CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211939Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BONSITY safely and effectively. See full prescribing information for BONSITY.

BONSITY (teriparatide injection), for subcutaneous use
Initial U.S. Approval: 1987

WARNING: POTENTIAL RISK OF OSTEOSARCOMA
See full prescribing information for complete boxed warning.

- **In rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor. (5.1, 13.1)**
- **Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe BONSITY only for patients for whom potential benefits outweigh potential risk. (5.1)**
- **BONSITY should not be prescribed for patients at increased baseline risk for osteosarcoma (e.g., those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton). (5.1)**

----------INDICATIONS AND USAGE----------
BONSITY is a parathyroid hormone analog (PTH 1-34) indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1)
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture (1.2)
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose is 20 mcg subcutaneously once a day (2.1, 2.2, 2.3)
- Administer as a subcutaneous injection into the thigh or abdominal wall (2.4)
- Administer initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (2.4)
- Use of the drug for more than 2 years during a patient's lifetime is not recommended (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 620 mcg/2.48 mL (250 mcg/mL) in single-patient-use pen containing 28 daily doses of 20 mcg (3)

----------CONTRAINDICATIONS----------

- Patients with hypersensitivity to teriparatide or to any of its excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Patients with Paget's disease of bone, pediatric and young adult patients with open epiphyses, and patients with prior external beam or implant radiation involving the skeleton: Should not be treated with BONSITY (5.1, 8.4)
- Treatment duration: Use of BONSITY for more than 2 years during a patient's lifetime is not recommended (5.2)
- Patients with bone metastases, history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders: Should not be treated with BONSITY (5.3, 5.4, 5.5)
- Laboratory alterations: BONSITY may increase serum calcium, urinary calcium, and serum uric acid (5 5, 5.6)
- Urolithiasis: Use with caution in patients with active or recent urolithiasis because of risk of exacerbation (5.6)
- Orthostatic hypotension: Transient orthostatic hypotension may occur with initial doses of BONSITY (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>10%) include: arthralgia, pain, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfenex, Inc., at 1-833-266-7489 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Digoxin: Use BONSITY with caution in patients receiving digoxin. Transient hypercalcemia may predispose patients to digitalis toxicity (5.8, 7.1, 12.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Consider discontinuing when pregnancy is recognized (8.1)
- Lactation: Breastfeeding is not recommended (8.2)
- Pediatric Use: BONSITY should not be used in pediatric and young adult patients with open epiphyses due to increased baseline risk of osteosarcoma (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20 mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe BONSITY™ only for patients for whom the potential benefits are considered to outweigh the potential risk. BONSITY should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) ***[see Warnings and Precautions (5.1), Adverse Reactions (6.2), and Nonclinical Toxicology (13.1)]*****.**

1 INDICATIONS AND USAGE

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

BONSITY 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, BONSITY reduces the risk of vertebral and nonvertebral fractures *[see Clinical Studies (14.1)]*.

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

BONSITY 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 (14.2)]*.

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

BONSITY 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 (14.3)]*.

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

- BONSITY should be administered as a subcutaneous injection into the thigh or abdominal wall. There are no data available on the safety or efficacy of intravenous or intramuscular injection of BONSITY.

- BONSITY 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 (5.7)]*.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. BONSITY is a clear and colorless liquid. Do not use if solid particles appear or if the solution is cloudy or colored.

- Patients and caregivers who administer BONSITY should receive appropriate training and instruction on the proper use of the BONSITY delivery device from a qualified health professional *[see Patient Counseling Information (17.5)]*.

2.5 Treatment Duration

The safety and efficacy of teriparatide have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patient's lifetime is not recommended.

3 DOSAGE FORMS AND STRENGTHS

Injection: 620 mcg/2.48 mL (250 mcg/mL)

Colorless solution in a single-patient-use pen containing 28 daily doses of 20 mcg.

4 CONTRAINDICATIONS

BONSITY is contraindicated in patients with:

- Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Osteosarcoma

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration *[see Boxed Warning and Nonclinical Toxicology (13.1)]*. BONSITY should not be prescribed for patients at increased baseline risk of osteosarcoma.

These include:

- Paget's disease of bone. Unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone.
- Pediatric and young adult patients with open epiphyses.
- Prior external beam or implant radiation therapy involving the skeleton.

5.2 Treatment Duration

The safety and efficacy of teriparatide have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended.

5.3 Bone Metastases and Skeletal Malignancies

Patients with bone metastases or a history of skeletal malignancies should not be treated with BONSITY.

5.4 Metabolic Bone Diseases

Patients with metabolic bone diseases other than osteoporosis should not be treated with BONSITY.

5.5 Hypercalcemia and Hypercalcemic Disorders

Teriparatide has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with teriparatide because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with BONSITY.

5.6 Urolithiasis or Pre-existing Hypercalciuria

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

5.7 Orthostatic Hypotension

BONSITY 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 with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved 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.

5.8 Drug Interactions

Hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, patients receiving digoxin should use BONSITY with caution *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

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.

Treatment of Osteoporosis in Men and Postmenopausal Women

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 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). 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 1000 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 teriparatide patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of teriparatide patients and 6% of placebo patients.

Table 1 lists adverse events from the two principal osteoporosis trials in men and postmenopausal women 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 increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with teriparatide. The number 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 (12.2)]*.

Serum Uric Acid — Teriparatide increased serum uric acid concentrations. In clinical trials, 3% of teriparatide patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo 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.

