Sondelbay® Injection 20mcg/80mcL
(Teriparatide)

1 INDICATIONS AND USAGE

Sondelbay is indicated:

- For the treatment of postmenopausal women with osteoporosis who are at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment. In postmenopausal women with osteoporosis, teriparatide increases BMD and reduces the risk of vertebral and nonvertebral fractures.
- To increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment. In men with primary or hypogonadal osteoporosis, teriparatide increases BMD. The effects of teriparatide on risk for fracture in men have not been studied.
- For the treatment of men and women with glucocorticoid-induced osteoporosis at high risk for fracture. See CLINICAL STUDIES (12.3).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is 20 mcg given subcutaneously once a day.

2.2 Administration Instructions

- Administer Sondelbay as a subcutaneous injection into the thigh or abdominal region. Sondelbay is not approved for intravenous or intramuscular use.
- Sondelbay 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 (4.4)].
- Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Sondelbay 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 Sondelbay should receive appropriate training and instruction on the proper use of the Sondelbay prefilled delivery device (pen) from a qualified health professional.

2.3 Recommended Treatment Duration

Use of Sondelbay for more than 2 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 (4.1)].

3 CONTRAINDICATIONS

Sondelbay is contraindicated in patients with hypersensitivity to teriparatide or to any of its excipients.

4 WARNINGS AND PRECAUTIONS

4.1 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 (2.3), ADVERSE REACTIONS (5.3) and NONCLINICAL TOXICOLOGY (11.1)].

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

- Open epiphyses (pediatric and young adult patients) (Sondelbay is not approved in pediatric patients) [see USE IN SPECIFIC POPULATIONS (7.3)]
- 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.

4.2 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 (5.1, 5.3)]. Avoid Sondelbay 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 Sondelbay in patients who develop calciphylaxis or worsening of previously stable cutaneous calcification.

4.3 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 Sondelbay-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.

4.4 Orthostatic Hypotension

Sondelbay 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.

4.5 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 Sondelbay is used in patients receiving digoxin [see DRUG INTERACTIONS (6.1) and CLINICAL PHARMACOLOGY (10.3)].

5 ADVERSE REACTIONS

5.1 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 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years) [see CLINICAL STUDIES (12.1, 12.2)]. 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 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 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 (10.2)]

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. Long-term evaluation of patients with severe renal insufficiency, patients undergoing acute or chronic dialysis, or patients who have functioning renal transplants has not been performed.

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 [see CLINICAL STUDIES (12.3)]. 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 1000 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.

Safety data from comparative pharmacokinetic and pharmacodynamic study of Sondelbay in healthy subjects
The clinical safety of Sondelbay was assessed and compared against with reference products Forteo® (United States) and Forsteo® (Europe) during an assessor-blind, randomized, three-treatment, three-period, single-dose, crossover study in healthy men and postmenopausal women after subcutaneous administration. In this study, 105 subjects were randomized to receive a single subcutaneous injection of 20 micrograms each of Sondelbay, Forteo® and Forsteo® in three periods separated by 24-hour of wash-out period. All subjects were included in safety set (all subjects who received at least one dose of any product). A total of 19 adverse events were reported in 13 of 105 subjects during the study: 11 adverse events in 8 of 105 subjects after administration of Sondelbay, 5 adverse events in 4 of 105 subjects after administration of Forsteo® and 3 adverse events in 2 of 105 subjects after administration of Forteo®. All adverse events were mild. The most frequently (≥5% of subjects) reported adverse event was nausea, reported in 5 of 105 subjects. No subject discontinued from the study due to adverse events. No deaths or serious adverse events were reported during the study.

5.2 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 (12.1)], 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.

Immunogenicity data from comparative pharmacokinetic and pharmacodynamic study of Sondelbay in healthy subjects

The immunogenicity data of Sondelbay is based on single-dose study with short follow-up. The immunogenicity of Sondelbay and reference products Forteo® (United States) and Forsteo® (Europe) was assessed during an assessor-blind, randomized, three-treatment, three-period, single-dose, crossover study in healthy men and postmenopausal women after subcutaneous administration. In this study, 105 subjects were randomized to receive a single subcutaneous injection of 20 micrograms each of Sondelbay, Forteo® and Forsteo® in three periods separated by 24-hour of wash-out period. Blood samples for immunogenicity analysis were collected before the first dose and at the end of study (28 days after dosing of third period). Analysis for anti-drug antibodies against teriparatide was performed in 105 subjects included in safety set (all subjects who received at least one dose of any product). None of the subjects was found to be positive for neutralizing anti-drug antibodies at pre-dose or end of study.

5.3 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 (4.1)]
- Hypercalcemia greater than 13 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, urticarial
- 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.

