TERROSA®

TERIPARATIDE 250 MCG/ML solution for subcutaneous injection

FULL PRESCRIBING INFORMATION

Terrosa is a biosimilar medicinal product that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Forteo. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. Information regarding biosimilar products can be found on the website of the Ministry of Health: https://www.gov.il/he/Departments/General/biosimilar

1 INDICATIONS AND USAGE

1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

Terrosa is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Terrosa increases bone mineral density (BMD), reduces the risk of vertebral and non-vertebral fractures *[see Clinical Studies (13.1)]*.

1.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture

Terrosa is indicated to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy *[see Clinical Studies (13.2)]*.

1.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture

Terrosa is indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy *[see Clinical Studies (13.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.2 Increase of Bone Mass in Men with Primary or Hypogonadal Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis at High Risk for Fracture

The recommended dose is 20 mcg subcutaneously once a day.

2.4 Administration Instructions

- Administer Terrosa as a subcutaneous injection into the thigh or abdominal region. Terrosa is not approved for intravenous or intramuscular use.
- Terrosa should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur *[see Warnings and Precautions (5.4)]*.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration (Terrosa is a clear and colorless liquid). Do not use if solid particles appear or if the solution is cloudy or colored.
- Patients and/or caregivers who administer Terrosa must receive appropriate training and instruction on the proper use of the Terrosa delivery device from a qualified health professional [see storage and handling (14.2)]. A User's Manual, which is included in the carton of the delivery system, is also available to instruct patients on the correct use of the pen.

2.5 Recommended Treatment Duration

Use of teriparatide for more than 2 years and up to 3 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Solution for injection. One cartridge of 2.4 mL of solution contains 600 mcg of teriparatide (corresponding to 250 mcg/mL). Colourless, clear solution in a cartridge intended to deliver 28 daily doses of 20 mcg.

4 CONTRAINDICATIONS

Terrosa is contraindicated in patients with hypersensitivity to teriparatide or to any of its excipients. Hypersensitivity reactions have included angioedema and anaphylaxis *[see Adverse Reactions (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Osteosarcoma

An increase in the incidence of osteosarcoma (a malignant bone tumor) was observed in male and female rats treated with teriparatide. Osteosarcoma has been reported in patients treated with teriparatide in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of teriparatide use *[see Dosage and Administration (2.5), Adverse Reactions (6.3), and Nonclinical Toxicology (12.1)]*.

Avoid teriparatide use in patients with (these patients are at increased baseline risk of osteosarcoma):

- Open epiphyses (pediatric and young adult patients) (Teriparatide is not approved in pediatric patients) *[see Use in Specific Populations (8.4)]*.
- Metabolic bone diseases other than osteoporosis, including Paget's disease of the bone.
- Bone metastases or a history of skeletal malignancies.
- Prior external beam or implant radiation therapy involving the skeleton.
- Hereditary disorders predisposing to osteosarcoma.

5.2 Hypercalcemia and Cutaneous Calcification

Hypercalcemia

Teriparatide has not been studied in patients with pre-existing hypercalcemia. Teriparatide may cause hypercalcemia and may exacerbate hypercalcemia in patients with pre-existing hypercalcemia *[see Adverse Reactions (6.1, 6.3)]*. Avoid teriparatide in patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism.

Risk of Cutaneous Calcification Including Calciphylaxis

Serious reports of calciphylaxis and worsening of previously stable cutaneous calcification have been reported in the post-marketing setting in patients taking teriparatide. Risk factors for development of calciphylaxis include underlying auto-immune disease, kidney failure and concomitant warfarin or systemic corticosteroid use. Discontinue teriparatide in patients who develop calciphylaxis or worsening of previously stable cutaneous calcification.

