. Osteoporosis: Disease Burden and Diagnostic Benchmarks 01

II. Clinical Evaluation of Teriparatide in the Management of Osteoporosis and Fractures 06

III. Clinical Safety and Efficacy Studies for Teriparatide 11

I. Osteoporosis: Disease Burden and Diagnostic Benchmarks

General epidemiology and disease burden of osteoporosis

Osteoporosis is a skeletal disorder characterized by bone loss, low bone mass, and structural degradation of bone tissue, especially trabecular bone, yielding attenuated bone strength that, in turn, **increases the risk of fracture**. Bone strength reflects not only changes in bone density, but also in bone quality-which encompasses bone architecture, the presence or absence of microfractures, mineralization, and bone turnover.[1]

The National Osteoporosis Foundation (NOF) estimates that, in the United States, 10 million individuals, 80% of whom are women, already have osteoporosis, with an additional 34 million individuals at risk because of low bone mass.[1,2] The prevalence of low bone density increases dramatically with age, affecting 37% of women between the ages of 50 and 59 years, 50% between the ages of 60 and 69 years, 75% between 70 and 79 years, and 87% of women over age 80.[2] The lifetime **fracture risk of a patient with osteoporosis is as high as 40%**, and fractures **most commonly occur in the spine, hip, or wrist**, but other bones such as the trochanter, humerus, or ribs can also be affected. From a patient's perspective, a fracture and the subsequent loss of mobility and autonomy often represent a major drop in quality of life.[3,4] Although the majority of research on osteoporosis in the past has focused on women, osteoporosis is also becoming an increasingly important problem in men. **One in 8 men ≥50 yrs of age will have an osteoporosis-related fracture**, and this figure is predicted to rise with an aging male population. Although fragility fractures in men occur an average of 10 years later compared with those in women[5], most clinical fractures result in greater morbidity and mortality.[6]

The population of India is expected to increase to 1,613 million by 2050, of which 19.6% (315 million), will be adults over 60 years. This indicates that in the years to come, a very large population will be at risk for osteoporosis, especially with the increase in the elderly population. Indians have a lower BMD compared to Western countries and studies suggest that **20% of women and about 10-15% of men are osteoporotic in India**. Osteoporotic fractures are common in both sexes, and may occur at a younger age than in the western countries.[7,8]

A clinical evaluation should assess risk factors for osteoporosis to identity high-risk patients who require additional testing or preventive interventions. Advancing age, low bone density, personal or family history of fracture, thin body frame, and hypogonadism increase the risk of a fracture both in women and men. A number of additional lifestyle factors, disorders, and medications also increase the risk of an osteoporosis-related fracture (Figure 1). In general, the greater the number of risk factors present, the greater the risk of a fracture. Primary osteoporosis is the result of bone loss related to the decline in gonadal function associated with aging. Secondary osteoporosis may result from chronic diseases, exposures, or nutritional deficiencies that adversely impact bone metabolism.[9-11]

Figure 1. Factors associated with an increased risk of osteoporosis-related fractures

Reversible lifestyle factors

- Low calcium intake
- Immobilization
- Low body mass index
- High salt, cola, or caffeine intake
- Vitamin D insufficiency
- Inadequate physical activity
- Smoking
- Alcohol (>3 drinks/day)

Rheumatic and autoimmune diseases

- Rheumatoid arthritis
- Lupus
- Ankylosing spondylitis

Hypogonadal states

- Androgen insensitivity
- Hyperprolactinemia
- Ovarian failure

Liver diseases

- Autoimmune hepatitis
- Alcoholic cirrhosis

Endocrine disorders

- Adrenal insufficiency
- Hyperparathyroidism
- Type 1 diabetes
- Cushing's syndrome
- Hypothyroidism

Gastrointestinal disorders

- Celiac disease
- Inflammatory bowel disease
- GI surgery, gastric bypass

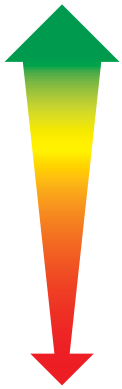
Medications

- Anticoagulants (heparin)
- Anticonvulsants
- Immunosuppresants
- Lithium
- Glucocorticoids (≥5mg/d prednisone or Equivalent for ≥ 3months)
- Aromatase inhibitors
- Barbiturates
- Gonadotropin-releasing hormone agonists

How can we diagnose osteoporosis before a fracture occurs?

Measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) is the most widely used method of diagnosing osteoporosis. Hip, spine, or wrist **BMD is expressed as a T-score**, the number of standard deviations (SD) above (+) or below (-) the young adult mean value. The World Health Organization[12] classifies bone mineral density on the basis of this T-score (Figure 2).

Figure 2. World Health Organization definitions of BMD



Normal bone mass	Bone density no lower than 1 standard deviation (SD) below the mean for young adult women (T-score equal to or above -1.0)
Low bone mass (osteopenia)	Bone density between 1.0 and 2.5 SD below the mean for young adult women (T-score between -1.0 and -2.5)
Osteoporosis	Bone density 2.5 SD or more below the young adult normal mean (T-score at or below -2.5)
Established or severe osteoporosis	Bone density of less than -2.5 SD in the presence of one or more fractures

DXA technology can measure BMD at virtually any skeletal site, but clinical use has been concentrated on the lumbar spine, proximal femur, forearm and total body. Although other factors, such as trabecular bone structure, are important, central BMD measurements via DXA are helpful in the diagnosis of osteoporosis for estimating the risk of nontraumatic fracture and in choosing and monitoring treatments.[13,14]

What are the National Osteoporosis Foundation guidelines for treatment?

Many medical organizations have issued clinical practice guidelines for treating osteoporosis, with some recommendations that differ and therefore confuse more than enlighten. In an effort to unify these disparate recommendations, the National Osteoporosis Foundation, with the support and endorsement of numerous professional societies, developed the **Clinician's Guide to Prevention and Treatment of Osteoporosis**.[9] This document addresses post-menopausal women and men age 50 and older of all ethnic groups in the United States and is intended for use by clinicians in making decisions in the care of individual patients. These recommendations have not been designed as rigid standards of practice globally, but rather as a framework for making clinical decisions with consideration of the needs of each individual patient (Figure 3).[9]

Figure 3. National Osteoporosis Foundation recommendations for all patients

A daily intake of elemental calcium of at least 1,200 mg with diet plus supplements (with no more than 500-600 mg of calcium supplementation in a single dose due to absorption of higher doses)

Vitamin D3 800-1,000 IU per day, with more needed in some patients to bring the serum 25-hypoxyvitamin D to a desirable level of 30 ng/mL (75 nmol/L) or higher

Regular weight-bearing exercise

Fall prevention

Avoidance of tobacco use and excessive alcohol intake

Who should be tested?

The National Osteoporosis Foundation (NOF) recommends testing of all women age 65 and older. NOF also provides indications for the use of DXA in other patient populations as well (Figure 4).[9]

NOF Recommendations for Osteoporosis Testing

- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Younger postmenopausal women and men age 50 to 69 with clinical risk factors for osteoporosis
- Women in the menopausal transition with specific factors associated with increased fracture risk such as low body weight, prior low-trauma fracture, or high-risk medication
- Adults who have a fracture after age 50
- Adults with a condition such as rheumatoid arthritis who are taking a medication associated with low bone mass or bone loss. e.g, glucocorticoids in a daily dose ≥5mg prednisone or equivalent for ≥3 months
- Anyone being considered for pharmacologic therapy for osteoporosis
- To monitor treatment efficacy in anyone receiving pharmacotherapy for osteoporosis

Figure 4. NOF recommendations for osteoporosis testing

Which patient groups does the NOF recommend for treatment?

In 2008, NOF released updated recommendations to assist in clinical decision-making for the treatment of osteoporosis. The decision to initiate pharmacologic treatment should consider bone mineral density (BMD), diagnostic workups, risk of fracture, and clinical judgment. Clinical guidelines also provide direction for selecting patients who would most benefit from treatment. The National Osteoporosis Foundation (NOF) recommends that treatment be considered in postmenopausal women and men age 50 and older with the following (Figure 5):[9]

NOF recommendations for treatment in postmenopausal women and men age 50 and older

- Hip or vertebral (clinical or morphometric) fracture
- T-score of -2.5 or less at the femoral neck or spine after appropriate evaluation to exclude secondary causes of osteoporosis
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture of 3% or greater OR a 10-year probability of major osteoporosis-related fracture of 20% or greater based on the US-adapted World Health Organization FRAX* algorithm

*Fracture Risk Assessment Tool

Figure 5. NOF recommendations for treatment in postmenopausal women and men age 50 and older

The most recent American Association of Clinical Endocrinologists (AACE) postmenopausal osteoporosis guidelines endorse the NOF recommendations for initiation of treatment in postmenopausal women.[15]

What is the current treatment paradigm for osteoporosis? Are there any unmet needs?

Advances in the management of osteoporosis have been accomplished over the last couple of years. Although a great variety of drugs are available today, treatment of osteoporosis is primarily based on antiresorptive agents, like bisphosphonates; estrogens; the selective estrogen receptor modulator, raloxifene; calcitonin and strontium ranelate. The mechanisms of action differ within and between these classes of drugs, but inhibition of osteoclast-mediated bone reabsorption can be considered a final common pathway.[16]

Antiresorptive drugs are an ideal way of preventing osteoporosis progression. However, they **have limited usefulness in more advanced stages of the disease, when the quality of bone architecture is seriously compromised**.[17.18] Patients with severe osteoporosis and vertebral fractures are especially susceptible to subsequent osteoporotic fractures, regardless of ongoing antiresorptive therapy. In these patients, the fracture risk reduction obtained during antiresorptive treatment (approximately 50%) is insufficient to half the QoL (quality of life) drop that comes with the simultaneously growing risk of premature morbidity and mortality.[18]

An entirely new therapeutic strategy **based on bone reconstruction factors** (i.e. parathyroid hormone [PTH] analogues) would be a real breakthrough in the management of patients with severe osteoporosis. **Anabolic drugs** have recently widened therapeutic options, as they **influence processes associated with bone formation** to a greater extent and earlier than bone reabsorption. Human recombinant parathyroid hormone (hrPTH 1-84) and human recombinant PTH peptide 1-34 (teriparatide) belong to this group of agents.[19]

Reference:

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001 Feb 14;285(6):785-95. **2.** Tucci JR. Importance of early diagnosis and treatment of osteoporosis to prevent fractures. Am J Manag Care. 2006 May;12(7 Suppl):S181-90. **3.** Burge R, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007. **4.** Center JR, Nguyen TV, Schneider D, et al. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999 Mar 13;353(9156):878-82. **5.** Bilezikian JP. Gender specificity and osteoporosis. J Gend Specif Med. 2000 Oct;3(7):6-12. **6.** Johnell O, Kanis J, Gullberg G. Mortality, morbidity, and assessment of fracture risk in male osteoporosis. Calcif Tissue Int. 2001 Oct;69(4):182-4. **7.** Malhotra N, Mithal A. Osteoporosis in Indians. Indian J Med Res. 2008 Mar;127(3):263-8. **8.** Khajuria DK, 1, Razdan R, Mahapatra DR. Drugs for the management of osteoporosis: a review. Rev Bras Reumatol. 2011 Jul-Aug;51(4):365-71, 379-82. **9.** National Osteoporosis Foundation. Clinicians Guide to prevention and treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2010. **10.** Rawlins S. Approaches to osteoporosis: screening and implementing treatment in clinical practice. J Fam Pract. 2009 Jul;58(7 Suppl Osteoporosis):S39-44. **11.** Lewiecki EM. Managing osteoporosis: challenges and strategies. Cleve Clin J Med. 2009 Aug;76(8):457-66. **12.** Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group. World Health Organ Tech Rep Ser. 1994; 843:1-129. **13.** Hans D, Downs RW Jr, Duboeuf F. Skeletal sites for osteoporosis diagnosis: the 2005 ISCD Official Positions. J Clin Densitom. 2006 Jan-Mar;9(1):15-21. **14.** Maghraoui AE, Roux C. DXA scanning in clinical practice. QJM. 2008 Aug;101(8):605-17. **15.** Watts NB, Bilezikian JP, Camacho PM. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. Endocr Pract 2010 Nov-Dec;16 Suppl 3(Suppl 3):1-37. **16.** Pleiner-Duxneuner, J., Zwettler, E., Paschalis, E. et al. Treatment of Osteoporosis with Parathyroid Hormone and Teriparatide. Calcif Tissue Int 84, 159–170 (2009). **17.** Lewiecki EM. Nonresponders to osteoporosis therapy. J Clin Densitom 2003 Winter;6(4):307-14. **18.** Miller PD. Greater risk, greater benefits: true or false (editorial) J. Clin Endocrinol Metab.2003;88:538-541. **19.** Gagnon C, Li V, Ebeling PR. Osteoporosis in men: its pathophysiology and the role of teriparatide in its treatment. Clin Interv Aging. 2008;3(4):635-45.