Studies in 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 ≥5 mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to teriparatide and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

The incidence of all cause mortality was 4% in the teriparatide group and 6% in 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 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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.

- Osteosarcoma: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to teriparatide use is unclear. Long term osteosarcoma surveillance studies are ongoing *[see Warnings and Precautions (5.1)]*.
- Hypercalcemia: Hypercalcemia greater than 13.0 mg/dL has been reported with teriparatide use.

Adverse events reported since market introduction that were temporally (but not necessarily causally) 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

6.3 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 to teriparatide in the study described below with the incidence of antibodies in other studies or to other teriparatide products may be misleading.

The immunogenicity profile of BONSITY was evaluated in a 24-week randomized trial comparing the effects of BONSITY 20 mcg daily with another teriparatide product 20 mcg daily. In this trial, 2.2% (2/90) subjects who received BONSITY and 2.2% (2/91) subjects who received the other teriparatide product had detectable antibodies to teriparatide and one out of the two BONSITY treated patients developed neutralizing antibodies to teriparatide.

7 DRUG INTERACTIONS

7.1 Digoxin

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). However, because teriparatide may transiently increase serum calcium, BONSITY should be used with caution in patients taking digoxin *[see Warnings and Precaution (5.8) and Clinical Pharmacology (12.2)]*.

7.2 Hydrochlorothiazide

The coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 mcg. The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied *[see Clinical Pharmacology (12.2)]*.

7.3 Furosemide

Coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg in healthy people and patients with mild, moderate, or severe renal impairment (CrCl 13 to 72 mL/min) resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important *[see Clinical Pharmacology (12.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on BONSITY use in pregnant women to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Consider discontinuing BONSITY 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 8 to 267 times the human dose (based on body surface area, mcg/m^2). At 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

subcutaneous 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 breast fed infant.

Because of the potential for osteosarcoma shown with teriparatide in animal studies, advise patients that breastfeeding is not recommended during treatment with BONSITY [*see Warnings and Precautions (5.1)*].

8.4 Pediatric Use

The safety and efficacy of teriparatide have not been established in any pediatric population. BONSITY should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, BONSITY is not indicated for use in pediatric or young adult patients with open epiphyses *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Of the patients receiving teriparatide in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving teriparatide in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No studies have been performed in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In 5 patients with severe renal impairment (CrCl <30 mL/min), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

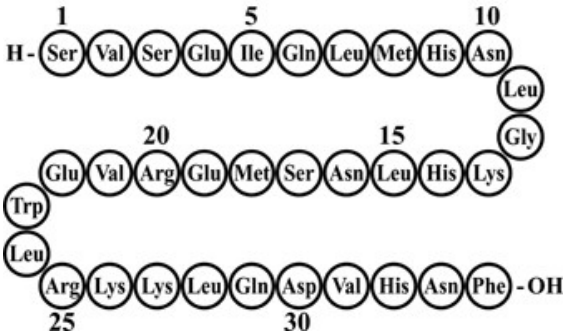
In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the teriparatide delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases,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

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

11 DESCRIPTION

BONSITY (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 the molecular weight is 4117.8 daltons. Its amino acid sequence is shown below:



Teriparatide is manufactured using a strain of *Pseudomonas fluorescens* modified by recombinant DNA technology. BONSITY is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a single-patient-use delivery device (pen) for subcutaneous injection. Each pen is filled to deliver 2.48 mL. Each mL contains 250 mcg teriparatide (as a free base), 0.41 mg glacial acetic acid, 0.10 mg sodium acetate, 45.4 mg mannitol, 3 mg metacresol, and water for injection. The drug product is a pH 4.0 solution.

Each cartridge, pre-assembled into a delivery device, delivers 20 mcg of teriparatide per dose each day for up to 28 days.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Pharmacodynamics in Men 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 is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16 to 24 hours after each dose.

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

In this study, 11.1% of women treated with teriparatide had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with 1.5% of women treated with placebo. The percentage of women treated with teriparatide whose serum calcium was

above the upper limit of normal on consecutive 4- to 6-hour post-dose measurements was 3.0% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or 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 2.35 mmol/L (9.44 mg/dL) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dL) in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6.0% of men treated with teriparatide daily had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dL)] compared with none of the men treated with placebo. The percentage of men treated with teriparatide whose serum calcium was above the upper limit of normal on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Although calcium supplements and/or teriparatide doses could have been reduced in these men, only calcium supplementation was reduced *[see Warnings and Precautions (5.5) 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 injection was increased by 0.09 to 0.14 mmol/L (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 >2.76 mmol/L (11.0 mg/dL), and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >2.76 mmol/L (11.0 mg/dL). The highest serum calcium reported was 3.12 mmol/L (12.5 mg/dL). None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

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 1000 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 4.8 mmol/day (190 mg/day) at 6 months and 4.2 mmol/day (170 mg/day) at 12 months. These levels were 0.76 mmol/day (30 mg/day) and 0.3 mmol/day (12 mg/day) higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the women treated with teriparatide or placebo.

In a clinical study of men with either primary or hypogonadal osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily teriparatide had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 5.6 mmol/day (220 mg/day) at 1 month and 5.3 mmol/day (210 mg/day) at 6 months. These levels were 0.5 mmol/day (20 mg/day) higher and 0.2 mmol/day (8.0 mg/day) lower,

respectively, than in men treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the men treated with 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 (<0.74 mmol/L or 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.

