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1. Name of the medicinal product

1.1 Product Name
OSTEOTIDE [Teriparatide (r- Human Parathyroid Hormone) Injection USP 750mcg/3 mL]

1.2 Dosage Strength
250mcg / mL

1.3 Dosage form
Injection

2. Qualitative and quantitative composition

Description: Clear, colorless solution

Shelf life: 24 Months

Composition:

Each mL of TERIPARATIDE (r-Human Parathyroid Hormone) Injection contains:

Recombinant human Parathyroid Hormone (1-34) USP 250 mcg

3. Pharmaceutical form
Injection

4. Clinical particulars

4.1 Therapeutic indications
OSTEOTIDE is indicated for the treatment of patients with severe osteoporosis.

4.2 Posology and method of administration
Route/ Way of administration: Subcutaneous
Osteotide Cartridge to be used with Osteotide Delivery device Pen.

The recommended dose of formulated rhPTH (1-34) injection is 80µl containing 20µg teriparatide to be administrated once daily by subcutaneous injection in the thigh or

abdomen. rhPTH (1-34) (teriparatide for injection) should be administered initially in an environment in which the patient can assume a supine or sitting position if orthostatic hypotension should occur.

The maximum total duration of treatment with rhPTH (1-34) (teriparatide for injection) should be 2 years. Patients should receive supplemental calcium and vitamin D supplements if dietary intake is inadequate.

Following cessation of rhPTH (1-34) (teriparatide for injection) therapy, patients may be continued on other osteoporosis therapies,

Use in renal impairment: rhPTH (1-34) (teriparatide for injection) should not be used in patients with severe renal impairment. In patients with moderate renal impairment, rhPTH (1-34) (teriparatide for injection) should be used with cautions.

Use in hepatic impairment: No data are available in patients with impaired hepatic function.

Pediatric: There is no experience in children. rhPTH (1-34) (teriparatide for injection) should be not used in pediatric patients or young adults with open epiphyses.

Geriatric: Dosage adjustment based on age is not required

MISSED DOSE: If you miss a dose, use it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

4.3 Contraindications:

r- Human Parathyroid Hormone injection is contraindicated in the following patients.

- Hypersensitivity to teriparatide or to any of the excipients of this product
- Pre-existing hypercalcemia
- Severe renal impairment
- Metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone).
- Unexplained elevations of alkaline phosphatase
- Prior external beam or implant radiation therapy to the skeleton
- Patients with skeletal malignancies or bone metastases

4.4 Special warnings and precautions for use

Warnings

Reported studies in rats indicate an increased risk of osteosarcoma with long-term administration of teriparatide. The treatment should not exceed 24 months. Since the pediatric patients and young adults with open epiphyses have an increased baseline risk of osteosarcoma, teriparatide should not be used.

Precautions

General

OSTEOTIDE has not been studied in patients with active urolithiasis in reported clinical trials. OSTEOTIDE should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

In reported short-term clinical studies with teriparatide injection, isolated episodes of transient orthostatic hypotension were observed. 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, and was relieved by placing subjects in a reclining position. However, it did not preclude continued treatment.

In a reported study of 15 healthy people who were administered digoxin daily to steady state, a single dose of teriparatide 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 rhPTH transiently increases serum calcium, teriparatide should be used with caution in patients taking digitalis.

In normocalcemic patients, slight and transient elevations of serum calcium concentrations have been observed following teriparatide injection. Serum calcium concentrations reach a peak between 4 and 6 hours and return to baseline by 16 to 24 hours after each dose of teriparatide. Routine calcium monitoring during therapy is not required. Therefore, if any blood samples are taken from a patient, this should be done at least 16 hours after the most recent teriparatide injection. Teriparatide may cause small increases in urinary calcium excretion. Limited information is available on safety in patients with hepatic, renal, and cardiac disease.

No clinically important adverse renal effects were observed in reported 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 reported. Caution should be exercised in patients with moderate renal impairment.