5.3 Risk of Urolithiasis

In clinical trials, the frequency of urolithiasis was similar in patients treated with teriparatide and patients treated with placebo. However, teriparatide has not been studied in patients with active urolithiasis. If teriparatide-treated patients have pre-existing hypercalciuria or suspected/known active urolithiasis, consider measuring urinary calcium excretion. Consider the risks and benefits of use in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

5.4 Orthostatic Hypotension

Teriparatide should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies of teriparatide in healthy volunteers, transient episodes of symptomatic orthostatic hypotension were observed in 5% of volunteers. Typically, these events began within 4 hours of dosing and resolved (without treatment) within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

5.5 Risk of Digoxin Toxicity

Hypercalcemia may predispose patients to digitalis toxicity because teriparatide transiently increases serum calcium. Consider the potential onset of signs and symptoms of digitalis toxicity when teriparatide is used in patients receiving digoxin *[see Drug Interactions (7.1) and Clinical Pharmacology (11.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Men with Primary or Hypogonadal Osteoporosis and Postmenopausal Women with Osteoporosis

The safety of teriparatide in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1,382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years) *[see Clinical Studies (13.1, 13.2)]*. The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to teriparatide and 691 patients to placebo. All patients received 1,000 mg of calcium plus at least 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 1% in the teriparatide group and 1% in the placebo group. The incidence of serious adverse events was 16% in the teriparatide group and 19% in the placebo group. Early discontinuation due to adverse events occurred in 7% in the teriparatide group and 6% in the placebo group.

Table 1 lists adverse events from these two trials that occurred in ≥2% of teriparatide-treated and more frequently than placebo-treated patients.

Table 1: Percentage of Patients with Adverse Events Reported by at Least 2% of Teriparatide-Treated Patients and in More Teriparatide-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality

	Teriparatide 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

Laboratory Findings

Serum Calcium — Teriparatide transiently increased 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 teriparatide administration was 11% of women and 6% of men treated with teriparatide compared to 2% of women and 0% of the men treated with placebo. The percentage of patients treated with teriparatide whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men.

Urinary Calcium — Teriparatide increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with teriparatide and placebo *[see Clinical Pharmacology (11.2)]*.

Serum Uric Acid — Teriparatide increased serum uric acid concentrations. In clinical trials, 3% of teriparatide-treated patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo-treated patients. However, the hyperuricemia did not result in an increase in gout, arthralgia or urolithiasis.
Renal Function — No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment.

Men and Women with Glucocorticoid-Induced Osteoporosis
The safety of teriparatide in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5mg per day prednisone or equivalent for a minimum of 3 months *[see Clinical Studies (13.3)]*. The duration of the trial was 18 months with 214 patients exposed to teriparatide and 214 patients exposed to an oral daily bisphosphonate (active control). All patients received 1,000 mg of calcium plus 800 IU of vitamin D supplementation per day.

There was no increase in mortality in the teriparatide group compared to the active control group. The incidence of serious adverse events was 21% in teriparatide patients and 18% in active control patients, and included pneumonia (3% teriparatide, 1% active control). Early discontinuation because of adverse events occurred in 15% of teriparatide patients and 12% of active control patients, and included dizziness (2% teriparatide, 0% active control).

Adverse events reported at a higher incidence in the teriparatide group and with at least a 2% difference in teriparatide-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively.

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other teriparatide products may be misleading.

In the clinical trial of postmenopausal women with osteoporosis *[see Clinical Studies (13.1)]*, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) who received teriparatide. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

6.3 Postmarketing Experience

Adverse Reactions from Postmarketing Spontaneous Reports
The following adverse reactions have been identified during postapproval use of teriparatide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period *[see Warnings and Precautions (5.1)]*.
- Hypercalcemia greater than 13 mg/dL has been reported with teriparatide use.

Adverse events reported since market introduction that were temporally related to teriparatide therapy include the following:

- Allergic Reactions: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria
- Investigations: Hyperuricemia
- Respiratory System: Acute dyspnea, chest pain
- Musculoskeletal: Muscle spasms of the leg or back
- Other: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema

Adverse Reactions from Observational Studies to Assess Incidence of Osteosarcoma
Two osteosarcoma surveillance safety studies (U.S. claims-based database studies) were designed to obtain data on the incidence rate of osteosarcoma among teriparatide-treated patients. In these two studies, three and zero osteosarcoma cases were identified among 379,283 and 153,316 teriparatide users, respectively. The study results suggest a similar risk for osteosarcoma between teriparatide users and their comparators. However, the interpretation of the study results calls for caution owing to the limitations of the data sources which do not allow for complete measurement and control for confounders.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

7 DRUG INTERACTIONS

7.1 Digoxin

Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Teriparatide may transiently increase serum calcium. Consider the potential onset of signs and symptoms of digitalis toxicity when teriparatide is used in patients receiving digoxin *[see Warnings and Precaution (5.5) and Clinical Pharmacology (11.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on teriparatide use in pregnant women to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Consider discontinuing Terrosa when pregnancy is recognized.