II. Clinical Evaluation of Teriparatide in the Management of Osteoporosis and Fractures

What is Teriparatide?

The native hormone secreted by the parathyroid gland chief cell is human parathyroid hormone (hPTH (1-84)], a single chain polypeptide with 84 amino acids which plays a central role in the maintenance of calcium and phosphate homeostasis in mammals. The ambient extracellular calcium level signals an increase in PTH secretion in response to a decrease in calcium concentration via the calcium-sensing receptors on the parathyroid cellular membrane. PTH acts directly to increase renal tubular calcium reabsorption and indirectly to enhance intestinal calcium absorption via its stimulatory action on renal 1-cholecalciferol hydroxylase (thereby increasing circulating calcitriol).[1]

The knowledge of the molecular structure of PTH allowed the production of hPTH (1-84) for treatment in humans. Moreover, the discovery that the **N-terminal 34 amino acid portion of the native PTH molecule could fully activate the PTH/PTHrP (parathormone-related peptide analogue) receptor**, has led to the generation of pharmacological products comprising only this portion, such as hPTH (1-34) and recombinant human PTH [hPTH (1-34)) (Figure 1). Teriparatide is the generic name for all PTH (1-34) molecules. It has a molecular weight of 4117.8 daltons[1-6] and is manufactured using a strain of Escherichia coli modified by recombinant DNA technology.

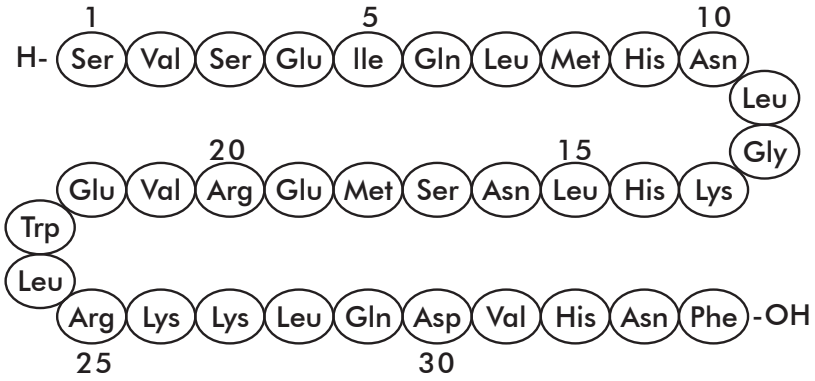


Figure 1.
Molecular structure of Teriparatide

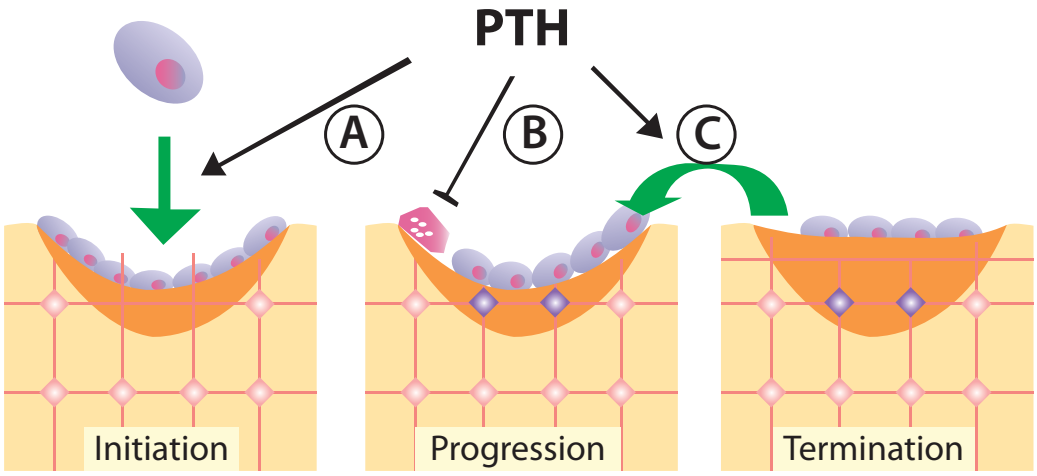
How does Teriparatide exert its anabolic actions?

A continuous endogenous production or exogenous administration of PTH, as is the case in primary or secondary hyperparathyroidism, can lead to deleterious consequences to the skeleton, particularly for cortical bone. However, **intermittent administration of PTH results in an increase in the number and activity of osteoblasts** leading to an increase in bone mass and improvement in skeletal architecture at both trabecular and cortical bone. Although there have been advances in understanding the molecular and cellular events associated with activation of the PTH receptor in bone, the mechanism of action of Teriparatide remains incompletely elucidated.[7]

The classical actions of parathyroid hormone (PTH) are mediated by the PTH/PTH related peptide receptor, or type 1 PTHR (PTH1R), a member of the B subfamily of heptahelical G-protein coupled receptors (GPCRS). **Osteoblasts, bone lining cells, and bone marrow stromal cells have PTH receptors, and Teriparatide stimulates these cells through the modulation of cAMP concentrations and cAMP-dependent protein kinase A. The PTH receptor also activates the calcium protein kinase C pathway, stimulating proliferation of cells in the osteoblastic lineage**.[8]

Teriparatide exert its anabolic effect, at least in part, by modulating the differentiation, proliferation, and activity of osteoblast pool by (Figure 2i).[7-9]

Figure 2i. Proposed cellular mechanisms involved in the anabolic effect of Teriparatide



Intermittent PTH has been proposed to increase osteoblast number by acting on the three stages of bone formation. The various mechanisms include (A) increasing the development of osteoblasts, (B) inhibiting osteoblast apoptosis, and (C) reactivating lining cells to resume their matrix synthesizing function.

Figure 2ii. PTH-stimulated survival signaling in osteoblasts

In vitro and in vivo studies have shown that **Teriparatide directly activates survival signaling in osteoblasts; and that delay of osteoblast apoptosis** is a major contributor to the increased osteoblast number. This effect requires Runx2-dependent expression of antiapoptotic genes like Bcl-2 (Figure 2ii). The Runx2 protein (Runt-related transcription factor 2) is a member of the RUNX family of transcription factors and has a Runt DNA-binding domain. It is essential for osteoblastic differentiation and skeletal morphogenesis and acts as a scaffold for nucleic acids and regulatory factors involved in skeletal gene expression.[9]

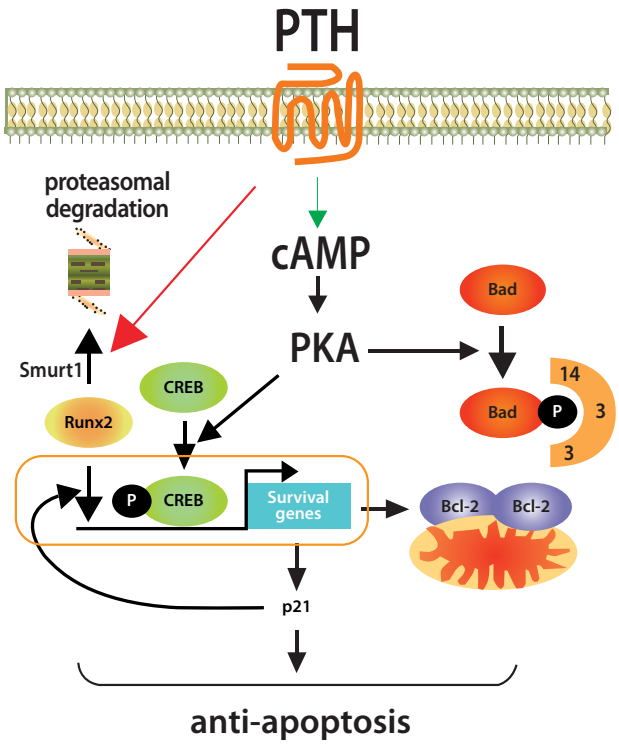
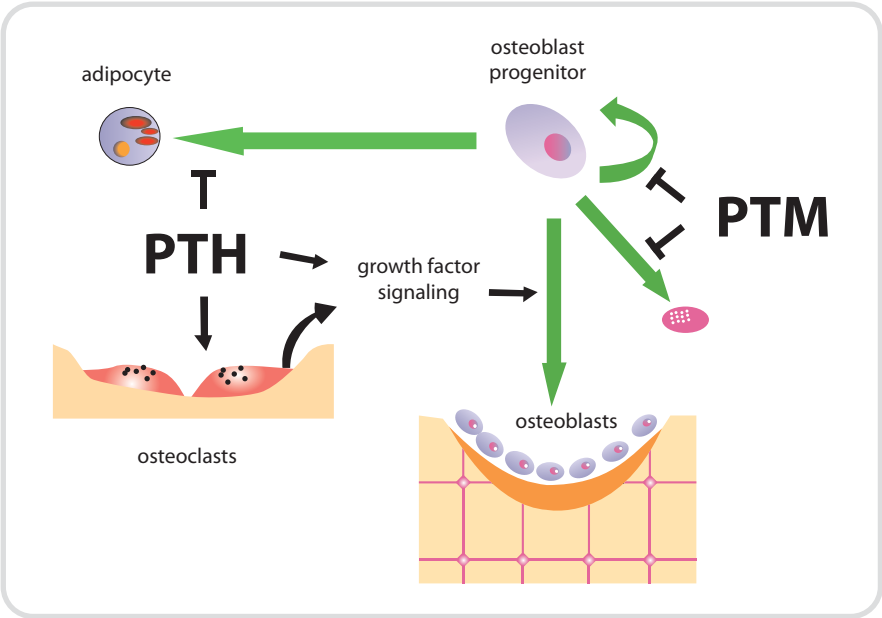


Figure 2iii. Actions of Teriparatide on osteoblast progenitors



Teriparatide exerts anti-mitotic effects on replicating osteoblast progenitors, and may also inhibit their apoptosis. The anti-mitotic effects may be necessary for differentiation in response to locally produced autocrine/paracrine growth factors (TGF, FGF, IGF) regulated by PTH, as well as factors released from the bone matrix during bone resorption. Teriparatide may also increase the number of osteoblast progenitors by preventing the differentiation of adipocytes from pleuripotent progenitors (Figure 2iii).[9]

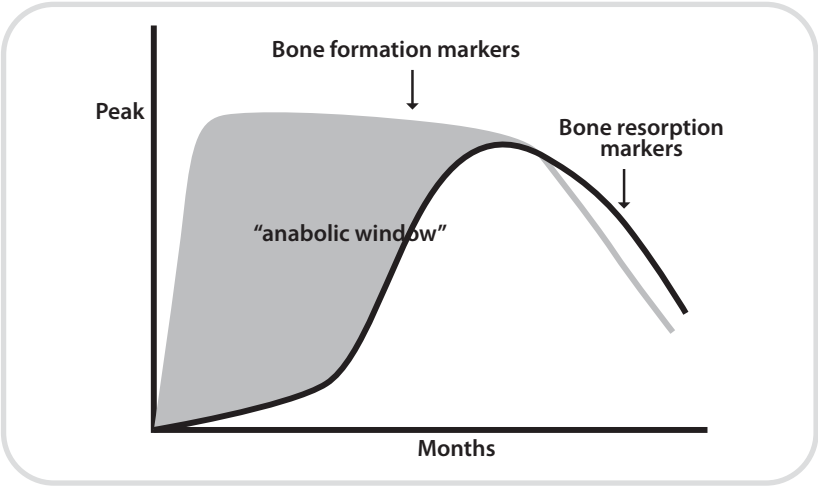
Teriparatide stimulates bone formation through an increase in the bone remodeling rate with bone formation favored over bone resorption, thereby resulting in a net gain of bone deposited in each basic multicellular unit (BMU).[10]

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. This cumulatively manifests as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength.