6 DRUG INTERACTIONS

6.1 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 PRECAUTIONS (4.5) and CLINICAL PHARMACOLOGY (10.3)].

7 USE IN SPECIFIC POPULATIONS

7.1 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. Teriparatide should not be administered to women who are pregnant.

In animal reproduction studies, teriparatide increased skeletal deviations and variations in mouse offspring at subcutaneous doses equivalent to more than 60 times the recommended 20mcg 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 recognised 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.

7.2 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. Teriparatide should not be administered to nursing women.

7.3 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 (4.1)].

7.4 Geriatric Use

Of the patients who received teriparatide in the osteoporosis trial of 1637 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 over and 13% were 75 years of age and over. 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.

7.5 Hepatic Impairment

No studies have been performed in patients with hepatic impairment [see CLINICAL PHARMACOLOGY (10.3)].

7.6 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 (10.3)].

8 OVERDOSAGE

In postmarketing spontaneous reports, there have been cases of medication error in which the entire contents (up to 800 mcg) (40 times the recommended dose) of the teriparatide prefilled 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.

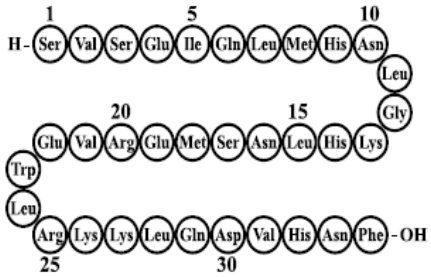
Overdose management

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

9 DESCRIPTION

Sondelbay is a biosimilar of Forteo®.

Sondelbay [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 4117.8 daltons. Its amino acid sequence is shown below:



Sondelbay is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. Sondelbay is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a disposable delivery device (pen) delivers 20 mcg of Sondelbay per dose each day for up to 28 days. Each delivery device (pen) is filled with 2.7 mL to deliver 2.4 mL. Each mL contains 250 mcg of Sondelbay (as a free base), 0.41 mg of glacial acetic acid, 0.10 mg of sodium acetate (anhydrous), 45.4 mg of mannitol, 3.0 mg of Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the pH to 4. .

Each prefilled delivery device (pen) delivers 20 mcg of Sondelbay per dose for up to 28 days.

10 CLINICAL PHARMACOLOGY

Pharmaco-therapeutic group: Calcium homeostasis, parathyroid hormones and analogues, ATC code: H05 AA02

10.1 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.

10.2 Pharmacodynamics

Effects on mineral metabolism

Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (eg, increases serum calcium and decreases serum phosphorus).

Serum calcium concentration

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 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 (ULN) [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 ULN 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% of men treated with teriparatide daily had at least 1 serum calcium value above the ULN [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 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 (4.2) and ADVERSE REACTIONS (5.1)].

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 0.09 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.

10.3 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.

Metabolism and Excretion

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.

Geriatric

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.

Frusemide

In a study of 9 healthy people and 17 patients with CrCl 13 to 72 mL/minute, coadministration of intravenous frusemide (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.

Comparative pharmacokinetic and pharmacodynamic study of Sondelbay and reference products

The pharmacokinetic and pharmacodynamic effects of Sondelbay were compared with reference products Forteo® (United States) and Forsteo® (Europe) during an assessor-blind, randomized, three-treatment, three-period, single-dose, crossover study in healthy men and postmenopausal women after subcutaneous administration. In this study, 105 subjects were randomized to receive single subcutaneous injection of 20 micrograms each of Sondelbay, Forteo® and Forsteo® in three periods separated by 24-hour of wash-out period. Primary objective of the study was to demonstrate pharmacokinetic equivalence of Sondelbay against Forteo® and Forsteo® after single subcutaneous injection of 20 micrograms. Peak serum concentration (C_{max}), area under serum concentration versus time curve till the last time point (AUC_{0-t}), and area under serum concentration versus time curve extrapolated to the infinity (AUC_{0-inf}) were primary pharmacokinetic parameters. The secondary objectives were to assess local tolerance, safety as well as tolerability and to assess and compare pharmacodynamics (effect on serum calcium level) of Sondelbay against Forteo® and Forsteo® after single subcutaneous injection of 20 micrograms.

The summary of statistical comparisons for primary pharmacokinetic parameters of Sondelbay against Forteo® and Forsteo® is provided in Table 2. The 90% confidence intervals of the geometric least square mean ratios of ln-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for the comparisons of Sondelbay against Forteo® and Forsteo® were within 80.00% to 125.00%.