In animal reproduction studies, teriparatide increased skeletal deviations and variations in mouse offspring at subcutaneous doses equivalent to more than 60 times the recommended 20 mcg human daily dose (based on body surface area, mcg/m^2), and produced mild growth retardation and reduced motor activity in rat offspring at subcutaneous doses equivalent to more than 120 times the human dose *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. The background risk in the US general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

In animal reproduction studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses equivalent to 8 to 267 times the human dose (based on body surface area, mcg/m^2). At subcutaneous doses ≥ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received teriparatide during organogenesis at subcutaneous doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study in pregnant rats dosed subcutaneously from organogenesis through lactation, mild growth retardation was observed in female offspring at doses ≥120 times the human dose. Mild growth retardation in male offspring and reduced motor activity in both male and female offspring were observed at maternal doses of 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

8.2 Lactation

Risk Summary

It is not known whether teriparatide is excreted in human milk, affects human milk production or has effects on the breastfed infant. Avoid Terrosa use in women who are breastfeeding.

8.3 Pediatric Use

The safety and effectiveness of teriparatide have not been established in pediatric patients. Pediatric patients are at higher baseline risk of osteosarcoma because of open epiphyses *[see Warnings and Precautions (5.1)]*.

8.4 Geriatric Use

Of the patients who received teriparatide in the osteoporosis trial of 1,637 postmenopausal women, 75% were 65 years of age and older and 23% were 75 years of age and older. Of the patients who received teriparatide in the trial of 437 men with primary or hypogonadal osteoporosis, 39% were 65 years of age and older and 13% were 75 years of age and older. Of the 214 patients who received teriparatide in the glucocorticoid induced osteoporosis trial, 28% were 65 years of age and older and 9% were 75 years of age and older. No overall differences in safety or effectiveness of teriparatide have been observed between patients 65 years of age and older and younger adult patients.

8.5 Hepatic Impairment

No studies have been performed in patients with hepatic impairment *[see Clinical Pharmacology (11.3)]*.

8.6 Renal Impairment

In 5 patients with severe renal impairment (CrCl<30 mL/minute), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and

77%, respectively. Maximum serum concentration of teriparatide was not increased. It is unknown whether teriparatide alters the underlying metabolic bone disease seen in chronic renal impairment *[see Clinical Pharmacology (11.3)]*.

9 OVERDOSAGE

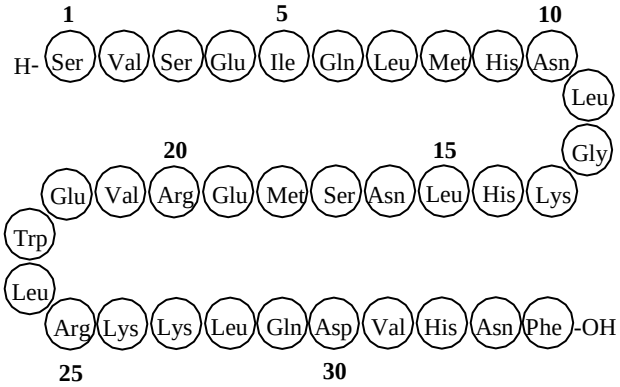
In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) (40 times the recommended dose) of the teriparatide delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. No fatalities associated with overdose have been reported. Additional signs, symptoms and complications of teriparatide overdosage may include a delayed hypercalcemic effect, vomiting, dizziness, and headache.

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

10 DESCRIPTION

Terrosa (teriparatide injection) is a recombinant human parathyroid hormone analog (PTH 1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and molecular weight is 4,117.8 daltons. Its amino acid sequence is shown below:



Teriparatide is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. Terrosa is supplied as a colorless, clear solution in a glass cartridge for subcutaneous injection. Each cartridge contains 2.4 mL of solution. Each mL contains 250 mcg teriparatide, mannitol, metacresol, glacial acetic acid, sodium acetate trihydrate, water for injections, hydrochloric acid and sodium hydroxide.