What is the "anabolic window"?

Clinical studies have shown that Teriparatide induces large increases in biochemical markers of bone formation after one month of therapy followed by a delayed increase in bone resorption markers.[11] This difference in the rise of bone markers produces what has been termed "**the anabolic window**", a period **when bone formation is greater than bone resorption** (Figure 3),[12] The anabolic window is based on the bone marker response to Teriparatide, and is the time of its maximum anabolic effect. The anabolic window also has implications for monitoring of patients who are receiving osteoporosis pharmacotherapy with Teriparatide.[13]

Figure 3. PTH as an anabolic agent for bone: A kinetic model



A study published by Glover et al. showed a rapid and robust **increase of PINP** (type I collagen C-terminal propeptide) by 8.2% during the first two days of Teriparatide therapy, which reached 110% by the end of the 28-day treatment period. Other bone formation markers, namely, osteocalcin and bone-specific alkaline phosphatase increased by at least 75% by the end of treatment.[14]

What are the indications for Gemfrac® (Teriparatide) use?

- Treatment of **postmenopausal women with osteoporosis at high risk for fracture** (a prior history of osteoporotic fracture, multiple risk factors for fracture), or patients who have failed or are intolerant to other available osteoporosis therapies.
- Increase of bone mass in men with primary or **hypogonadal osteoporosis at high risk for fracture**, or patients who have failed or are intolerant other available osteoporosis therapies.
- Treatment on men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent and women ≥5mg of prednisone) at high risk for fracture, or patients who have failed or are intolerant to other available osteoporosis therapies.

How is Gemfrac® (Teriparatide) supplied and what is its dose?

- Gemfrac® (Teriparatide) is supplied as a sterile, colorless, clear, isotonic solution in a pre-filled syringe only for subcutaneous use.
  - Each Gemfrac® pre-filled syringe contains 600µg of Teriparatide in 2.4ml.
- Each pre-filled syringe is to deliver 20µg of Teriparatide per dose each day for up to a 28 day period.
- The recommended dose for Gemfrac® (Teriparatide) is 20µg subcutaneously once a day into the thigh or abdominal wall. Gemfrac® (Teriparatide) is administered via a multi-dose prefilled pen delivery device containing 28 daily doses of 20µg.
  - It should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur.
  - The delivery device should be stored under refrigeration at 2 to 8°C (36 to 46°F) at all times.
  - While the delivery device is in use, the time out of the refrigerator should be minimized, the dose may be delivered immediately following removal from the refrigerator.
  - It is important to recap the delivery device when not in use to protect the pre-filled syringe from physical damage and light.

What are the pharmacokinetic attributes of Gemfrac® (Teriparatide)?

- The absolute **bioavailability is approximately 95%** based on pooled data from 20, 40, and 80µg doses. Rates of absorption and elimination are rapid.
  - Reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20µg dose, and declines to non quantifiable concentrations within 3 hours.
  - The half-life in serum is approximately 1 hour.
- 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.
- No metabolism or excretion studies have been performed with Teriparatide. However, its peripheral metabolism is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

- Pharmacokinetic data in pediatric patients are not available
- No age-related differences in Teriparatide pharmacokinetics have been detected (range 31 to 85 years).
- Although systemic exposure to Teriparatide is approximately 20% to 30% lower in men than women, the **recommended dose for both genders is 20µg/day**.
- The influence of race on pharmacokinetic parameters has not been determined.
- No pharmacokinetic differences have been identified in patients with mild or moderate renal impairment [creatinine clearance (CrCl) of 30 to 72 mL/min] administered a single dose of Teriparatide.
    - Elevations in the AUC and T½ of Teriparatide have been observed in patients with severe renal impairment (CrCl<30 mL/min). However, the maximum serum concentration of Teriparatide has not been seen to increase.
    - No studies have been performed in patients undergoing dialysis for chronic renal failure.
- No studies have been performed in patients with hepatic impairment. Non-specific proteolytic enzymes in the liver (possibly from Kupffer cells) cleave Teriparatide into fragments that are cleared from the circulation mainly by the kidney.

Is there any potential for drug interactions with Gemfrac® (Teriparatide)?

- Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because Teriparatide may transiently increase serum calcium, it should be used with caution in patients taking digoxin.
- The 24-hour urinary excretion of calcium has been observed to be reduced by a clinically insignificant amount (15%) following co-administration of hydrochlorothiazide with Teriparatide.
- Co-administration of intravenous furosemide (20 to 100 mg) with Teriparatide 40µg may result in small, clinically insignificant increases in the serum calcium (2%) and 24-hour urinary calcium (37%).

Reference:

1. Quattrocchi. Teriparatide: a review. Clin Ther.2004 Jun;26(6):841-54. **2.** Pleiner-Duxneuner, J., Zwettler, E., Paschalis, E. et al. Treatment of Osteoporosis with Parathyroid Hormone and Teriparatide. Calcif Tissue Int 84, 159–170 (2009). **3.** Lewiecki EM. Nonresponders to osteoporosis therapy. J Clin Densitom 2003 Winter;6(4):307-14. **4.** Miller PD. Greater risk, greater benefits: true or false (editorial) J. Clin Endocrinol Metab.2003;88:538-541. **5.** Gagnon C, Li V, Ebeling PR. Osteoporosis in men: its pathophysiology and the role of teriparatide in its treatment. Clin Interv Aging. 2008;3(4):635-45 **6.** Reeve J, Meunier PJ, Parsons JA, et al. Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. Br Med J. 1980 Jun 7;280(6228):1340-4. **7.** Neuprez A, Reginster JY. Bone-forming agents in the management of osteoporosis. Best Pract Res Clin Endocrinol Metab. 2008 Oct;22(5):869-83. **8.** Yang D, Singh R, Divieti P, et al. Contributions of parathyroid hormone (PTH)/PTH-related peptide receptor signaling pathways to the anabolic effect of PTH on bone. Bone. 2007 Jun;40(6):1453-61. **9.** Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. Bone. 2007 Jun;40(6):1434-46. **10.** Hodsman AB, Bauer DC, Dempster DW et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 2005 Aug;26(5):688-703. **11.** Recker RR, Marin F, Ish-Shalom S, et al. Comparative effects of teriparatide and strontium ranelate on bone biopsies and biochemical markers of bone turnover in postmenopausal women with osteoporosis. J Bone Miner Res. 2009 Aug;24(8):1358-68. **12.** Rubin MR, Bilezikian JP. New anabolic therapies in osteoporosis. Endocrinol Metab Clin North Am. 2003 Mar;32(1):285-307. **13.** Glover SJ, Eastell R, McCloskey EV, et al. Rapid and robust response of biochemical markers of bone formation to teriparatide therapy. Bone. 2009 Dec;45(6):1053-8.

III. Clinical Safety and Efficacy Studies for Teriparatide

Clinical trial data has indicated significant benefits of Teriparatide 20µg in comparison to placebo with regards to the following outcomes –

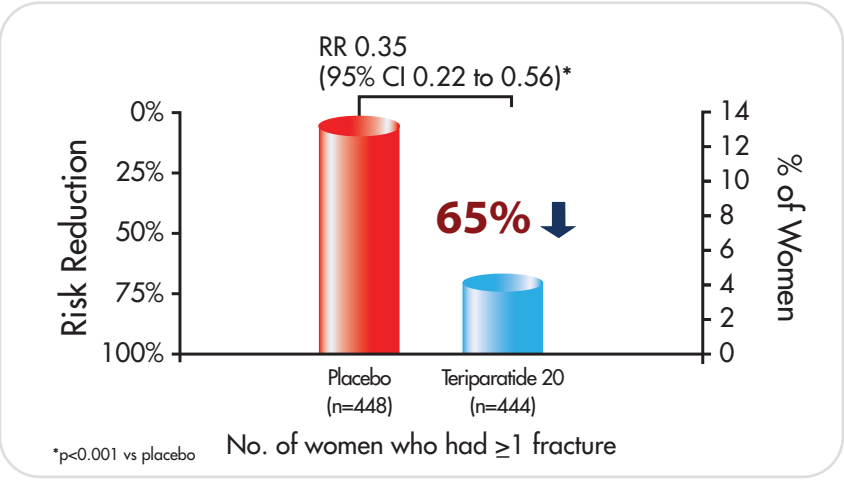
a) Reduction in the number of new vertebral fractures
b) Reduction in the number of new non-vertebral fractures
c) Increased lumbar and femoral BMD
d) Improvement in bone microarchitecture
e) Improvement in fracture healing

Treatment of postmenopausal osteoporosis with Teriparatide decreases the risk of vertebral and non–vertebral fractures — The Fracture Prevention Trial[1]

- Postmenopausal women (n=1637; 99 centers in 17 countries) with prior vertebral fractures were randomized to receive either Teriparatide (20µg or 40µg) or placebo, administered subcutaneously by the women daily over 21 months.
- Women were eligible for enrolment if they were ambulatory, if a period of at least 5 years had elapsed since menopause, and if they had at least one moderate or two mild atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine.
- Vertebral radiographs and serial measurements of bone mass were obtained by DXA.

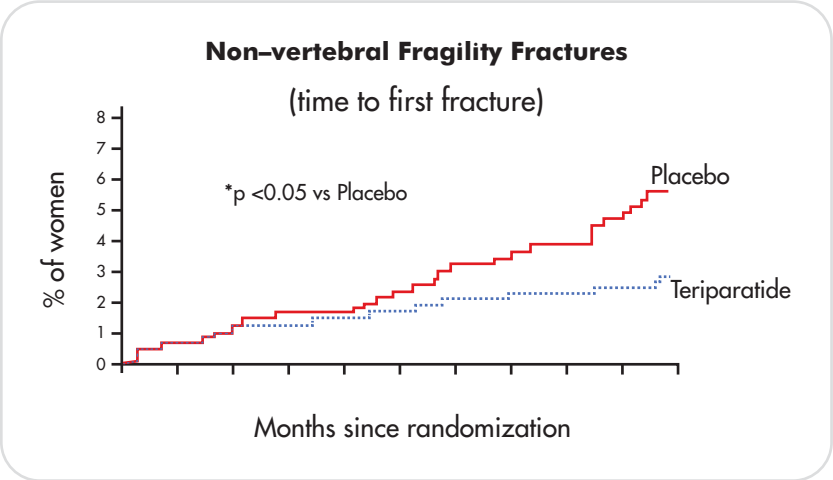
- At the 20µg dose, the risk of new radiographic vertebral fractures was reduced by 65% compared with placebo ($p<0.001$) over a median treatment period of 19 months (Figure 1).
  - Relative risk of fracture in the 20µg and 40µg groups as compared to placebo group, were 0.35 and 0.31.
  - If the analysis of the vertebral fractures was restricted to moderate or severe deformities (>26% reduction in vertebral height), the risk reduction was 90%.