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). However, sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide may transiently increase serum calcium, BONSITY should be used with caution in patients taking digoxin *[see Drug Interactions (7.1)]*.

Hydrochlorothiazide — In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 mcg. The 24-hour urine excretion of calcium was reduced by a clinically unimportant amount (15%). The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied *[see Drug Interactions (7.2)]*.

Furosemide — In a study of 9 healthy people and 17 patients with mild, moderate, or severe renal impairment (CrCl 13 to 72 mL/min), coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important *[see Drug Interactions (7.3)]*.

12.3 Pharmacokinetics

The pharmacokinetic parameters of teriparatide following single subcutaneous administration of BONISTY in patients with osteoporosis are shown in Table 2.

Table 2. Pharmacokinetic Parameters of Teriparatide Following Administration of a Single Dose, 20 mcg, of BONISTY

	Mean ± S.D.	**n**
T_{max} (hour)*	0.25 (0.12, 1.08)	83
C_{max} (pg/mL)	109.5 ± 62.8	83
$AUC_{0\text{-}t}$ (pg·hr/mL)	134.8 ± 79.7	83
$AUC_{0\text{-}inf}$ (pg·hr/mL)	149.8 ± 68.1	72
$t_{1/2}$ (hour)	0.79 ± 0.35	72

Arithmetic mean ± S.D.; *T_{max} = median (minimum, maximum)

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

Distribution — Systemic clearance of teriparatide (approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection. The longer half-life following subcutaneous administration reflects the time required for absorption from the injection site.

Elimination

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

Specific Populations

Pediatric Patients — Pharmacokinetic data in pediatric patients are not available *[see Warnings and Precautions (5.1)]*.

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

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

Race —The influence of race has not been determined.

Renal Impairment — No pharmacokinetic differences were identified in 11 patients with mild or moderate renal impairment [creatinine clearance (CrCl) 30 to 72 mL/min] administered a single dose of teriparatide. In 5 patients with severe renal impairment (CrCl <30 mL/min), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment — No studies have been performed in patients with hepatic impairment. *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

No pharmacokinetic drug-drug interaction studies have been conducted with teriparatide.

13 NONCLINICAL TOXICOLOGY

13.1 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 systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans 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 doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day 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.

The relevance of these animal findings to humans is uncertain.

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).

13.2 Animal Toxicology and/or Pharmacology

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 mcg/kg (2700 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.

14 CLINICAL STUDIES

14.1 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 1637 postmenopausal women with osteoporosis (teriparatide 20 mcg, n=541).

All women received 1000 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. 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 3*).

Table 3. 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*).

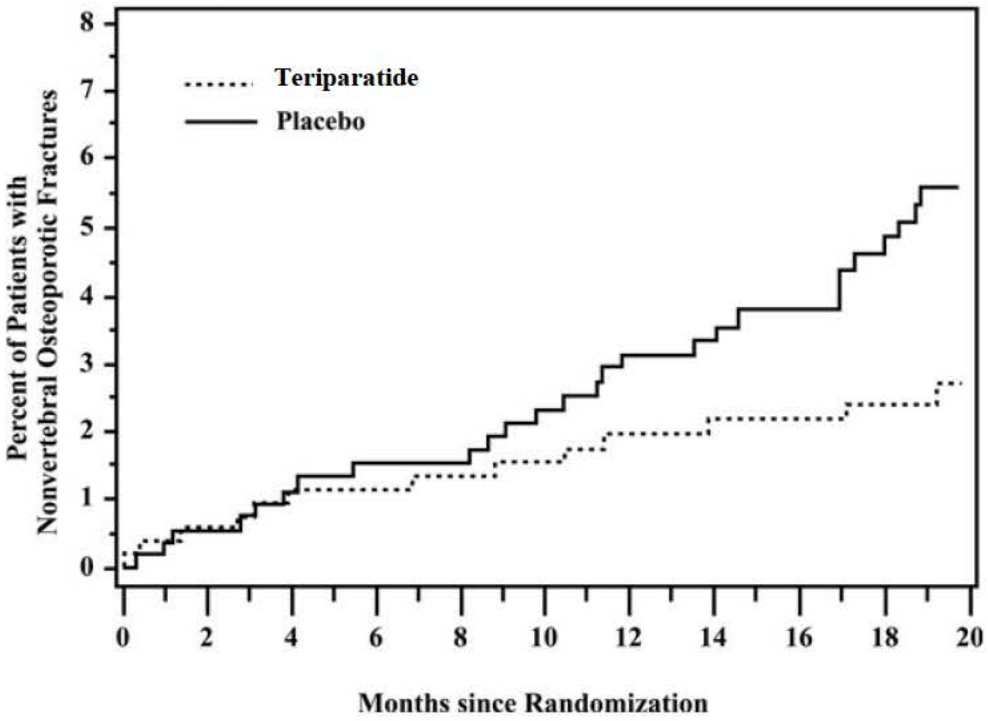


Figure 1. Cumulative Percentage of Postmenopausal Women with Osteoporosis Sustaining New Nonvertebral Osteoporotic Fractures

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 4*).

Table 4. 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 20 or 40 mcg/day. 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).

14.2 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 (teriparatide 20 mcg, n=151). All men received 1000 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 5.

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 5. 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.

14.3 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 with 214 patients exposed to teriparatide. In the teriparatide group, the baseline median glucocorticoid dose was 7.5 mg/day and the 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 1000 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BONSITY is available as single-patient-use pens in the following package size:

- 620 mcg/2.48 mL (250 mcg/mL) NDC 73374-652-89.