Each cartridge delivers 20 mcg of teriparatide per dose for up to 28 days.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

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

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

11.2 Pharmacodynamics

Pharmacodynamics in Men with Primary or Hypogonadal Osteoporosis and Postmenopausal Women with Osteoporosis

Effects on Mineral Metabolism — Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (e.g., increases serum calcium and decreases serum phosphorus).

Serum Calcium Concentrations — When teriparatide 20 mcg was administered once daily, the serum calcium concentration increased 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 began to decline approximately 6 hours after dosing and returned 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 teriparatide (20 mcg subcutaneous once daily) was 9.68 mg/dL at 12 months. The peak serum calcium remained below 11 mg/dL in >99% of women at each visit. Sustained hypercalcemia was not observed.

In this study, 11.1% of women treated with teriparatide had at least 1 serum calcium value above the upper limit of normal (ULN) (10.6 mg/dL) compared with 1.5% of women treated with placebo. The percentage of women treated with teriparatide whose serum calcium was above the ULN on consecutive 4- to 6-hour post-dose measurements was 3% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or teriparatide doses were reduced. The timing of these dose reductions was at the discretion of the investigator. Teriparatide 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 teriparatide was 9.44 mg/dL at 12 months. The peak serum calcium remained below 11 mg/dL in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6% of men treated with teriparatide daily had at least 1 serum calcium value above the ULN (10.6 mg/dL) compared with none of the men treated with placebo. The percentage of men treated with teriparatide whose serum calcium was above the ULN on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Calcium supplementation was reduced in these men *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

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 teriparatide treatment was increased by 0.36 to 0.56 mg/dL, after 1 to 6 months of teriparatide treatment compared with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium >11 mg/dL, and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >11 mg/dL. The highest serum calcium reported was 12.5 mg/dL. None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of teriparatide on serum calcium were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Urinary Calcium Excretion — In a clinical study of postmenopausal women with osteoporosis who received 1,000 mg of supplemental calcium and at least 400 IU of vitamin D, daily teriparatide increased urinary calcium excretion. The median urinary excretion of calcium was 190 mg/day at 6 months and 170 mg/day at 12 months. These levels were 30 mg/day and 12 mg/day higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>300 mg/day) was similar in the women treated with teriparatide or placebo.
In a clinical study of men with either primary or hypogonadal osteoporosis who received 1,000 mg of supplemental calcium and at least 400 IU of vitamin D, daily teriparatide had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 220 mg/day at 1 month and 210 mg/day at 6 months. These levels were 20 mg/day higher and 8 mg/day lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (>300 mg/day) was similar in the men treated with teriparatide or placebo.

Phosphorus and Vitamin D — In single-dose studies, teriparatide produced transient phosphaturia and mild transient reductions in serum phosphorus concentration. However, hypophosphatemia (<2.4 mg/dL) was not observed in clinical trials with teriparatide.

In clinical trials of daily teriparatide, 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.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of teriparatide on serum phosphorus were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Effects on Markers of Bone Turnover — Daily administration of teriparatide to men and postmenopausal women with *osteoporosis* in clinical studies stimulated bone formation, as shown by increases in the formation markers serum bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months. The maximum increases of BSAP were 45% above baseline in women and 23% in men. After discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption: urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling. Changes in BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic exposure to teriparatide in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of teriparatide on serum markers of bone turnover were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

11.3 Pharmacokinetics

Absorption — Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses (1-, 2- and 4- times the recommended dosage, respectively). 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.

Distribution — Volume of distribution following intravenous injection is approximately 0.12 L/kg.

Elimination - Systemic clearance of teriparatide (approximately 62 L/hour in women and 94 L/hour in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. The half-life of teriparatide in serum was approximately 1 hour when administered by subcutaneous injection.

No metabolism or excretion studies have been performed with teriparatide. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

Specific Populations

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

Male and Female Patients — Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than women, the recommended dosage for men and women is the same.

Racial Groups — The influence of race has not been determined.

Patients with Renal Impairment — No pharmacokinetic differences were identified in 11 patients with creatinine clearance (CrCl) 30 to 72 mL/minute administered a single dose of teriparatide. In 5 patients with severe renal impairment (CrCl<30 mL/minute), 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.

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

Drug Interaction Studies

Digoxin — In a study of 15 healthy people administered digoxin daily to steady state, a single teriparatide dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect).