Figure 1. Risk reduction in new vertebral fractures



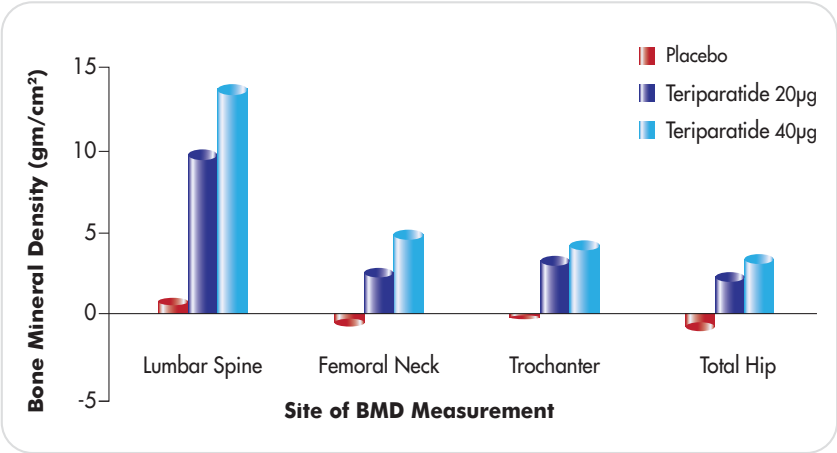
- The abosolute risk of one or more new non-vertebral fragility fractures was 6% in the placebo group, and 3% in both Teriparatide groups (relative risk, 0.47 and 0.46, respectively, p<0.05) [Figure 2].

Figure 2. Cumulative incidence of new non–vertebral fragility fractures



- As compared with placebo, there were statistically significant improvements in bone mineral density in the lumbar spine, femoral neck, trochanter and total hip for both the 20-and 40µg doses of Teriparatide (p<0.001) [Figure 3].

Figure 3. Improvements in BMD at lumbar spine and hip



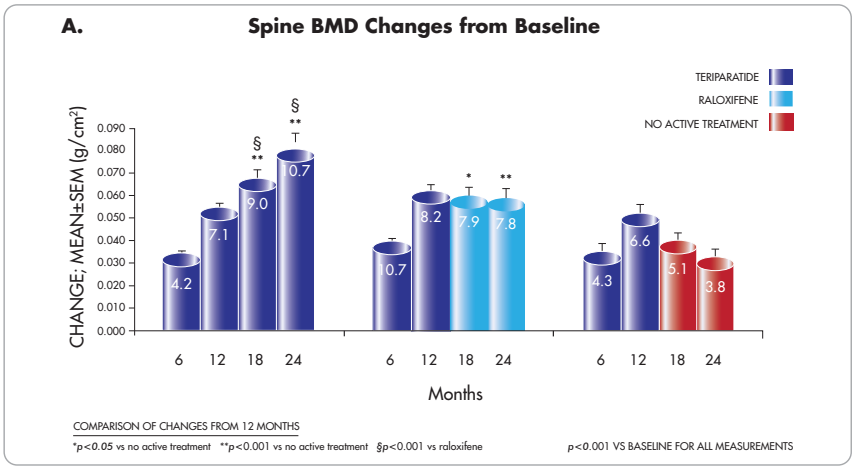
- Only minor side effects were reported for the Teriparatide groups i.e., nausea and headache.

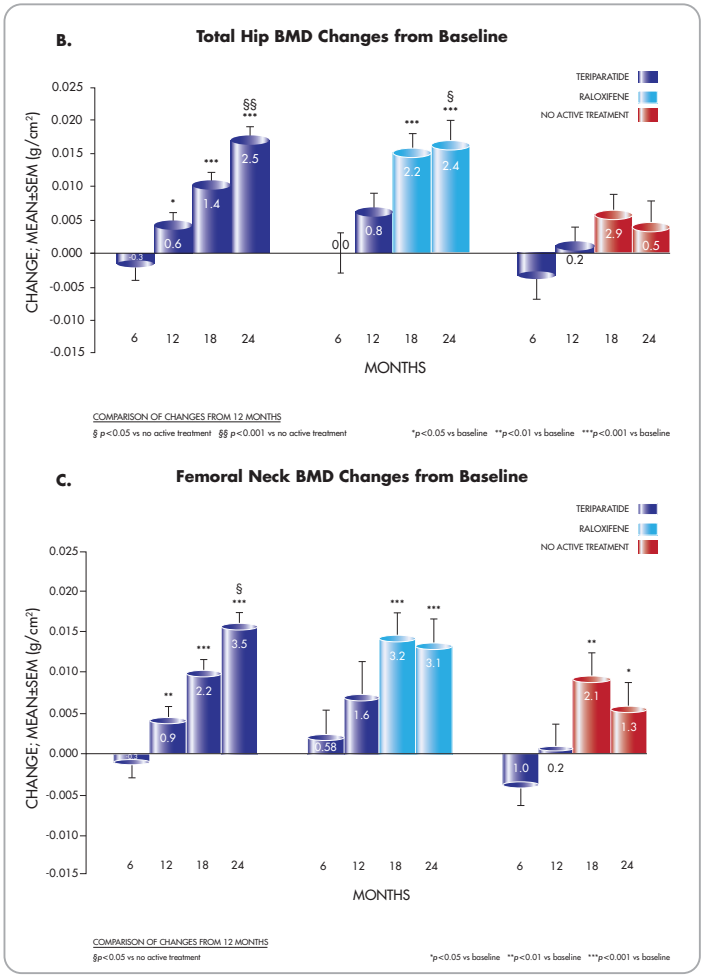
BMD increases progressively over 2 yrs of Teriparatide therapy in women with severe osteoporosis[2]

- EUROFORS was a 2-yr, prospective, controlled, randomized trial of postmenopausal women with established osteoporosis, designed to investigate the safety and efficacy of three follow-up treatments (anabolic with Teriparatide, antiresorptive with raloxifene, or no active treatment) after 1 year of Teriparatide 20µg/day.
  - The study was conducted at 95 centers across 10 European countries.
  - Trial population included ambulatory women ≥55 yr of age who were at least 2 yrs postmenopausal with a T-score of ≤2.5 for BMD at the lumbar spine, total hip, or femoral neck; and had at least one documented vertebral or non-vertebral fragility fracture in the past 3 yrs.
  - After a 1month screening period during which eligibility for enrolment was determined, all participants received once-daily subcutaneous self-injections of Teriparatide (20µg/day) together with supplements of calcium (500mg/day) and vitamin D (400-800 IU/day) throughout the first year of treatment. At 12 months, all participants were randomized (3:1:1) to continue Teriparatide (treatment arm 1; n=305), switch to raloxifene 60mg/d (treatment arm 2; n=100), or receive no active treatment (treatment arm 3; n=102) for the second year.

- Daily Teriparatide treatment for 2 yrs significantly increased spine BMD by 10.7%. Patients receiving raloxifene in year 2 had no further changes in spine BMD from year 1 (change from baseline, 7.9%), whereas patients receiving no active treatment had a BMD decrease of 2.5% in year 2 (change from baseline, + 3.8%) [Figure 4A].
- Daily Teriparatide therapy was also associated with a significant improvement in hip BMD.f
  - At the total hip, BMD increases from baseline at 2 yr were 2.5% with Teriparatide, 2.3% with raloxifene, and 0.5% with no active treatment [Figure 4B].
  - The respective BMD improvements at the femoral neck were 3.5%, 3.1%, and 1.3% [Figure 4C].
- During the first year of treatment (when all patients received Teriparatide), the most common treatment-emergent adverse events were nausea (12.4%), arthralgia (7.9%), headache (6.9%), and pain in extremities (5.1%) Hypercalcemia was reported in 4.3% of patients assigned to daily Teriparatide.
- However, during the second year of treatment, the incidences of hypercalcemia and nephrolithiasis remained <3% in all groups.

Figure 4A–C. BMD Changes from baseline for spine, hip, femoral neck





Teriparatide induces positive effects on BMD and markers of bone formation in postmenopausal women with established osteoporosis, regardless of previous long–term exposure to antiresorptive therapies – A secondary analysis from the EUROFORS Trial[3]

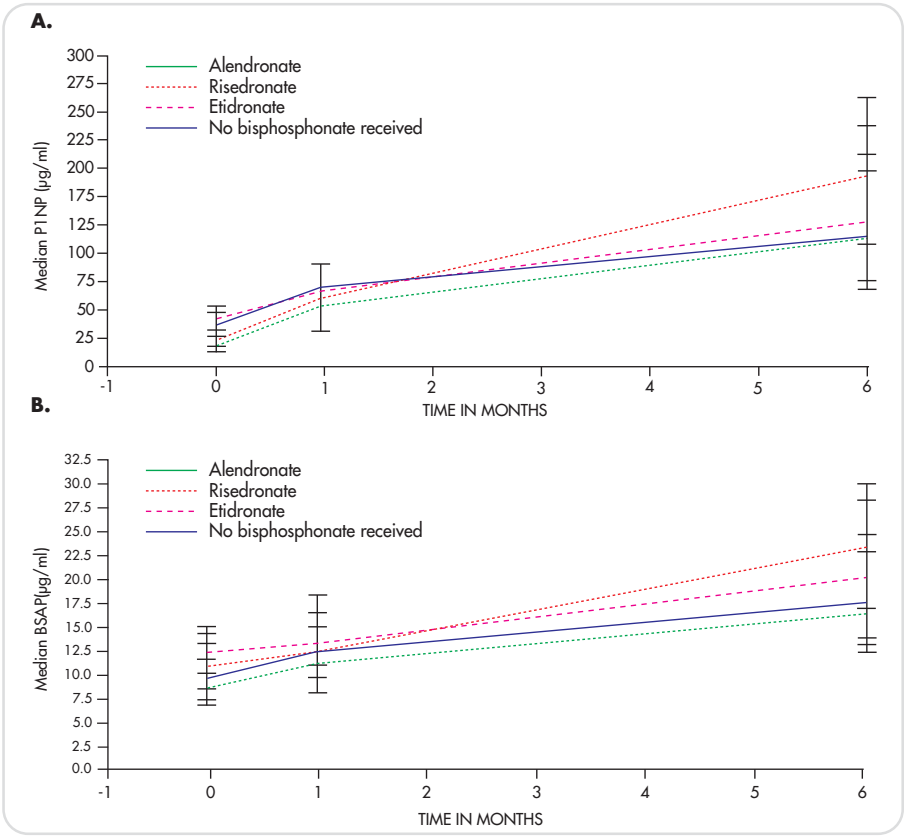
A secondary sub-analysis of the EUROFORS study examined the effects of 2 yrs of open-label Teriparatide in women previously treated with antiresorptive drugs for at least 1 yr.

A subgroup of 245 postmenopausal women with osteoporosis who already had 2 yrs of Teriparatide treatment was stratified by previous antiresorptive pharmacotherapy into four groups:- alendronate (n=107), risedronate (n=59), etidronate (n=30), and non-bisphosphonate (n=49).

After 1 month of Teriparatide treatment, all subgroups showed statistically significant increases from baseline ($p<0.001$) for the serum bone formation markers, P1NP and BSAP at all time points (Figure 5).

- Treatment-emergent adverse events were very similar to those reported in treatment-naive patients.
  - Hypercalcemia developed in 6.1% of study participants and was not statistically significant between study groups No patient discontinued the study due to hypercalcemia.