Table 2. Summary of statistical comparisons of primary pharmacokinetic parameters of Sondelbay with Forteo® and Forsteo®

Sondelbay versus Forteo®				
Parameter	**Geometric least square means**			**90% confidence interval**
	Sondelbay	**Forteo®**	**Test/reference (%)**	
lnC_{max}	106.457	96.345	110.5	105.18 – 116.07
$lnAUC_{0-t}$	125.992	115.030	109.5	104.48 – 114.83
$lnAUC_{0-inf}$[1]	144.378	138.255	104.4	98.15 – 111.11

Sondelbay versus Forsteo®				
Parameter	**Geometric least square means**			**90% confidence interval**
	Sondelbay	**Forsteo®**	**Test/reference (%)**	
lnC_{max}	106.634	94.875	112.4	107.78 – 117.20
$lnAUC_{0-t}$	126.363	115.958	109.0	103.74 – 114.48
$lnAUC_{0-inf}$[1]	144.851	137.245	105.5	100.92 – 110.38

[1]N=103

For the pharmacodynamic endpoint of effect on calcium level, the geometric least square mean ratios for baseline-adjusted maximum observed serum calcium concentration (E_{max}) and area under serum calcium versus time curve from zero to the last measurable concentration ($AUEC_{0-t}$) were 102.4% and 98.1%, respectively for the comparison of Sondelbay against Forsteo®. The geometric least square mean ratios for baseline-adjusted E_{max} and $AUEC_{0-t}$ were 106.8% and 121.7%, respectively for the comparison of Sondelbay against Forteo®.

11 NONCLINICAL TOXICOLOGY

11.1 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 (11.2)].

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/m2).

11.2 Animal Toxicology

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.

12 CLINICAL STUDIES

12.1 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, multi-center, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis. In this study 541 postmenopausal women were treated with 20 mcg teriparatide subcutaneously once daily.

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 method. 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 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).

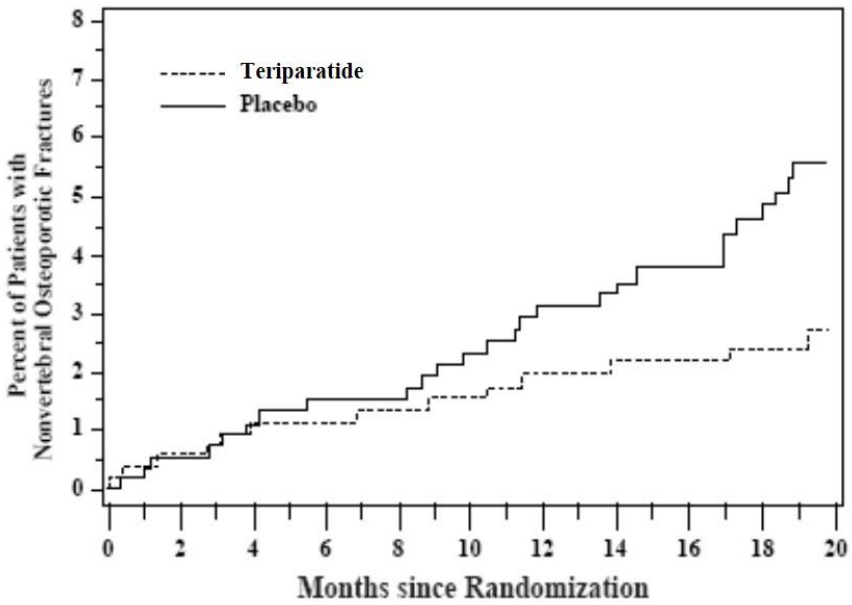


Figure 1. Cumulative percentage of postmenopausal women with osteoporosis sustaining new nonvertebral osteoporotic fractures

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* 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[a]	1.1
Femoral neck BMD	2.8[b]	-0.7
Total hip BMD	2.6[b]	-1.0
Trochanter BMD	3.5[b]	-0.2
Intertrochanter BMD	2.6[b]	-1.3
Ward's triangle BMD	4.2[b]	-0.8
Total body BMD	0.6[b]	-0.5
Distal 1/3 radius BMD	-2.1	-1.3
Ultradistal radius BMD	-0.1	-1.6

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

12.2 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 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* 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[a]	0.5
Femoral neck BMD	1.5[b]	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

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

12.3 Treatment of Men and Women with Glucocorticoid-induced Osteoporosis

The efficacy of teriparatide in men and women (N=428) receiving sustained systemic glucocorticoid therapy (equivalent to 5 mg or greater of prednisone for at least 3 months) was demonstrated in an 18-month, randomised, double-blind, comparator-controlled study (alendronate 10 mg/day). Twenty-eight percent of patients had one or more radiographic vertebral fractures at baseline. All patients receive 1000 mg calcium per day and 800 IU vitamin D per day.