Hydrochlorothiazide — In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with 40 mcg of teriparatide (2 times the recommended dose) did not affect the serum calcium response to teriparatide. 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 CrCl 13 to 72 mL/minute, coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg (2 times the recommended dose) resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%); however, these changes did not appear to be clinically important.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

No bone tumors were detected in a long-term monkey study *[see Nonclinical Toxicology (12.2)]*.

Mutagenesis

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

Impairment of Fertility

No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100 or 300 mcg/kg/day prior to mating and in females continuing through gestation Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m^2).

12.2 Animal Toxicology

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1,000 mcg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 mcg/kg (2,700 times the human dose based on surface area, mcg/m^2).

In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

13 CLINICAL STUDIES

13.1 Treatment of Osteoporosis in Postmenopausal Women

The safety and efficacy of once-daily teriparatide, median exposure of 19 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 1,637 postmenopausal women with osteoporosis. In this study 541 postmenopausal women were treated with 20 mcg teriparatide subcutaneously once daily.

All women received 1,000 mg of calcium and at least 400 IU of vitamin D per day. Baseline and endpoint spinal radiographs were evaluated using the semiquantitative scoring. Ninety percent of the women in the study had 1 or more radiographically diagnosed vertebral fractures at baseline. The primary efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height of previously undeformed vertebrae. Such fractures are not necessarily symptomatic.

Effect on Fracture Incidence

New Vertebral Fractures — Teriparatide, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, reduced the risk of 1 or more new vertebral fractures from 14.3% of women in the placebo group to 5.0% in the teriparatide group (444 of the 541 patients treated with 20 mcg once daily of teriparatide were included in this analysis). This difference was statistically significant ($p<0.001$); the absolute reduction in risk was 9.3% and the relative reduction was 65%. Teriparatide was effective in reducing the risk for vertebral fractures regardless of age, baseline rate of bone turnover or baseline BMD (*see* Table 2).

Table 2: Effect of Teriparatide on Risk of Vertebral Fractures in Postmenopausal Women with Osteoporosis

	Percent of Women With Fracture			
	Teriparatide (N=444)	**Placebo (N=448)**	**Absolute Risk Reduction (%, 95% CI)**	**Relative Risk Reduction (%, 95% CI)**
New fracture (≥1)	5.0[a]	14.3	9.3 (5.5-13.1)	65 (45-78)
1 fracture	3.8	9.4		
2 fractures	0.9	2.9		
≥3 fractures	0.2	2.0		

[a] $p \leq 0.001$ compared with placebo.

New Nonvertebral Osteoporotic Fractures — Teriparatide significantly reduced the risk of any nonvertebral fracture from 5.5% in the placebo group to 2.6% in the teriparatide group ($p<0.05$). The absolute reduction in risk was 2.9% and the relative reduction was 53%. The incidence of new nonvertebral fractures in the teriparatide group compared with the placebo group was ankle/foot (0.2%, 0.7%), hip (0.2%, 0.7%), humerus (0.4%, 0.4%), pelvis (0%, 0.6%), ribs (0.6%, 0.9%), wrist (0.4%, 1.3%), and other sites (1.1%, 1.5%), respectively.

The cumulative percentage of postmenopausal women with osteoporosis who sustained new nonvertebral fractures was lower in women treated with teriparatide than in women treated with placebo (*see* Figure 1).