Figure 5 A–B. Increase in bone formation markers from baseline for Teriparatide vs. placebo

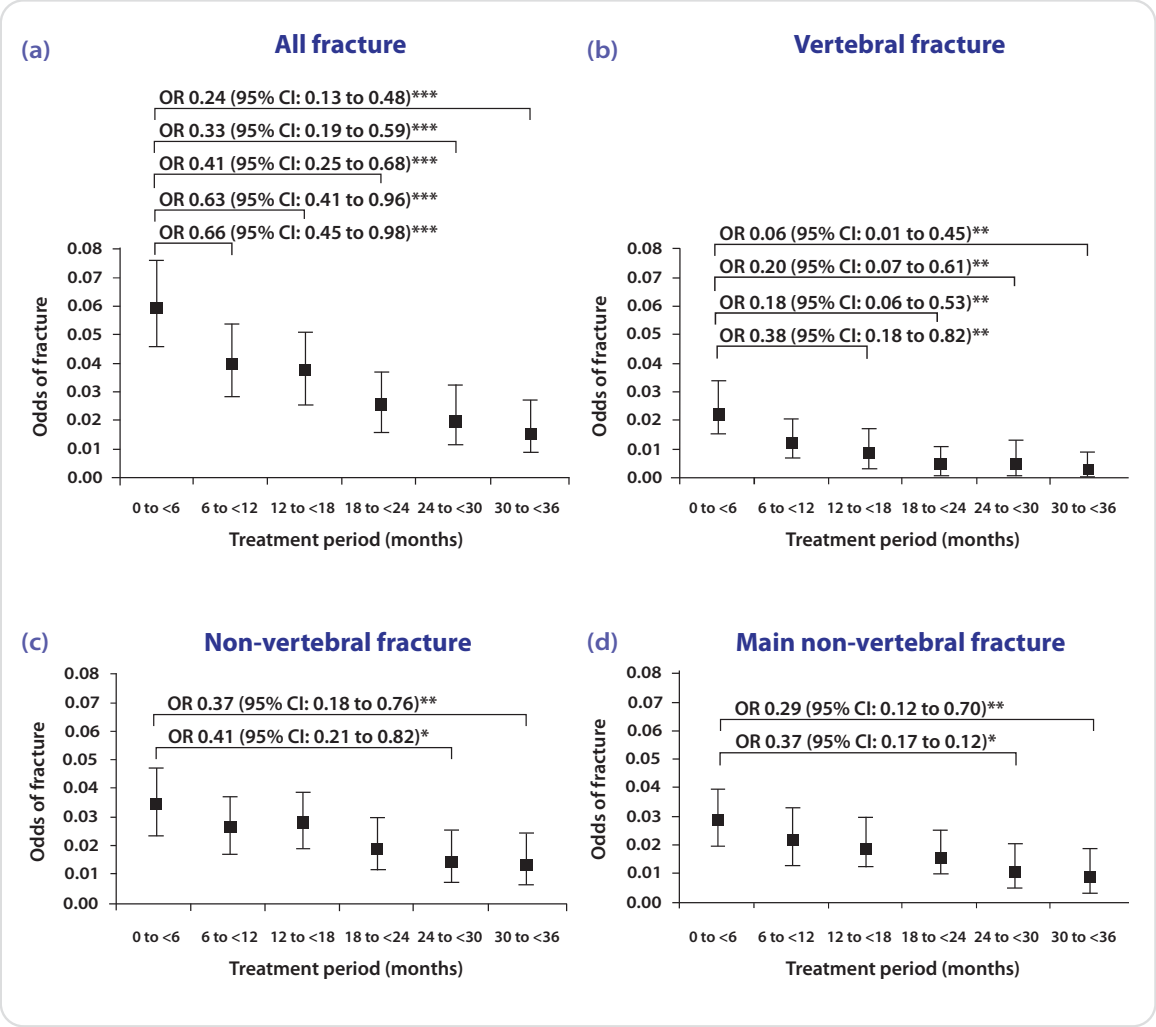


Postmenopausal women with severe osteoporosis and prior bisphosphonate therapy had a significant reduction in fracture rates, back pain and an improvement in health–related quality of life (HRQoL) following 36 months of Teriparatide use[4]

- The European Forsteo Observational Study (EFOS) was a 36 month, multi-center (Austria, Denmark, France, Germany, Greece, Ireland, The Netherlands, and Sweden), prospective, observational study initiated soon after the European approval of Teriparatide for the treatment of postmenopausal women with established osteoporosis at high risk for fracture. EFOS was designed to collect data from an outpatient setting and to evaluate fracture outcomes, back pain, and HRQoL in postmenopausal women with severe osteoporosis treated with Teriparatide for up to 18 months, followed by a post-Teriparatide treatment period of a further 18 months.
- The study enrolled 1649 postmenopausal women with a diagnosis of established osteoporosis who, at the discretion of their physician, were about to initiate Teriparatide treatment.
  - Patients were followed for the duration of their Teriparatide (20µg once daily by s.c. injection) and were asked to return for two additional visits after discontinuing Teriparatide, (irrespective of when).
  - Of the 1581 enrolled patients with follow-up data, 1161 (73.4%) had a history of prior bisphosphonate use (median duration: 36 months). Of them, 169 (14.6%) sustained ≥1 fracture during 36-month follow-up.

- Adjusted odds of fractures (all fractures; vertebral; non-vertebral) were significantly decreased at each 6-month interval compared with the first 6 months of Teriparatide treatment (Figure 6):

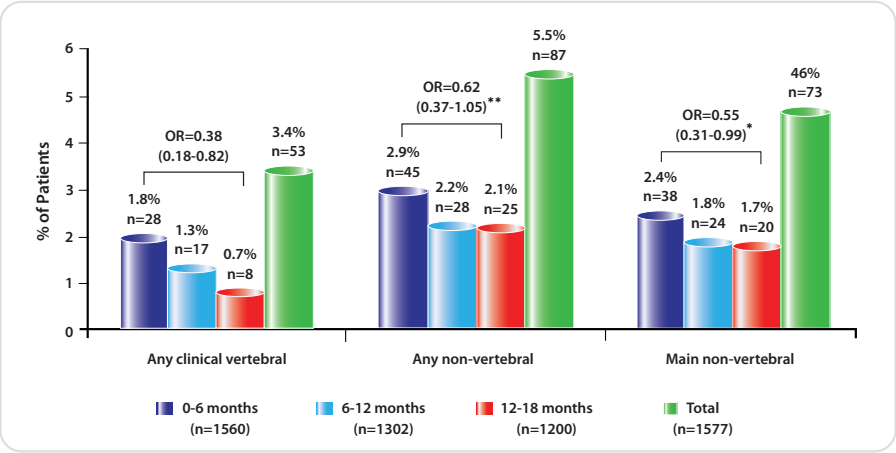
Figure 6. Risk of fracture (adjusted odds with 95% confidence intervals [CIs]) by fracture type: (a) all fractures pooled, (b) clinical vertebral, (c) non–vertebral, and (d) main non–vertebral, in each 6 month interval for the prior bisphosphonate user group.



Odds ratios (ORs) and 95% CI for the comparison with the first 6 months of treatment are given where significant.
*p<0.05, **p<0.01 and ***p<0.001 vs 0 to <6 months interval.

- The clinical vertebral and main non-vertebral fracture rates were significantly decreased between the first 6-month period and the last 6-month period on treatment (Figure 7).

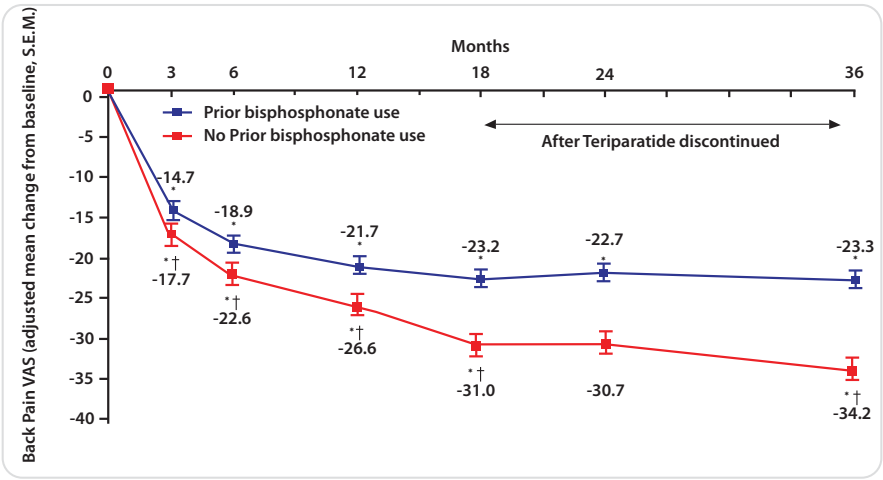
Figure 7. Number and percent patients with incident fractures in each 6–month period by fracture type.



*p<0.05, **p<0.10. Adjusted models by age, prior bisphosphonate use and history of fracture in the last 12 months before starting Teriparatide *** Forearm/wrist, hip, humerus, leg, and sternum/ribs

- There were statistically significant reductions (p<0.001) in the adjusted mean change in back pain VAS from baseline at each post-baseline visit in the groups with and without prior bisphosphonate use (Figure 8).
  - Intergroup analysis revealed that the reduction in the back pain VAS score was significantly higher (p<0.05) in the group with no prior bisphosphonate use at all post-baseline time points.

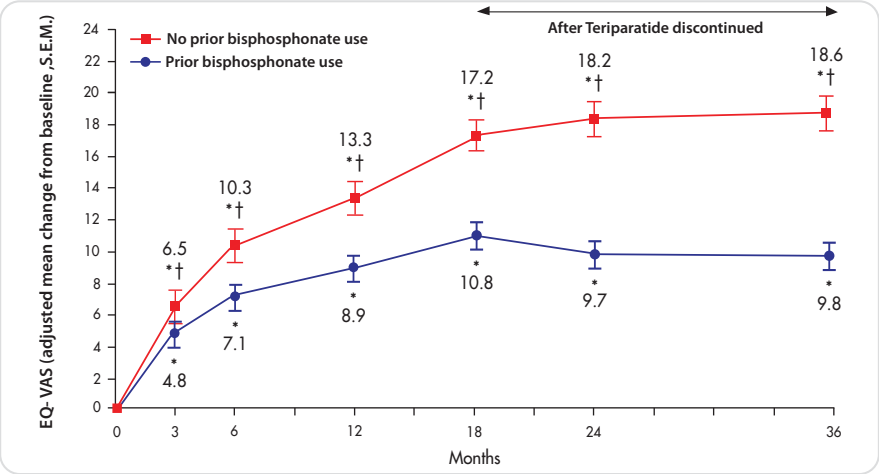
Figure 8. Back pain VAS: adjusted mean change (S.E.M.) from baseline during and after Teriparatide treatment in patients with and without prior bisphosphonate (BP) use.



*p<0.001 vs baseline and †p<0.05 vs prior BP users

- There were significant increases in EQ-VAS (i.e. improvement in HRQoL) from baseline in both the prior and non-prior bisphosphonate user groups at all post-baseline visits (p<0.001) [Figure 9].
  - The increase in EQ-VAS was significantly higher in the no prior bisphosphonate user group from the 6-month visit onwards (p<0.05).

Figure 9. EQ–VAS: adjusted mean change (S.E.M.) from baseline during and after Teriparatide treatment in patients with and without prior bisphosphonate (BP) use.



*p<0.001vs.Baseline and †p<0.05 vs.prior bisphosphonate users

- In the subgroup of postmenopausal women (n=589) aged ≥75 years[5]
  - 87 (14.8 %) women aged ≥75 years sustained a total of 111 new fractures: 37 (33.3 %) vertebral fractures and 74 (66.7 %) non–vertebral fractures.
  - Adjusted odds of fracture was decreased by 80% in the 30 to <36-month interval compared with the first 6-month interval (p<0.009).
- Although the older subgroup had higher back pain scores and poorer HRQoL at baseline than the younger subgroup, both the groups showed significant reductions in back pain and improvements in HRQoL post-baseline, which lasted for at least 18 months after Teriparatide discontinuation when patients were taking other osteoporosis medications.