16.2 Storage and Handling

- The BONSITY delivery device should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) at all times.
- Recap the delivery device when not in use to protect the cartridge from physical damage and light.
- During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator.
- Do not freeze. Do not use BONSITY if it has been frozen.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and User Manual).

17.1 Potential Risk of Osteosarcoma

Patients should be made aware that, in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration.

17.2 Orthostatic Hypotension

BONSITY should be administered initially under circumstances where the patient can immediately sit or lie down if symptoms occur. Patients should be instructed that if they feel lightheaded or have palpitations after the injection, they should sit or lie down until the symptoms resolve. If symptoms persist or worsen, patients should be instructed to consult a physician before continuing treatment *[see Warnings and Precautions (5.7)]*.

17.3 Hypercalcemia

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

17.4 Other Osteoporosis Treatment Modalities

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

17.5 Use of Delivery Device (Pen)

Patients and caregivers who administer BONSITY should be instructed on how to properly use the delivery device (refer to *User Manual*), properly dispose of needles, and be advised not to share their delivery device with other patients. The contents of the delivery device should NOT be transferred to a syringe.

Each BONSITY delivery device can be used for up to 28 days including the first injection from the delivery device. After the 28-day use period, discard the BONSITY delivery device, even if it still contains some unused solution.

17.6 Availability of Medication Guide and User Manual

Patients should read the *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with BONSITY and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the BONSITY delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

Marketed by: Pfenex, Inc.
San Diego, CA 92121, USA

www.bonsity.com

Medication Guide

BONSITY™ (bon si tee)

teriparatide injection

Read this Medication Guide before you start taking BONSITY™ and each time you get a refill. There may be new information. Also, read the User Manual that comes with the BONSITY device (pen) for information on how to use the device to inject your medicine the right way. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about BONSITY?

- **Possible bone cancer.** During drug testing, the medicine in BONSITY caused some rats to develop a bone cancer called osteosarcoma. In people, osteosarcoma is a serious but rare cancer. Osteosarcoma has rarely been reported in people who took BONSITY. It is not known if people who take BONSITY have a higher chance of getting osteosarcoma.
- You should not take BONSITY for more than 2 years over your lifetime.

What is BONSITY?

- BONSITY is a prescription medicine that is like a hormone made by the body called parathyroid hormone or PTH.
- BONSITY may help to form new bone, increase bone mineral density and bone strength.
- BONSITY can lessen the number of fractures of the spine and other bones in postmenopausal women with osteoporosis.
- The effect on fractures has not been studied in men.
- BONSITY is used in both men and postmenopausal women with osteoporosis who are at high risk for having fractures. BONSITY can be used by people who have had a fracture related to osteoporosis, or who have several risk factors for fracture, or who cannot use other osteoporosis treatments.
- BONSITY is used in both men and women with osteoporosis due to use of glucocorticoid medicines, such as prednisone, for several months, who are at high risk for having broken bones (fractures). These include men and women with either a history of broken bones, who have several risk factors for fracture, or who cannot use other osteoporosis treatments.

It is not known if BONSITY is safe and effective in children.

BONSITY should not be used in children and young adults whose bones are still growing.

Who should not use BONSITY?

Do not use BONSITY if you are allergic to any of the ingredients in BONSITY. See the end of this Medication Guide for a complete list of the ingredients in BONSITY.

Before you take BONSITY, tell your healthcare provider if you:

- have the condition listed in the section “Who should not use BONSITY?”
- have Paget's disease or other bone disease
- have cancer in your bones
- have trouble injecting yourself and do not have someone who can help you
- are a child or young adult whose bones are still growing
- have or have had kidney stones
- have had radiation therapy
- have or have had too much calcium in your blood
- have any other medical conditions
- are pregnant or thinking about becoming pregnant. It is not known if BONSITY will harm your unborn baby.
- are breast-feeding or plan to breast-feed. You should not breast-feed while taking BONSITY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Your healthcare provider needs this information to help keep you from taking BONSITY with other medicines that may harm you.

Especially tell your doctor if you take medicines that contain digoxin (Digoxin*, Lanoxicaps*, Lanoxin*).

How should I use BONSITY?

- Inject BONSITY one time each day in your thigh or abdomen (lower stomach area). Talk to a healthcare provider about how to rotate injection sites.
- Before you try to inject BONSITY yourself, a healthcare provider should teach you how to use the BONSITY delivery device to give your injection the right way.
- Read the detailed *User Manual*.
- You can take BONSITY with or without food or drink.
- The BONSITY delivery device has enough medicine for 28 days. It is set to give a 20-microgram dose of medicine each day. Do not inject all the medicine in the BONSITY delivery device at any one time.
- Do not transfer the medicine from the BONSITY delivery device to a syringe. This can result in taking the wrong dose of BONSITY. If you do not have pen needles to use with your BONSITY delivery device, talk with your healthcare provider.
- BONSITY should look clear and colorless. Do not use BONSITY if it has particles in it, or if it is cloudy or colored.
- Inject BONSITY right away after you take the delivery device out of the refrigerator.
- After each use, safely remove the needle, recap the delivery device, and put it back in the refrigerator right away.
- You can take BONSITY at any time of the day. To help you remember to take BONSITY, take it at about the same time each day.
- If you forget or cannot take BONSITY at your usual time, take it as soon as you can on that day. Do not take more than one injection in the same day.
- If you take more BONSITY than prescribed, call your healthcare provider. If you take too much BONSITY, you may have nausea, vomiting, weakness, or dizziness.
- Follow your healthcare provider's instructions about other ways you can help your osteoporosis, such as exercise, diet, and reducing or stopping your use of tobacco and alcohol. If your healthcare provider recommends calcium and vitamin D supplements, you can take them at the same time you take BONSITY.