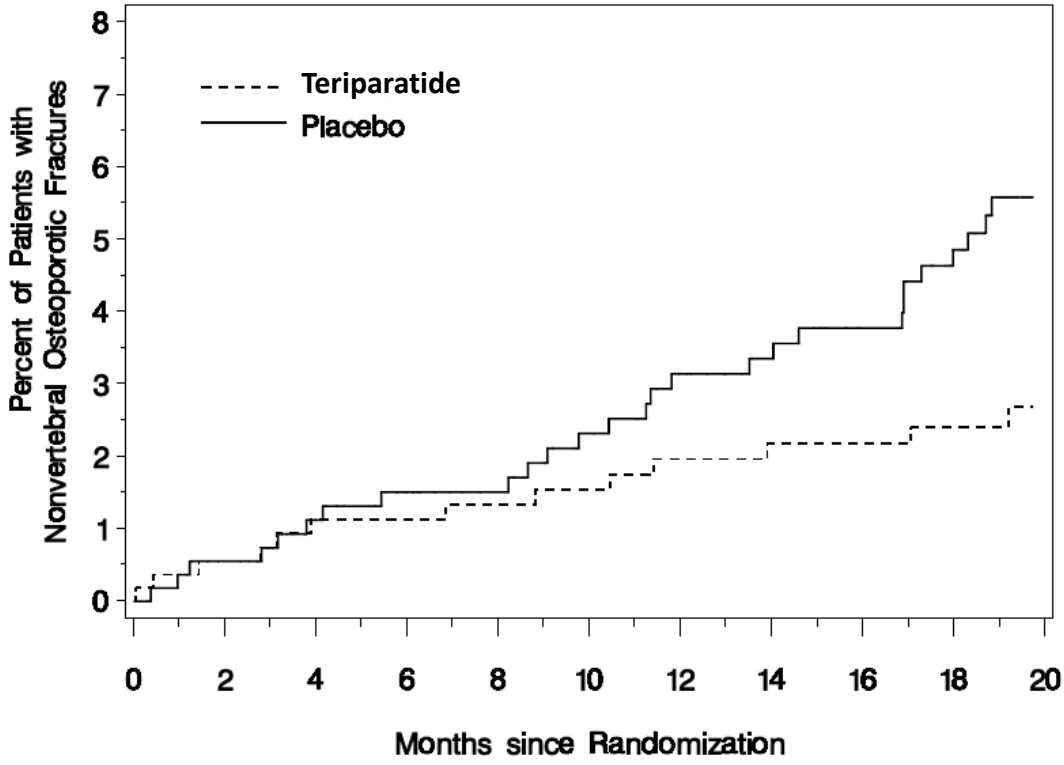


Figure 1: Cumulative Percentage of Postmenopausal Women with Osteoporosis Sustaining New Nonvertebral Osteoporotic Fractures

Effect on Bone Mineral Density (BMD)

Teriparatide increased lumbar spine BMD in postmenopausal women with osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Postmenopausal women with osteoporosis who were treated with teriparatide had statistically significant increases in BMD from baseline to endpoint at the lumbar spine, femoral neck, total hip, and total body (*see* Table 3).

Table 3: Mean Percent Change in BMD from Baseline to Endpoint[a] in Postmenopausal Women with Osteoporosis, Treated with Teriparatide or Placebo for a Median of 19 Months

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

[a] Intent-to-treat analysis, last observation carried forward.

[b] $p<0.001$ compared with placebo.

[c] $p<0.05$ compared with placebo.

Teriparatide treatment increased lumbar spine BMD from baseline in 96% of postmenopausal women treated. Seventy-two percent of patients treated with teriparatide achieved at least a 5% increase in spine BMD, and 44% gained 10% or more.
Both treatment groups lost height during the trial. The mean decreases were 3.61 and 2.81 mm in the placebo and teriparatide groups, respectively.

Bone Histology
The effects of teriparatide on bone histology were evaluated in iliac crest biopsies of 35 postmenopausal women treated for 12 to 24 months with calcium and vitamin D and teriparatide. Normal mineralization was observed with no evidence of cellular toxicity. The new bone formed with teriparatide was of normal quality (as evidenced by the absence of woven bone and marrow fibrosis).

13.2 Treatment to Increase Bone Mass in Men with Primary or Hypogonadal Osteoporosis

The safety and efficacy of once-daily teriparatide, median exposure of 10 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis. In this study, 151 men received 20 mcg of teriparatide given subcutaneously once daily. All men received 1,000 mg of calcium and at least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine BMD.

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

Teriparatide treatment for a median of 10 months increased lumbar spine BMD from baseline in 94% of men treated. Fifty-three percent of patients treated with teriparatide achieved at least a 5% increase in spine BMD, and 14% gained 10% or more.