Teriparatide has significant efficacy in male osteoporosis

- Two key studies have evaluated the effect of Teriparatide on BMD in men.[6,7]

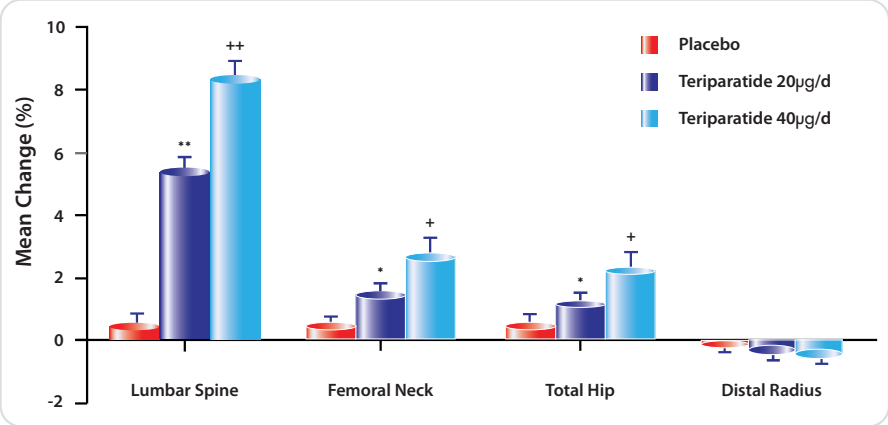
In the first study[6,8] men aged 30-69 years with idiopathic osteoporosis with or without a previous fracture (prevalence of fracture of 70% and 90% in the placebo and treatment groups, respectively) were randomized to either placebo or 400 IU (25µg) of Teriparatide for 18 months. BMD was measured at baseline and every 6 months at the lumbar spine, hip and radius.

- A linear increase in lumbar spine BMD was observed in the treatment group and was already significant at 6 months (4.8 ±2.0% at 6 months and 13.5 ± 3.0% at 18 months), whereas no significant change was remarkable in the placebo group.
- In contrast, the increase in BMD at the femoral neck in the Teriparatide recipients was slower, only reaching significance at 18 months (2.9 ± 1.5% p<0.05).

These results were reproduced in a study involving 437 men aged 30 – 85 years with primary osteoporosis or primary hypogonadism treated for a median of 11 month with either Teriparatide 20µg or 40µg daily or placebo.[7]

- Although the increase in lumbar spine BMD was less in this study, it was already significant at 3 months (Figure 10).
  - Bone mineral density responses to Teriparatide were similar regardless of gonadal status, age, baseline BMD, body mass index, smoking, or alcohol intake.
  - Adverse events were similar in the placebo and 20-µg groups, but more frequent in the 40-µg group.

Figure 10. Mean percentage changes in bone mineral density at the lumbar spine, femoral neck, total hip and distal radius following a median of 11 months of Teriparatide 20 or 40µg/d vs placebo.



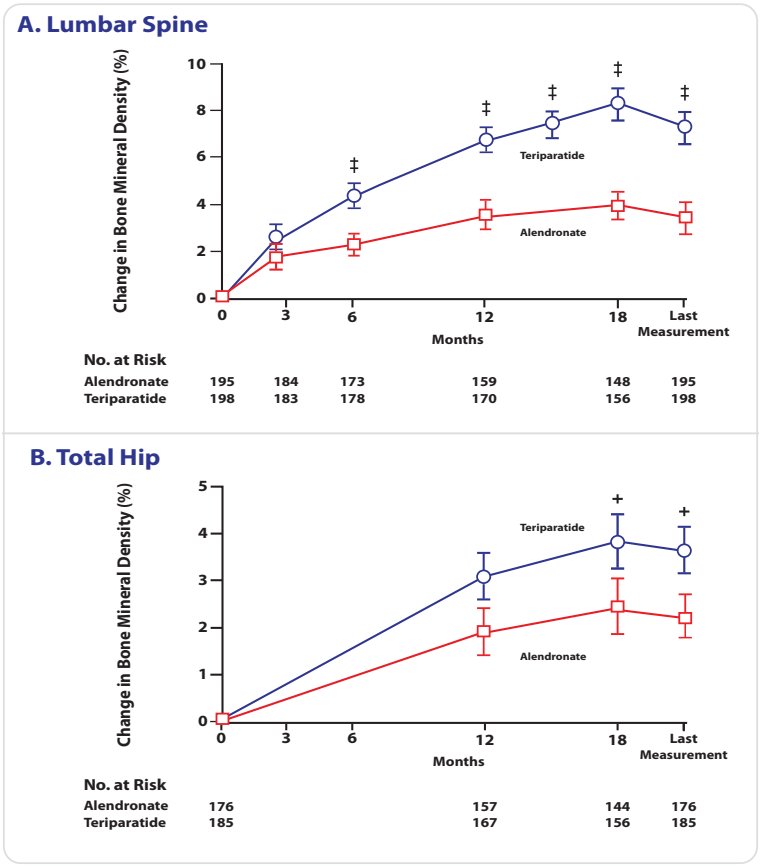
Bars represent the SEM. *p<0.05, Teriparatide 20µg/day vs. placebo; **p<0.001,Teriparatide 20µg/day vs. placebo; +p<0.05, Teriparatide 20µg/day vs.Teriparatide 40µg/day; ++p<0.001, Teriparatide 20µg/day vs Teriparatide 40µg/day

Among patients with glucocorticoid–induced osteoporosis at high risk for fracture, BMD increased more in patients receiving Teriparatide than in those receiving alendronate.[9]

- An 18-month, randomized, double-blind trial compared Teriparatide with alendronate in 428 women and men with glucocorticoid-induced osteoporosis (ages=22 to 89 years; had received glucocorticoids for ≥3 month [prednisone equivalent ≥5mg daily]).
- A total of 214 ambulatory patients received 20µg of Teriparatide once daily, 214 received 10mg of alendronate once daily.
- Primary outcome: Change in BMD at the lumbar spine.
- Secondary outcomes: Changes in BMD at the total hip; changes in markers of bone turnover; time to changes in BMD; incidence of fractures; and safety.

- Patients in the Teriparatide group had a significantly greater increase in lumbar BMD from baseline compared with the alendronate group (Mean ± SE; 7.2 ± 0.7% vs 3.4 ± 0.7% p<0.001). A significant difference between the groups was reached by 6 months (p<0.001) [Figure 11A].
- At 12 months, BMD at the total hip had increased significantly more in the Teriparatide group [Figure 11B].
- Fewer new vertebral fractures occurred in the Teriparatide group than in the alendronate group (0.6% vs 6.1%, p=0.004); the incidence of non-vertebral fractures was similar in the two groups (5.6% vs 3.7% p=0.36).

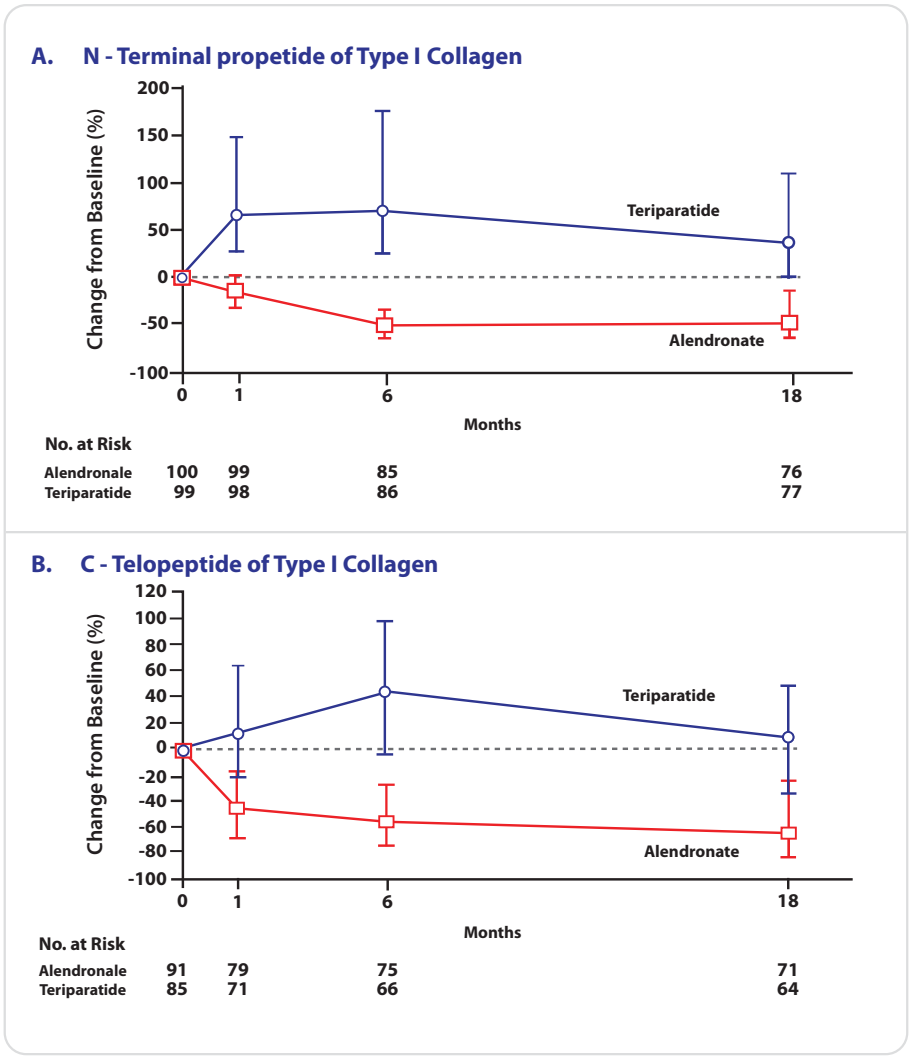
Figure 11 A–B. Percent change in mean bone mineral density at the lumbar spine and total hip from baseline to 18 months or the last measurement.



*p<0.05; †p<0.01; and ‡p<0.001 for between-group comparisons

- In the Teriparatide group, N-terminal propeptide of type I collagen, a marker of bone formation, and C-Telopeptide of type I collagen, a marker of resorption, were increased at 1 month and peaked at 6 months (an increase of 69.8% and 44.8% from baseline, respectively). In the alendronate group, these markers decreased at 1month and remained suppressed at 18 months (Figure 12A).
- Levels of C-terminal propeptide of type I collagen and bone-specific alkaline phosphatase significantly increased in the Teriparatide group and decreased in the alendronate group (Figure 12B).
- Safety profiles in the two study groups were similar, with no significant differences in the overall incidence of adverse events, the incidence of serious adverse events, or the incidence of events either leading to withdrawal from the study or considered to be possibly related to a study drug.
  - More patients in the Teriparatide group reported having nausea, insomnia, pharyngitis, and viral infection; more patients in the alendronate group reported having rash, a decrease in weight, sciatica, and asthma.
  - The occurrence of sporadic hypercalcemia was more frequent in the Teriparatide group than in the alendronate group.

Figure 12 A–B. Percent Change in Markers of Bone Formation and Resorption



p<0.001 for all comparisons between study groups at 1 , 6, and 18 months

Daily Teriparatide treatment exerts anabolic action on cortical bone in patients with osteoporosis and also can improve cancellous bone microarchitecture.

- Paired iliac crest bone biopsy specimens from patients with osteoporosis before and after treatment with daily injections of 20μg of Teriparatide were evaluated in 2 groups of patients.
  - The first group was comprised of 8 men with an average age 49 years. They were treated with Teriparatide for18 months.
  - The second group was comprised of 8 postmenopausal women with an average age 54 years. They were treated with Teriparatide for 36 months.
- Patients were supplemented with an average daily intake of 1500mg of elemental calcium and 400 IU of vitamin D.
- The biopsy specimens were subjected to routine histomorphometric analysis and microcomputed tomography (CT).