What are the possible side effects of BONSITY?

BONSITY can cause serious side effects, including:

- See **"What is the most important information I should know about BONSITY?"**
- **Decrease in blood pressure when you change positions.** Some people feel dizzy, get a fast heartbeat, or feel faint right after the first few doses. This usually happens within 4 hours of taking BONSITY and goes away within a few hours. For the first few doses, take your injections of BONSITY in a place where you can sit or lie down right away if you get these symptoms. If your symptoms get worse or do not go away, stop taking BONSITY and call your healthcare provider.
- **Increased calcium in your blood.** Tell your healthcare provider if you have nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs that there is too much calcium in your blood.

Common side effects of BONSITY include:

- nausea
- joint aches
- pain

Your healthcare provider may take samples of blood and urine during treatment to check your response to BONSITY. Also, your healthcare provider may ask you to have follow-up tests of bone mineral density.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BONSITY. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BONSITY?

- Keep your BONSITY delivery device in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze the BONSITY delivery device. Do not use BONSITY if it has been frozen.
- Do not use BONSITY after the expiration date printed on the delivery device and packaging.
- Throw away the BONSITY delivery device after 28 days even if it has medicine in it (see the User Manual).

Keep BONSITY and all medicines out of the reach of children.

General information about BONSITY

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BONSITY for a condition for which it was not prescribed. Do not give BONSITY to other people, even if they have the same condition you have.

This Medication Guide summarizes the most important information about BONSITY. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about BONSITY that is written for healthcare professionals. For more information, go to www.BONSITY.com or call Pfenex, Inc., at 1-833-266-7489.

What are the ingredients in BONSITY?

Active ingredient: teriparatide
Inactive ingredients: glacial acetic acid, sodium acetate, mannitol, metacresol, and water for injection.

What is Osteoporosis?

Osteoporosis is a disease in which the bones become thin and weak, increasing the chance of having a broken bone. Osteoporosis usually causes no symptoms until a fracture happens. The most common fractures are in the spine (backbone). They can shorten height, even without causing pain. Over time, the spine can become curved or deformed and the body bent over. Fractures from osteoporosis can also happen in almost any bone in the body; for example, the wrist, rib, or hip. Once you have had a fracture, the chance for more fractures greatly increases.

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

- past broken bones from osteoporosis
- very low bone mineral density (BMD)
- frequent falls
- limited movement, such as using a wheelchair
- medical conditions likely to cause bone loss, such as some kinds of arthritis
- taking steroid medicines called glucocorticoids, such as prednisone
- other medicines that may cause bone loss; for example: seizure medicines (such as phenytoin), blood thinners (such as heparin), and high doses of vitamin A

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: October 2019

BONSITY™
teriparatide injection
User Manual

Storage Information

Always store the device in the refrigerator with the white cap on.

DO NOT store the device with a needle attached.

The device can be stored in the refrigerator after first use for **28 days**.

Dispose device after 28 days of use.

IMPORTANT INFORMATION

DO NOT start the administration procedure until you have read the Medication Guide and this User Manual contained in your BONSITY carton thoroughly. Follow the instructions carefully whenever using the BONSITY device.

DO NOT share your BONSITY device or needles with anyone else. Infection or disease can be spread from one person to another.

DO NOT use the BONSITY device for more than 28 days. The BONSITY device contains 28 days of medicine. After 28 days of use dispose of this device even if it is not completely empty.

DO NOT inject more than one dose of BONSITY in the same day.

DO NOT attempt to transfer BONSITY from the device provided to syringe or any other device.

BONSITY Device and Parts

Needles not included. Becton, Dickinson and Company pen needles from 29 to 31 gauge are recommended for use with this device.

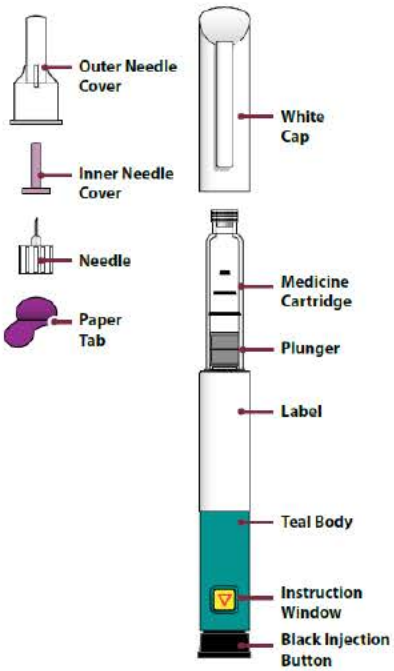


Figure A

Prepare for Injection

1 Prepare Site and Remove the White Cap

A) Wash hands prior to use.
B) Prepare the injection site (thigh or abdomen) as recommended by your healthcare provider.
C) Remove the white cap by pulling it straight off of the device (Figure B).