Table 4: Mean Percent Change in BMD from Baseline to Endpoint[a] in Men with Primary or Hypogonadal Osteoporosis, Treated with Teriparatide or Placebo for a Median of 10 Months

	Teriparatide N=151	**Placebo N=147**
Lumbar spine BMD	5.9[b]	0.5
Femoral neck BMD	1.5[c]	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

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

13.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis

The efficacy of teriparatide for treating glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active- controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥5 mg/day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months. In the trial 214 patients were treated with teriparatide 20 mcg given subcutaneously once daily. In the teriparatide group, the baseline median glucocorticoid dose was 7.5 mg/day and the baseline median duration of glucocorticoid use was 1.5 years. The mean (SD) baseline lumbar spine BMD was 0.85 ± 0.13 g/cm^2 and lumbar spine BMD T-score was –2.5 ± 1 (number of standard deviations below the mean BMD value for healthy adults). A total of 30% of patients had prevalent vertebral fracture(s) and 43% had prior non-vertebral fracture(s). The patients had chronic rheumatologic, respiratory or other diseases that required sustained glucocorticoid therapy. All patients received 1,000 mg of calcium plus 800 IU of vitamin D supplementation per day.

Because of differences in mechanism of action (anabolic vs. anti-resorptive) and lack of clarity regarding differences in BMD as an adequate predictor of fracture efficacy, data on the active comparator are not presented.

Effect on Bone Mineral Density (BMD)

In patients with glucocorticoid-induced osteoporosis, teriparatide increased lumbar spine BMD compared with baseline at 3 months through 18 months of treatment. In patients treated with teriparatide, the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck ($p<0.001$ all sites). The relative treatment effects of teriparatide were consistent in subgroups defined by gender, age, geographic region, body mass index, underlying disease, prevalent vertebral fracture, baseline glucocorticoid dose, prior bisphosphonate use, and glucocorticoid discontinuation during trial.

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

3 mL cartridge (siliconised Type I glass), with a plunger stopper (bromobutyl) and disc seal (aluminium and rubber liner seals), packed in a plastic tray sealed with lid foil and packed in a carton.

Each Terrosa cartridge contains 2.4 mL of solution corresponding to 28 doses of 20 mcg (per 80 mcl).
Pack sizes:
1 cartridge or 3 cartridges.
Terrosa cartridge and pen pack:
1 inner carton of Terrosa cartridge (containing 1 cartridge) and 1 inner carton of Terrosa Pen (containing 1 pen).

Not all pack sizes may be marketed.

14.2 Storage and Handling

- Store in a refrigerator (2-8°C). Do not freeze. Keep the cartridge in the outer carton in order to protect from light.
- After insertion of the cartridge into the pen, the combined pen and cartridge should be returned to the refrigerator immediately after use.

- Do not store the injection device with the needle attached. Do not remove the cartridge from the pen during the 28 days of use.
- Once opened, the product may be stored for a maximum of 28 days within its shelf life at 2-8°C.
- The expiry date of the product is indicated on the packaging materials.

Terrosa solution for injection is supplied in a cartridge. Terrosa cartridges are to be used in Terrosa Pen reusable, multidose pen exclusively. Terrosa cartridges must not be used with any other pen. The pen and injection needles are not included with this medicinal product. However, for the treatment initiation a cartridge and pen pack should be used containing one carton of Terrosa cartridge and one carton of Terrosa Pen.
Each cartridge and pen should be used by only one patient. The pen can be used with injection needles developed according to the pen needle ISO standard of a gauge between 29 G and 31 G (diameter 0.25-0.33 mm) and a length between 5 mm to 12.7 mm for subcutaneous injection only.
A new sterile pen needle must be used for every injection.

The expiry date on the cartridge label must always be checked before inserting the cartridge into Terrosa Pen. To avoid medication errors, make sure that the date when starting to use a new cartridge is at least 28 days before its expiry date.

The patient should write down the batch number (Lot) of each cartridge and its first injection date on a calendar.
The date of first injection should also be written on the outer carton of Terrosa (see the provided space on the box).

Before using the pen device for the first time, the patient should read and understand the User's Manual on how to use the pen which is provided with the pen.

After each injection, the pen should be returned to the refrigerator. After the first use, the cartridge should not be removed from the pen during the 28 days of usage.

Each cartridge should be properly disposed of after 28 days of first use, even if it is not completely empty.

Terrosa solution for injection must not be transferred to a syringe.
Empty cartridges must not be refilled.

15. MARKETING AUTHORISATION HOLDER
Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

16. MARKETING AUTHORISATION NUMBER
163-82-35787-00

Revised in September 2024 according to MOH guidelines