Figure 13. Percentage changes in three variables of iliac bone structure after Teriparatide treatment (men and women). All variables were measured by micro–CT

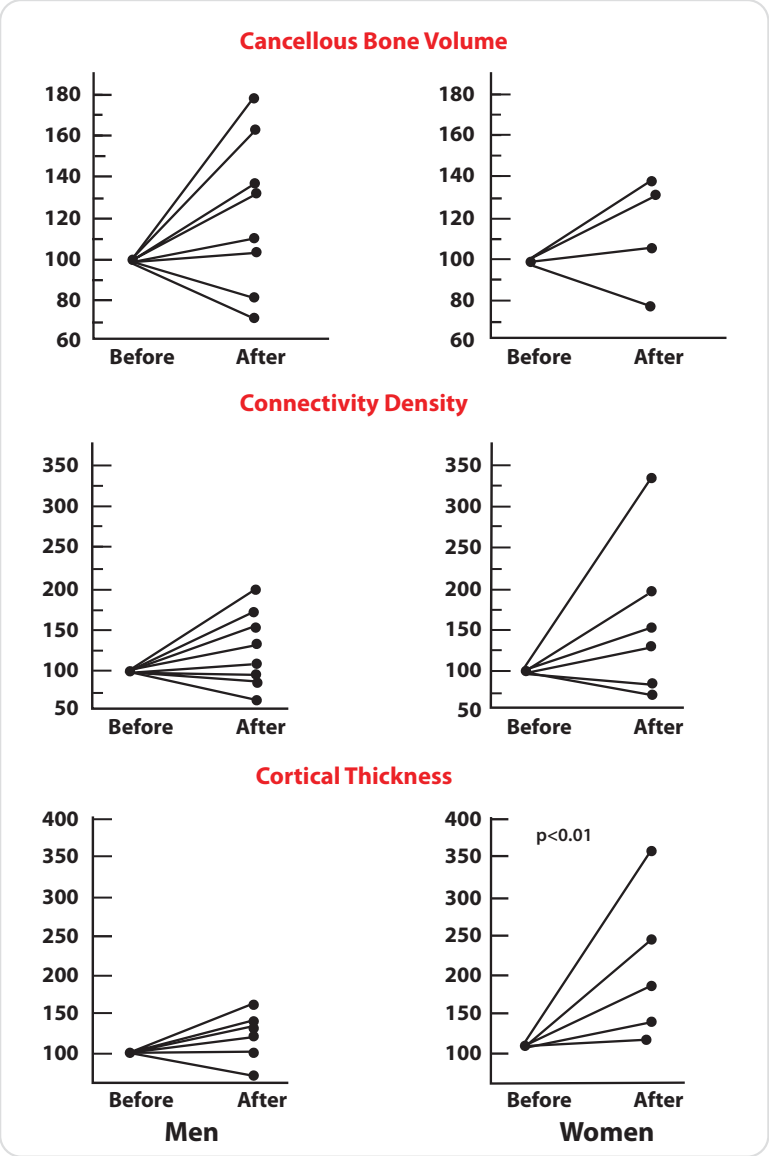
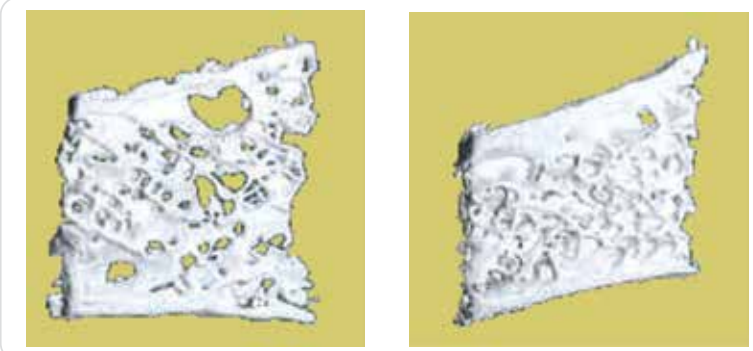
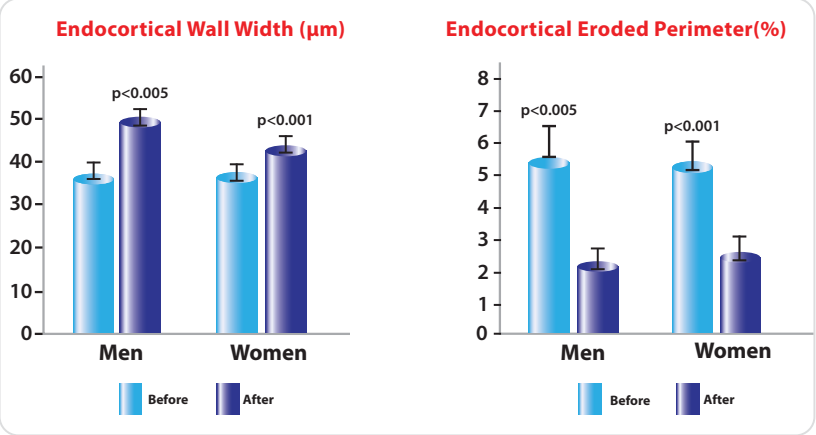


Figure 14. Images of bone structure from 1 woman before and after treatment with Teriparatide



- Cancellous bone volume was maintained in both groups. Micro-CT revealed an increase in connectivity density, a 3D measure of trabecular connectivity.
- Although there was some heterogeneity in individual responses, 75% of the men and 66% of the women showed maintenance or improvement by 12-253% in connectivity density (Figure 13).
- Cortical thickness was slightly increased in men and was significantly ($p<0.01$) increased in women (Figure 13)
- There was no increase in cortical porosity.
- The underlying mechanism for the improvement in trabecular architecture (Figure 14) is uncertain, but could involve the initial thickening of trabeculae followed by intra-trabecular tunnelling.
- There were no significant changes in dynamic indices of bone formation on either the subperiosteal (outer) or the endocortical (inner) surface.
- There was a significant increase in endocortical wall width (μm) and a significant decrease in eroded perimeter (%) [Figure 15).

Figure 15. Endocortical wall width and surface eroded perimeter

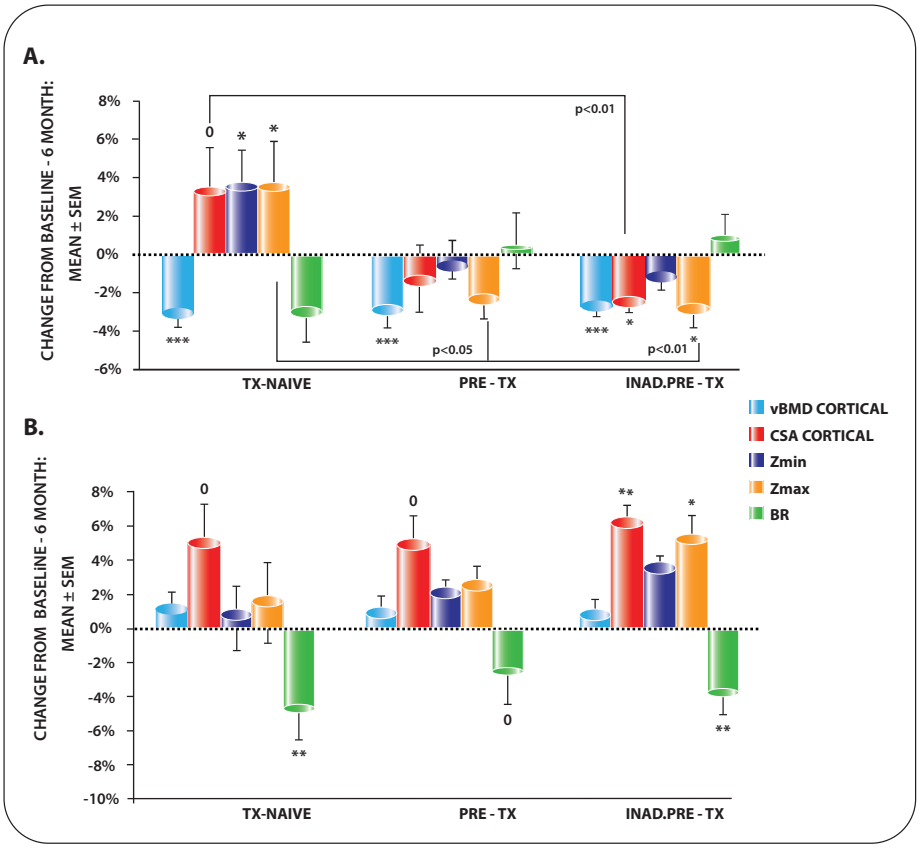


Teriparatide improves periosteal bone apposition and bone geometry.[12]

- 52 postmenopausal women with severe osteoporosis were divided into three subgroups based on their prior treatment with osteoporosis drugs: treatment-naive (Tx-naive; n=8), pretreated (pre-Tx; n=12), and pretreated showing an inadequate response to treatment (inad. pre-Tx; n=32).
- OCT scans were performed at baseline, and after 6, 12, and 24 months of treatment.
- Minimum and maximum section modulus, buckling ratio (BR), and cross-sectional area (CSA) were calculated as measurements of bending strength, risk of buckling, and bone apposition, respectively.
  - Relevant structural measures to assess bone strength are section modulus (Z) and buckling ratio (BR).
  - Z is inversely related to maximum stresses exerted by bending loads.
  - QCT as a 3D measurement allows evaluating Z along the strongest (Zmax) and weakest axes (Zmin). When Zmax and Zmin both considered, they reflect strength in torsion of the structure.
  - Buckling ratio (BR) is a measure of cortical elastic instability as a result of excessive cortical thinning. BR relates the cortical thickness to the width of the femoral neck and is defined as BR=r/ct where 'r' is the radius and 'ct' is the corresponding cortical thickness.
  - The bone is considered to be vulnerable to the failure mode of buckling when this ratio exceeds 10:1; that is, BR>10.

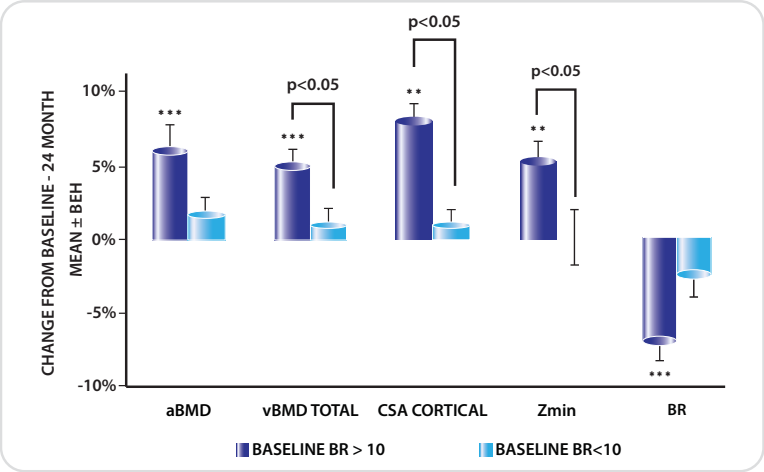
- After 24 months of Teriparatide treatment, areal (aBMD) and volumetric femoral neck BMD (vBMD) increased significantly by 4.0% and 3.0%, respectively, compared with baseline.
- Cortical CSA increased by 4.3%, whereas total CSA remained unchanged over the study duration, indicating that endosteal but no periosteal growth was observed.
  - The Tx-naive group showed significant increases for both Zmin and Zmax (4.4%, $p<0.05$, for both variables) and a trend toward endosteal expansion of the cortical area (Figure 16).
  - In contrast, patients in the inad. pre-Tx group presented a significant decrease in bending strength indicators in the stronger plane (Zmax), but no significant change in the weaker (Zmin) plane (Figure 16).
- Parameters for bucking did not change at 6 and 12 months, but improved significantly at 24 months. Measures of bending strength showed a trend toward improvement.
- Baseline values of Z and BR were associated with the magnitude of the changes under Teriparatide treatment, thus the patients with poorest mechanical competence at baseline showed the largest improvement over time (Figure 17).