Figure B

2 Check Device, Device Label and Medication

A) Check the device.
DO NOT use the BONSITY device if it is damaged.
B) Check the label on the device.
DO NOT use if the device contains the incorrect medication or if the medication has expired (Figure C).
C) Check the medication cartridge. The liquid medication should be clear and colorless.
DO NOT use the medication if it is cloudy, colored, or has floating particles. (Figure C).

Figure C

3 Attach New Needle

A) Peel off the paper tab (Figure D).

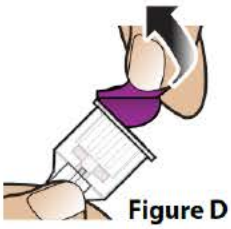


Figure D

B) Push the needle **straight** onto medicine cartridge. Screw on needle clockwise until firmly attached (Figure E and Figure F).

DO NOT over-tighten the needle.

Figure E

Figure F

4 Remove Outer Needle Cover

Pull off large outer needle cover (Figure G), and **save it for later** (see Step 9).

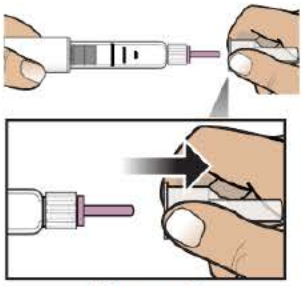


Figure G

5 Set Dose

Pull out the black injection button **until it stops** (Figure H).

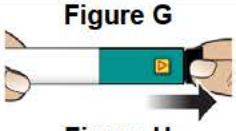


Figure H

Check to make sure red stripe shows. Additionally, the instruction window will show an arrow pointing towards the needle end of the device (Figure I).

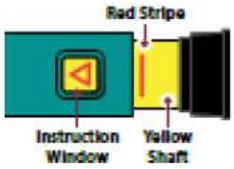


Figure I

Troubleshooting

If the device does not set fully or if you cannot pull back on the black injection button refer to Troubleshooting Problem E on the back page.

Administer Injection

6 Remove Inner Needle Cover

A) Pull off small inner needle protector and throw it away (Figure J).

B) CAUTION: The needle will be exposed.

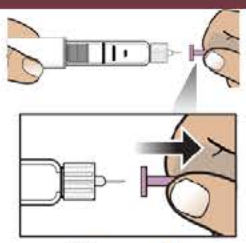


Figure J

7 Inject Dose

A) Gently hold a fold of skin on your thigh or abdomen and insert the needle straight into the folded skin (Figure K).

Figure K

B) Press the black injection button down until it stops and hold (Figure L).

Figure L

C) Hold it in and **count to 5 slowly. You must wait until the count of 5** to make sure the full dose has been delivered (Figure M).

Figure M

D) Remove the needle from the skin (Figure N).
Once needle is removed from skin, take your thumb off the black injection button.

Note: You may not see the plunger moving.
To confirm that your dose has been delivered, see Step 8.

Figure N

After Injection

8 Confirm Dose

Check to make sure the black injection button is all the way down. The instruction window will show an arrow pointing towards the black button.

If the yellow shaft does not show, you have finished the injection steps the right way (Figure O).

Figure O

Important

You should **not** see any of the yellow shaft. If you do and have already injected the medicine, **do not** inject yourself a second time in the same day.

Instead, **you must reset the device**.

Refer to **Troubleshooting Problem A** on the back page for more information.

9 Remove Needle and Dispose

A) Put the large outer needle cover on the needle by scooping it up and pressing it on (Figure P and Figure Q). Do not try to put the needle cover back on with your hands.

Figure P

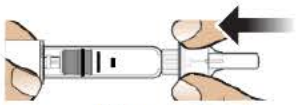


Figure Q

B) Unscrew the covered needle all the way by giving the large needle cover 3-5 counter-clockwise turns (Figure R).

Pull the needle straight off (Figure S).

Figure R

Figure S

C) Dispose of the needle into a puncture resistant container according to local regulations (Figure T).

DO NOT reuse needle.

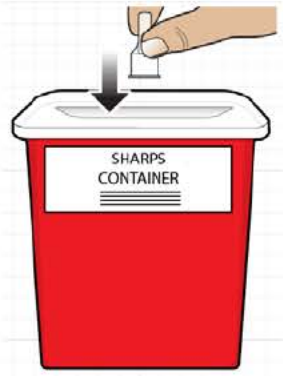


Figure T

Disposal Information

For more information about how to correctly dispose of the needle refer to the Disposal Information section on the back page.

10 Recap Device and Store

A) Push white cap back on (Figure U).


Figure U

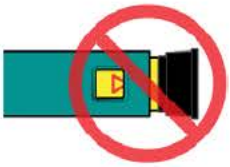
B) Always store the device in the refrigerator with the white cap on right after use (Figure V).

DO NOT store the device with a needle attached.


Figure V

Revised October 2019
See Reverse Side for More Information

Troubleshooting

Problem	Solution
A The yellow shaft is still showing after I push in the black injection button. How do I reset my BONSITY delivery device? 	**To reset the BONSITY delivery device, follow the steps below:** **1)** If you have already injected, **DO NOT** inject yourself a second time on the same day. **2)** Remove the needle and dispose in a sharps container according to local regulations. **3)** Attach a new needle, pull off the large needle cover and save it. **4)** Pull off the inner needle cover and throw away. **5)** Point the needle down into an empty container. Push in the black injection button until it stops. Hold it in and slowly count to five. You may see a small stream or drop of fluid. When you have finished, the black injection button should be all the way in. **6)** If you still see the yellow shaft showing, contact Pfenex (see Contact Information below and to the right) or your healthcare provider. **7)** Remove the needle and dispose in a sharps container according to local regulations. Push the white cap back on, and put your BONSITY delivery device in the refrigerator. You can prevent this problem by always using a NEW needle for each injection, and by pushing the black injection button all the way in and slowly counting to five.