Teriparatide therapy was associated with increased incidence of elevated uric acid. However, adverse event data did not suggest an increased incidence of gout or arthralgia or of nephrolithiasis in teriparatide treated patients with normal, mild, or moderate renal impairment.

Pregnancy

Reported studies in rabbits have shown reproductive toxicity. The potential risk for humans is unknown. Given the indication, OSTEOTIDE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether teriparatide is secreted into milk. Given the indication, OSTEOTIDE should be used by breast-feeding women depending on the importance of the drug to the mother.

4.6 Pregnancy and lactation

Pregnancy

Reproductive toxicity has been reported in rabbits. The potential risk for humans is unknown. Given the indication, OSTEOTIDE (rhPTH (1-34) for Injection) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether rhPTH is distributed into milk. Given the indication, OSTEOTIDE (rhPTH (1-34) for Injection) should be used by breast-feeding women depending on the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, transient, orthostatic hypotension or dizziness was observed in some patients.

These patients should refrain from driving or the use of machines until symptoms have subsided.

4.8 Undesirable effects

The following convention has been used for the classification of the adverse reactions: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

The most commonly reported adverse events in patients treated with rhPTH are nausea, pain in limb, headache and dizziness. Tables I, II and III give an overview of all treatment emergent adverse events that have been reported with rhPTH during clinical trials conducted by the innovator.

Table I : Very Common Adverse Events (>1/10)			
System Organ Class	**Adverse Event**	**Teriparatide (%)**	**Placebo (%)**
Musculoskeletal and connective tissue and bone disorders	Pain in limb	10.0	9.0

Table II : Common Adverse Events (≥1/100 to < 1/10)			
System Organ Class	**Adverse Event**	**Teriparatide (%)**	**Placebo (%)**
Blood and lymphatic system disorders	Anemia	1.7	1.3
Metabolism and nutrition disorders	Hypercholesterolemia	2.6	2.3
Psychiatric disorders	Depression	4.1	2.5
Nervous system disorders	Dizziness	8.0	5.2
	Headache	7.7	7.4
	Sciatica	1.3	0.7
Ear and labyrinth disorders	Vertigo	3.6	2.5
Cardiac disorders	Palpitations	1.4	1.2
Vascular disorders	Hypotension	1.0	1.0
Respiratory, thoracic and mediastinal disorders	Dysponea	3.3	2.3
Gastro intestinal disorders	Nausea	8.5	6.2
	Vomiting	3.3	2.6
	Hiatus hernia	1.0	0.9
	Gastro – esophageal reflux disease	1.0	0.4
Skin and subcutaneous tissue	Sweating increased	1.9	1.3

disorders			
Muscoskeltal and connective tissue and bone disorders	Muscle cramps	3.6	2.9
General disorders and administration site conditions	Fatigue	4.8	4.3
	Chest pain	3.8	3.5
	Asthenia	1.6	1.2

Table III : Uncommon Adverse Events (>1/1,000 to <1/100)			
System Organ Class	**Adverse Event**	**Teriparatide (%)**	**Placebo (%)**
Cardiac disorders	Tachycardia	0.9	0.9
Respiratory, thoracic and mediastinal disorders	Emphysema	0.3	0
Gastro intestinal disorders	Hemorrhoids	0.9	0.4
Renal and urinary disorders	urinary incontinence	0.6	0.3
	Polyuria	0.3	0.1
	Micturition urgency	0.3	0
General disorders and administration site conditions	Injection site erythema	0.7	0
	Injection site reaction	0.3	0.1
Investigations	Weight increased	0.7	0.3
	Cardiac murmur	0.4	0.1

Teriparatide increases serum uric acid concentrations. However, the hyperuricemia does not result in an increase in gout, arthralgia or urolithiasis.

Antibodies that cross- reacted with teriparatide were detected in women receiving teriparatide. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions, allergic reactions, effects on serum calcium, or effects on bone mineral density (BMD) response.