Figure 16. Changes in density, geometry, and strength variables from baseline to 6– month visit (A) as well as between 6 and 24 months (B) of Teriparatide treatment evaluated separately for the three pretreatment groups.



°p<0.1;*p<0.05;**p<0.01;***p<0.001 vs baseline

Figure 17. Differences of density, geometry, and strength variables after 24 months of Teriparatide treatment for patients with baseline buckling ratio values larger and smaller than 10



[9]p<0.1; *p<0.05; **p<0.01; ***p<0.001 versus baseline

Teriparatide accelerates fracture healing.[12,13]

- Postmenopausal women (45 to 85 years of age) who had sustained a dorsally angulated distal radial fracture in need of closed reduction, but no surgery were randomly assigned to 8 weeks of once-daily injections of placebo (n=34) or Teriparatide 20µg (n=34) or Teriparatide 40µg (n=34) within 10 days of fracture.12
- Median time from fracture to first radiographic evidence of complete cortical bridging in three of four cortices was 9.1, 7.4, and 8.8 weeks for placebo and Teriparatide 20µg and 40µg, respectively (overall p=0.015). There was no significant difference between the Teriparatide 40µg versus placebo groups (p=0.52).
- In post-hoc analysis, the time to healing was shorter in Teriparatide 20µg vs, placebo (p=0.006) suggesting that cortical bridging and subsequent fracture repair can be accelerated by Teriparatide.
- Approximately 1262 patients from the Fracture Prevention Trial were invited to participate in a follow-up study to evaluate the efficacy of Teriparatide in reducing the risk of non-vertebral fragility fractures following discontinuation of treatment.[13]
- Approximately 60% of these patients received an osteoporosis treatment at some time during follow-up.
- The hazard ratios for non-vertebral fragility fractures in each Teriparatide group relative to placebo were statistically significant for the 50-month period including treatment and follow-up (p<0.03).
- Based on a Kaplan-Meier analysis of time to fracture, there was a significant reduction in fracture incidence for Teriparatide vs former placebo during the 50-month period, including follow-up (p=0.009).
- Total hip and femoral neck BMD remained stable or further increased in patients who received a bisphosphonate after Teriparatide treatment.
- While the study design is observational, the results support a sustained effect of Teriparatide in reducing the risk of non-vertebral fragility fractures up to 30 months after discontinuation of treatment.
- Teriparatide has displayed efficacy in the healing of delayed union and non-union fractures.

- A retrospective case analysis of painful delayed unions of type III odontoid fractures (fractures of the C2 vertebra) treated with Teriparatide has indicated both rapid clinical improvement and computed tomography evidence of fracture union.
- Three osteoporotic women had type III odontoid fractures which failed to unite with external immobilization over several months. The patients presented for follow-up with substantial, activity-limiting neck pain.
- All 3 were begun on Teriparatide doses therapeutic for osteoporosis (20µg/day, subcutaneous injection) and all 3 experienced both remarkable resolution of chronic neck pain and CT-confirmed union of the fractures.[14]

- Case reports indicate that a 5-9 month administration of Teriparatide can completely resolve humeral shaft atrophic non-union and non union of sternal fracture in Caucasian males.[15, 16]
- Based on a retrospective case report analysis, 24 months of Teriparatide treatment can improve osteointegration in hemiarthroplasty associated with radiographic signs of aseptic loosening. This is associated with clinical improvement, and a decrease in pathological radiotracer uptake in the bone scan.[17]

Warnings, Precautions and Use of Gemfrac® (Teriparatide) in Special Populations

What warnings and precautions need to be considered while using Gemfrac® (Teriparatide)?

- It is contraindicated in patients with hypersensitivity to Teriparatide or to any of its excipients.
- Patients with Paget's disease of bone, bone metastases, history of skeletal malignancies, open epiphyses (pediatric and young adult patients), and prior external beam/implant radiation involving the skeleton should not be treated with Teriparatide.
  - In rats, Teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor.
  - Because of the uncertain relevance of the rat osteosarcoma finding to humans, Teriparatide should only be prescribed for patients for whom potential benefits outweigh potential risk.
  - It should not be prescribed for patients at increased baseline risk for osteosarcoma (e.g., Paget's disease of bone or unexplained elevations of alkaline phosphatise; pediatric and young adult patients with open epiphyses; patient with prior external beam or implant radiation therapy involving the skeleton).
- Patients with metabolic bone diseases other than osteoporosis or patients with hypercalcemic disorders should not be treated with Teriparatide.
- Teriparatide may increase serum calcium, urinary calcium, and serum uric acid, and may exacerbate active or recent urolithiasis.
- Clinicians and patients need to be vigilant regarding the potential development of transient orthostatic hypotension while administering the initial doses of Teriparatide.
- Teriparatide should not be used for more than 2 yrs owing to insufficient clinical data beyond this time point.

What are the considerations for the use of Gemfrac® (Teriparatide) in specific populations?

- There are no adequate and well-controlled studies of Teriparatide in pregnant women.
  - In animal studies, Teriparatide has produced skeletal may on mations mild growth retardation and motor deficits in rodents, when administered in dose much higher than the equivalent human dose. Teriparatide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- It is not known whether Teriparatide is excreted in human milk. Because of the tumorigenic potential for Teriparatide based on animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk-benefit ratio for the mother.
- The safety and efficacy of Teriparatide has not been evaluated in the pediatric setting.
  - Teriparatide should not be prescribed in patients at an increased baseline risk of osteosarcoma i.e., pediatric and young adult patients with open epiphyses.
- No overall differences have been observed in therapeutic response, efficacy, and safety for Teriparatide for the geriatric vs the younger population. However, the potentially greater sensitivity of some older individuals cannot be ruled out.
- Teriparatide should be used with caution in patients with hepatic and renal impairment owing to the paucity of clinical data in these populations.
- Incidents of overdose have not been reported in clinical trials-effects of overdose that might be expected include delayed hypercalcemia, orthostatic hypotension, nausea, vomiting, dizziness, and headache.

Conclusion

- Teriparatide is an anabolic therapy that improves bone density, reduces vertebral and non-vertebral fracture incidence, improves the geometric and microarchitectural properties of bone, and has been observed to accelerate fracture healing.
- It is administered subcutaneously using a pen delivery device, has favourable pharmacokinetics, and is approved for the treatment of postmenopausal osteoporosis, osteoporosis in men, and glucocorticoid-induced osteoporosis.
- It should be considered as **first-line therapy in patients at high risk for fracture**, or in patients for whom the physician is not satisfied with the effectiveness of other registered therapies. Patients who experience a fracture on antiresorptive therapy, and treatment-naïve patients with prevalent fractures are eligible for Teriparatide therapy.
- Overall, Teriparatide is well tolerated and safe in most patients. However, administration beyond 2 years is not recommended owing to insufficient clinical data beyond this time point.

Reference:

1. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001 May 10;344(19):1434-41. **2.** Eastell R, Nickelsen T, Marin F, et al. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). J Bone Miner Res. 2009 Apr;24(4):726-36. **3.** Boonen S, Marin F, Obermayer-Pietsch B, et al. EUROFORS Investigators. Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2008 Mar;93(3):852-60. **4.** Jakob F, Oertel H, Langdahl B, et al. Effects of teriparatide in postmenopausal women with osteoporosis pre-treated with bisphosphonates: 36-month results from the European Forsteo Observational Study. Eur J Endocrinol. 2012 Jan;166(1):87-97. **5.** Walsh JB, Lems WF, Karras D, et al. Effectiveness of Teriparatide in women over 75 years of age with severe osteoporosis: 36-month results from the European Forsteo Observational Study (EFOS). Calcif Tissue Int. 2012 May;90(5):373-83. **6.** Kurland ES, Cosman F, McMahon DJ, et al. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab. 2000 Sep;85(9):3069-76. **7.** Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003 Jan;18(1):9-17. **8.** Yang D, Singh R, Divieti P, et al. Contributions of parathyroid hormone (PTH)/PTH-related peptide receptor signaling pathways to the anabolic effect of PTH on bone. Bone. 2007 Jun;40(6):1453-61. **9.** Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007 Nov 15;357(20):2028-39. **10.** Dempster DW, Cosman F, Kurland ES, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. J Bone Miner Res. 2001 Oct;16(10):1846-53. **11.** Borggrefe J, Graeff C, Nickelsen TN, et al. Quantitative computed tomographic assessment of the effects of 24 months of teriparatide treatment on 3D femoral neck bone distribution, geometry, and bone strength: results from the EUROFORS study. J Bone Miner Res. 2010 Mar;25(3):472-81. **12.** Aspenberg P, Genant HK, Johansson T, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res. 2010 Feb;25(2):404-14. **13.** Prince R, Sipos A, Hossain A, et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. J Bone Miner Res. 2005 Sep;20(9):1507-13. **14.** Rubery PT, Bukata SV. Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: a report of 3 cases. J Spinal Disord Tech. 2010 Apr;23(2):151-5. **15.** Chintamaneni S, Finzel K, Gruber BL. Successful treatment of sternal fracture nonunion with teriparatide. Osteoporos Int. 2010 Jun;21(6):1059-63. **16.** Oteo-Alvaro A, Moreno E. Atrophic humeral shaft nonunion treated with teriparatide (rh PTH 1-34): a case report. J Shoulder Elbow Surg. 2010 Oct;19(7):e22-8. **17.** Oteo-Álvaro Á, Matas JA, Alonso-Farto JC. Teriparatide (rh [1-34] PTH) improved osteointegration of a hemiarthroplasty with signs of aseptic loosening. Orthopedics. 2011 Sep 9;34(9):e574-7.

In Osteoporosis & Fracture

Rx

Gemfrac

Prefilled Teriparatide Inj. 600 mcg/2.4ml

Builds New Bone

Auto Priming

No air bubble removal required

Lateral Push

Easy dose administration

End to end cold chain management (2-8^0 C)

Dose Lock

20 mcg

For accurate dosing

Dose Calendar

28

Indicates remaining dose

ABRIDGED PRESCRIPTION INFORMATION

Gemfrac: [Teriparatide {Recombinant Human Parathyroid Hormone analogue (1-34)} 600 mcg/2.4 ml SC injection]. Composition: Each prefilled syringe contains Teriparatide 600mcg in 2.4ml (250mcg/ml). Each dose of 80 µl contains 20mcg of Teriparatide. Indications: Gemfrac is indicated for: Treatment of postmenopausal women with osteoporosis at high risk for fracture, Increase of bone mass in men with primary or hypo gonadal osteoporosis at high risk for fracture, Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture. Contraindications: Patients with Hypersensitivity to the active substance or to any of the excipients, Pregnancy and breast-feeding, Pre-existing hypercalcaemia, Severe renal impairment (CrCl<30 ml/min). Undesirable Effects: Nausea, Pain in limb, headache and dizziness. Special Warnings and Precautions: Paediatric and young adult patients with open epiphyses have increased risk of osteosarcoma, Hypercalcemia and hypercalcemic disorders, Urolithiasis, Orthostatic hypotension, Patients with renal impairment, Patients with hepatic impairment. Dosage and Administration: Recommended dose is 20 µg subcutaneously once a day, Administer as a subcutaneous injection into the thigh or abdominal wall, Administer initially under circumstances in which the patient can sit or lie down if symptoms orthostatic hypotension occur, Patients should receive supplemental Calcium and Vitamin D supplements if dietary intake is inadequate. Treatment Duration: Gemfrac should be used for 2 years (24 months) during a patient's lifetime. Storage: Store in sterile, tamper proof container at temperature of 2-8°C. Do not freeze. Keep out of reach of children. Shelf life not more than 24 months

For Further Information, Contact: Medical Affairs; Alkem House; Senapati Bapat Marg, Lower Parel; Mumbai, Maharashtra: 400013.

BERGEN NOVA