This study included postmenopausal women (N=277), premenopausal women (N=67), and men (N=83). At baseline, the postmenopausal women had a mean age of 61 years, mean lumbar spine BMD T score of −2.7, median prednisone equivalent dose of 7.5 mg/day, and 34% had one or more radiographic vertebral fractures; premenopausal women had a mean age of 37 years, mean lumbar spine BMD T score of −2.5, median prednisone equivalent dose of 10 mg/day, and 9% had one or more radiographic vertebral fractures; and men had a mean age of 57 years, mean lumbar spine BMD T score of −2.2, median prednisone equivalent dose of 10 mg/day, and 24% had one or more radiographic vertebral fractures.

Sixty-nine percent of patients completed the 18-month study. At endpoint, teriparatide significantly increased lumbar spine BMD (7.2%) compared with alendronate (3.4%) ($p<0.001$). Teriparatide increased BMD at the total hip (3.6%) compared with alendronate (2.2%) ($p<0.01$), as well as at the femoral neck (3.7%) compared with alendronate (2.1%) ($p<0.05$).

A preliminary analysis of 336 spinal X-rays showed that 10 patients in the alendronate group (6.1%) had experienced a new vertebral fracture compared with 1 patient in the teriparatide group (0.6%). In addition, 9 patients in the alendronate group (4.2%) had experienced a nonvertebral fracture compared with 12 patients in the teriparatide group (5.6%).

In premenopausal women, the increase in BMD from baseline to endpoint was significantly greater in the teriparatide group compared with the alendronate group at the lumbar spine (4.2% versus −1.9%; $p<0.001$) and total hip (3.8% versus 0.9%; $p=0.005$). However, no significant effect on fracture rates was demonstrated.

13 HOW SUPPLIED/STORAGE AND HANDLING

13.1 How Supplied

Sondelbay (teriparatide injection) is a clear and colorless solution. It is supplied in a cartridge contained in a pre-filled disposable pen. Each pre-filled pen contains 2.4 mL of solution for 28 doses. Sondelbay is available in packs containing one pre-filled pen and three pre-filled pens. Not all pack sizes may be available.

13.2 Storage and Handling

- Store Sondelbay under refrigeration at 2°C to 8°C at all times except when administering the product.
- Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
- When using Sondelbay, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
- Do not freeze. Do not use Sondelbay if it has been frozen.
- To prevent the possible transmission of disease, each pen must be used by one patient only, even if the needle is changed.
- Once opened, Sondelbay pen can be stored at temperature conditions up to 25^0C for a maximum of 3 days when refrigeration is not available, after which it should be returned to the refrigerator and used within 28 days of the first injection. Sondelbay pen should be discarded, if it has been kept out of refrigerator up to 25^0C for more than 3 days.

13.3 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

14. PATIENT COUNSELING INFORMATION
Advise the patient to read the Product Insert and the User Manual before starting Sondelbay and each time the prescription is renewed. Failure to follow the instructions may result in inaccurate dosing.

Osteosarcoma
Patients should be made aware that in rats, Teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor). Although cases of osteosarcoma have been reported in patients using teriparatide no increased risk of osteosarcoma was observed in adult humans treated with teriparatide [see WARNINGS and PRECAUTIONS (4.1)].

Hypercalcemia
Instruct patients taking Sondelbay to contact a health care provider if they develop persistent symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness) [see WARNINGS and PRECAUTIONS (4.2)].

Orthostatic Hypotension
When initiating Sondelbay treatment, instruct patients to be prepared to immediately sit or lie down during or after administration in case they feel lightheaded or have palpitations after the injection. Instruct patients to sit or lie down until the symptoms resolve. If symptoms persist or worsen, instruct patients to consult a healthcare provider before continuing treatment [see WARNINGS and PRECAUTIONS (4.4)].

Other Osteoporosis Treatment Modalities
Patients should be informed regarding the roles of supplemental calcium and/or vitamin D.

Use of the Prefilled Delivery Device (Pen)
Instruct patients and caregivers who administer Sondelbay on how to properly use the delivery device (refer to User Manual), to properly dispose of needles, and not to share their prefilled delivery device with other patients. Instruct patients and caregivers who administer Sondelbay that the contents of the delivery device should not be transferred to a syringe.

Inform patients that each Sondelbay delivery device can be used for up to 28. After the 28-day use period, instruct patients to discard the Sondelbay delivery device, even if it still contains some unused solution. Instruct patients not to use Sondelbay after the expiration date printed on the delivery device and packaging.

15 PRODUCT OWNER
Accord Healthcare Private Limited,
6 Shenton Way, OUE Downtown #38-01,
Singapore, 068809

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