There have been spontaneous reports of the following adverse reactions.

System Organ Class	**Adverse Event**
General disorders and administration site conditions	Rare: possible allergic events soon after injection: acute dysponea, oro/facial edema . generalized urticaria, chest pain, edema, (mainly peripheral) Common: mild and transient injection site events, including pain, swelling, erythema, localized bruising, Pruritus, and minor bleeding at injection site.

Metabolism and nutrition disorders	Uncommon: Hypercalcemia greater than 2.76 mmol/ L (11mg/dL). Rare: Hypercalcemia greater than 3.25 mmol/L (13mg/dL).
Muscoskeltal and connective tissue and bone disorders	Uncommon: Myalgia, Arthralgia.

4.9 Overdose

Signs and symptoms: No cases of overdose were reported. OSTEOTIDE has been administered in single dose of up to 100 mcg and in repeated doses of up to 60 micrograms/day for 6 weeks.

The effects of overdose that might be expected include delayed hypercalcaemia and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache can also occur.

Overdose experience based on post-marketing spontaneous reports: There have been cases of medication error where the entire contents (up to 800 mcg) of the rhPTH cartridge 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 transitory discontinuation of teriparatide, monitoring of serum calcium, and implementation of appropriate supportive measures, such as hydration.

5. Pharmacological properties

Mechanism of action
Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. OSTEOTIDE (rhPTH (1-34)) is the active fragment (1-34) of endogenous human parathyroid hormone. Physiological actions of PTH include stimulation of bone formation by direct effects on bone forming cells (osteoblasts), indirectly increasing the intestinal absorption of calcium and increasing the tubular reabsorption of calcium and excretion of phosphate by the kidney.

5.1 Pharmacodynamics properties

Teriparatide is a bone formation agent to treat osteoporosis. The skeletal effects of rhPTH depend upon the pattern of systemic exposure. Once daily administration of rhPTH increases apposition of new bone on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity.

Clinical Trials:

In a published clinical trial conducted on 1,637 postmenopausal women with established osteoporosis, the median duration of observation was 21 months. The results of study showed that rhPTH, in combination with 1,000 mg calcium and 400 IU vitamin D daily, increased bone density and reduced fractures. Bone mineral density (BMD) of lumbar spine increased by 9%, and of femoral neck increased by 3%. The incidence of new vertebral fractures was 14% in the placebo group, but only 5% in the rhPTH-treated group. New non-vertebral fragility fractures were 6% in the placebo group and 3% in the rhPTH group. These changes were seen regardless of baseline age or baseline bone density.

In a reported post-treatment follow-up study, 1,262 postmenopausal women were treated with rhPTH. During the observational period, other osteoporosis treatments were allowed and assessment of vertebral fractures was performed. During a median of 18months following discontinuation of rhPTH, there was a 41% reduction (P=0.004) compared with placebo in the number of patients with a minimum of one new vertebral fracture.

In another reported clinical trial conducted on 437 men with osteoporosis, the effect of rhPTH was compared to placebo, in combination with calcium and vitamin D. After a median duration of 11 months, lumbar spine BMD increased by 5.9% and by 0.5% with placebo. Femoral neck BMD increased by 1.5% with rhPTH, compared to 0.3% with placebo. Bone mineral density responses to rhPTH were similar regardless of gonadal status, age, baseline bone mineral density, body mass index, smoking, or alcohol intake. Subjects experienced expected changes in mineral metabolism.

5.2 Pharmacokinetic properties

Teriparatide is extensively absorbed after subcutaneous injections; peak plasma concentrations are reached after about 30 minutes. Absolute bioavailability is reported to be about 95%.

Teriparatide is eliminated through hepatic and extra-hepatic clearance (approximately 62 L/hr in women and 94 L/hr in men). The volume of distribution is approximately 1.7 L/kg. The half-life of rhPTH is approximately 1 hour when administered subcutaneously,

which reflects the time required for absorption from the injection site. No metabolism or excretion studies with rhPTH have been reported but the peripheral metabolism of parathyroid hormone is believed to occur predominantly in liver and kidney.