B How can I tell if my BONSITY delivery device works?

The black injection button should be all the way in to show that the full dose of medicine has been injected from the BONSITY delivery device. Use a new needle every time you inject to be sure your BONSITY delivery device will work properly.

C I see an air bubble in my BONSITY delivery device.

A small air bubble will not affect your dose and it will not harm you. You can continue to take your dose as usual.

D I cannot get the needle off.

1) Put the large needle cover on the needle.
2) Use the large needle cover to unscrew the needle.
3) Unscrew the needle all the way by giving the large needle cover 3 to 5 counter-clockwise turns.
4) If you still cannot get the needle off, ask someone to help you.

E What should I do if I have difficulty pulling out the black injection button?

Change to a new BONSITY delivery device to take your dose as instructed by your healthcare provider.

When the black injection button becomes hard to pull out, this means there is not enough medicine in your BONSITY delivery device for another dose. You may still see some medicine left in the cartridge.

Disposal Information

Put your used needles in a FDA-cleared sharps disposal container right away after use.

DO NOT throw away (dispose of) loose needles in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a container that is:

- Made of a heavy-duty plastic
- Can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
- Upright and stable during use
- Leak-resistant
- Properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles.
For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

DO NOT dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.

DO NOT recycle your used sharps disposal container.

Cleaning and Storage

Cleaning Your BONSITY Delivery Device

- Wipe the outside of the BONSITY delivery device with a damp cloth.
- Do not place the BONSITY delivery device in water, or wash or clean it with any liquid.

Storing Your BONSITY Delivery Device

- After each use, refrigerate the BONSITY delivery device right away. Read and follow the instructions in the Medication Guide section "How should I store BONSITY?".
- **DO NOT** store the BONSITY delivery device with a needle attached. Doing this may cause air bubbles to form in the medicine cartridge.

- Store the BONSITY delivery device with the white cap on.
- **DO NOT** freeze BONSITY. If the BONSITY delivery device has been frozen, throw the device away and use a new BONSITY delivery device. If the BONSITY delivery device has been left out of the refrigerator, do not throw the delivery device away. Place the delivery device back in the refrigerator and call Pfenex (see Contact Information below).

Other Important Notes

- The BONSITY delivery device contains 28 days of medicine.
- **DO NOT** transfer BONSITY to a syringe. This may result in you taking the wrong dose of medicine.
- Read and follow the instructions in the User Manual so that you use your BONSITY delivery device the right way.
- Check the BONSITY delivery device label to make sure you have the right medicine and that it has not expired.
- **DO NOT** use the BONSITY delivery device if it looks damaged. Look at the BONSITY medicine in the cartridge. If the medicine is not clear and colorless, or if it has particles, do not use it. Call Pfenex if you notice any of these (see Contact Information below).
- Use a new needle for each injection.
- During injection, you may hear one or more clicks – this is normal.
- The BONSITY delivery device is not recommended for use by the blind or by those who have vision problems without help from a person trained in the proper use of the device.
- Keep your BONSITY delivery device and needles out of the reach of children.

Disposal of Pen Needles and Delivery Device

Disposal of Pen Needles and the BONSITY Delivery Device

- Before throwing away the BONSITY delivery device, be sure to remove the pen needle.
- Throw away your BONSITY delivery device and used needles as instructed by your healthcare provider, local or state laws, or institutional policies.

Dispose of the BONSITY delivery device 28 days after first use.

1st Use Date: _____ / _____ / _____

Throw Away After: _____ / _____ / _____

Contact Information

If you have questions or need help with your BONSITY™ delivery device, contact Pfenex Inc. toll-free at 1-833-266-7489 or your healthcare provider.
For more information about BONSITY, go to www.bonsity.com.

Marketed by: Pfenex Inc., San Diego, CA 92121, USA

LOT XXXXXXX
EXP YYYY-MM

BONSITY™
teriparatide injection
620 mcg/2.48 mL (250 mcg/mL)

FOR POSITION ONLY
2D Barcode
9 9999-9999-99 9

NDC XXXXX-**652**-89

Rx only

20 mcg per dose
For subcutaneous use

Do NOT transfer contents to a syringe.
Read User Manual BEFORE Injecting.

Each single-patient-use pen will deliver 28 subcutaneous doses.
Throw away 28 days after first use.