Pharmacokinetics in special population

Geriatrics: No differences in rhPTH pharmacokinetics were detected with regard to age (range 31 to 85 years). Dosage adjustments based on age is not required.

Pediatric: Pharmacokinetic data in pediatric patients are not available.

Gender: Although systemic exposure to rhPTH was approximately 20-30% lower in men than women, the recommended dose for both genders is 20 g/day.

Race: The populations included in the pharmacokinetic analyses were 98.5% Caucasian. The influence of race has not been determined.

Renal Insufficiency: No pharmacokinetic differences were identified in 11 patients with mild or moderate renal insufficiency (creatinine clearance [CrCl] 30-72 mL/min) administered a single dose of rhPTH. In 5 patients with severe renal insufficiency (CrCl <30 mL/min), the AUC and t½ of rhPTH were increased by 73% and 77% respectively. Maximum serum concentration of rhPTH was not increased. No studies have been reported in patients undergoing dialysis for chronic renal failure.

Heart Failure: No clinically relevant pharmacokinetic, blood pressure, or pulse rate differences were identified in 13 patients with stable New York Heart Association Class I to III heart failure after the administration of two 20 mcg doses of rhPTH.

Hepatic Insufficiency: 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. No studies have been reported in patients with hepatic impairment.

5.3 Preclinical safety Data:

Teriparatide was not genotoxic in a standard battery of tests. It produced no teratogenic effects in rats, mice, or rabbits.

Rats treated with near-life time daily injection had dose-dependent exaggerated bone formation and increased incidence of osteosarcoma most probably due to an epigenetic mechanism. rhPTH (1-34) did not increase the incidence of any other type of neoplasia in rats. Due to the differences in bone physiology in rats and humans, the clinical relevance of these findings is probably minor. No bone tumors were observed in ovariectomised monkeys treated for 18 months. In addition, osteosarcoma has not been observed in reported clinical trials or during the post-treatment follow-up study.

Severely reduced hepatic blood flow decreases exposure of PTH to the principal cleavage system (Kupffer cells) and consequently the clearance of PTH (1-84) in experimental animals treated with rhPTH decreases.

6 Pharmaceutical particulars

6.1 List of excipients

INGREDIENTS	SPECIFICATION
Succinic acid	USP
Sodium Hydroxide	USP
Glycerol	USP
m-Cresol	USP
Water for injection	USP

6.2 Incompatibilities

rhPTH(1-34) injection is supplied in USP type I glass cartridges. The drug product is non-reactive to the primary packing material used. All the excipients used are pharmacopoeially accepted excipients and are compatible with drug substance.

6.3 Shelf life

2 years (24 months)

6.4 Special precautions for storage

Store at 2°C to 8°C. Do not freeze.

6.5 Nature and contents of container

Pack size: 3ml

Osteotide is supplied in multi dose USP type-I glass cartridge and the cartridge is stoppered at one end with bromobutyl solid rubber plunger and at the other end sealed with lined aluminum seal. Pack Presentation is done in following two packaging styles:

Presentation 1: Each 3 ml cartridge is blister-packed and each blister is packed into pre-printed carton along with pack insert. Osteotide Cartridge is to be used with Osteotide Pen. Each OSTEOTIDE Pen is packed in a carton along with user's manual.

Presentation 2: 3 ml Cartridge fitted in Disposable Pen Device. Each Disposable pen device is then packed in carton with user manual.

7 Marketing Authorization Holder:

Name	**:**	VIRCHOW HEALTHCARE PRIVATE LIMITED
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8 Marketing Authorization Number:

NAFDAC Reg No. A6-0497

9 Manufacturer Name

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10 Date of first authorization/renewal of the authorization

Not applicable

11 Date of revision of the text

Not applicable