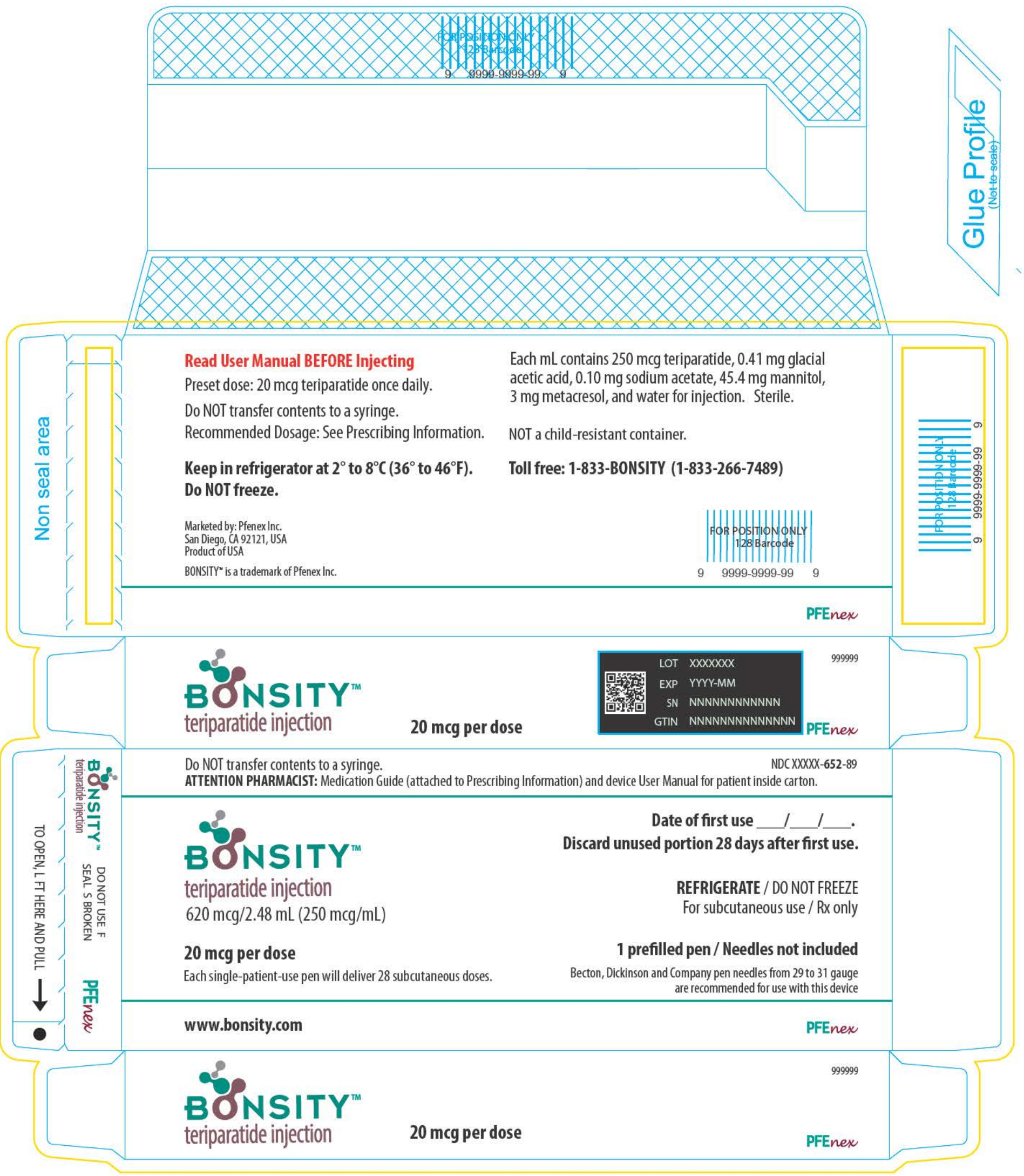
REFRIGERATE - DO NOT FREEZE

Marketed by: Pfenex, Inc.
San Diego, CA 92121, USA
Product of USA

PFEnex

FPO

Reference ID: 4501869


FOR POSITION ONLY
128 Barcode
9 9999-9999-99 9
Glue Profile
(Not to scale)
Non seal area
Read User Manual BEFORE Injecting
Preset dose: 20 mcg teriparatide once daily.
Do NOT transfer contents to a syringe.
Recommended Dosage: See Prescribing Information.
Keep in refrigerator at 2° to 8°C (36° to 46°F).
Do NOT freeze.
Each mL contains 250 mcg teriparatide, 0.41 mg glacial acetic acid, 0.10 mg sodium acetate, 45.4 mg mannitol, 3 mg metacresol, and water for injection. Sterile.
NOT a child-resistant container.
Toll free: 1-833-BONSITY (1-833-266-7489)
Marketed by: Pfenex Inc.
San Diego, CA 92121, USA
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BONSITY™ is a trademark of Pfenex Inc.
FOR POSITION ONLY
128 Barcode
9 9999-9999-99 9
PFEnex
BONSITY™
teriparatide injection
20 mcg per dose
LOT XXXXXXX
EXP YYYY-MM
SN NNNNNNNNNNNN
GTIN NNNNNNNNNNNNN
999999
PFEnex
Do NOT transfer contents to a syringe.
ATTENTION PHARMACIST: Medication Guide (attached to Prescribing Information) and device User Manual for patient inside carton.
NDC XXXXX-652-89
BONSITY™
teriparatide injection
620 mcg/2.48 mL (250 mcg/mL)
20 mcg per dose
Each single-patient-use pen will deliver 28 subcutaneous doses.
Date of first use ___/___/___.
Discard unused portion 28 days after first use.
REFRIGERATE / DO NOT FREEZE
For subcutaneous use / Rx only
1 prefilled pen / Needles not included
Becton, Dickinson and Company pen needles from 29 to 31 gauge are recommended for use with this device
www.bonsity.com
PFEnex
TO OPEN, L FT HERE AND PULL
BONSITY™ teriparatide injection
DO NOT USE F SEAL S BROKEN
PFEnex
BONSITY™
teriparatide injection
20 mcg per dose
999999
PFEnex

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/s/

CHRISTINE P NGUYEN
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