**Professional Information**

**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

**TERATYDE** 250 µg/ml, Solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of **TERATYDE** contains 250 µg of teriparatide

Teriparatide (rhPTH (1-34)) is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone and is manufactured using recombinant DNA technology.

Preservative: metacresol 0,3 % *m/v.*

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection

A clear colourless solution free from visible particulate matter, filled in a plunger stoppered glass cartridge.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**TERATYDE** is indicated for the treatment of established osteoporosis with or without vertebral fractures in postmenopausal women and primary osteoporosis in men.

**TERATYDE** is indicated for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

## 4.2 Posology and Method of Administration

The recommended dose of **TERATYDE** is 20 µg administered once daily by subcutaneous injection in the thigh or abdomen.

The maximum total duration of treatment with **TERATYDE** should be 24 months (see section 4.4 and 5.1). The 24-month course of **TERATYDE** should not be repeated over a patient's lifetime. **TERATYDE** is supplied in a 2,4 ml cartridge contained in a prefilled delivery device (pen) that delivers 20 µg per dose.

Patients must be educated to use the proper injection techniques. Please refer to the enclosed User Manual for instructions on the pen injector.

Calcium (1 000 mg per day) and Vitamin D (400 - 1 200 IU per day) must be administered concomitantly with **TERATYDE.**

### Special populations

*Patients with renal impairment*

**TERATYDE** must not be used in patients with severe renal impairment (see section 4.3.). In patients with moderate renal impairment, **TERATYDE** should be used with caution. No special caution is required for patients with mild renal impairment.

*Patients with hepatic impairment*

No data have been reported in patients with impaired hepatic function (see section 5.3). Therefore, **TERATYDE** should be used with caution.

*Paediatric population and young adults with open epiphyses*

The safety and efficacy of **TERATYDE** in children and adolescents less than 18 years has not been established. **TERATYDE** should not be used in paediatric patients (less than 18 years), or young adults with open epiphyses.

*Elderly patients*

Dosage adjustment based on age is not required (see section 5.2).

**Method of administration**

For Subcutaneous use

**4.3 Contraindications**

- **TERATYDE** should not be used in patients with:
- Hypersensitivity to teriparatide or to any of its excipients listed in section 6.1.
- Hypercalcaemia (see section 4.4).
- Unexplained elevations of alkaline phosphatase.
- Metabolic bone diseases (including hyperparathyroidism and Paget's disease of the bone) other than primary osteoporosis or glucorticoid-induced osteoporosis (see section 4.4).
- Skeletal malignancies or bone metastases (see section 4.4).
- Patients with prior external beam or implant radiation therapy involving the skeleton should be excluded from treatment with **TERATYDE**.
- Pregnancy: Safety in pregnancy has not been reported (see section 4.6).
- Lactation: The safety of **TERATYDE** has not been reported in breastfeeding women (see section 4.6).
- Severe renal impairment

## 4.4 Special warnings and precautions for use

Hypercalcaemia:

**TERATYDE** has not been studied in patients with pre-existing hypercalcaemia. These patients should be excluded from treatment with **TERATYDE** because of the possibility of exacerbating hypercalcaemia. Hypercalcaemia should be excluded before treatment with **TERATYDE**. Routine monitoring of serum calcium during therapy is required (see section 4.3).

Bone Disorders other than Osteoporosis:

Patients with metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone) and those with otherwise unexplained elevations of alkaline phosphatase should generally be excluded from treatment with **TERATYDE**. Patients with skeletal malignancies or bone metastases should also be excluded from treatment with **TERATYDE** (see section 4.3).

Children:

**TERATYDE** has not been studied in paediatric populations. **TERATYDE** should not be used in paediatric patients or young adults with open epiphyses.

Experience in the younger adult population, including premenopausal women, is limited.

Women of childbearing potential should use effective methods of contraception during use of teriparatide. If pregnancy occurs, teriparatide should be discontinued.

Urolithiasis:

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

Hypotension:

In reported short-term clinical studies with teriparatide, isolated episodes of transient orthostatic hypotension were observed (see section 4.7). Typically, it was reported that 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, was relieved by placing subjects in a reclining position and did not preclude continued treatment.

Carcinogenesis:

In reported studies where rats were treated with near-lifetime daily teriparatide injections had dose-dependent exaggerated bone formation and increased incidence of osteosarcoma. Teriparatide did not increase the incidence of neoplasms in other tissues. A reported second rat study (of up to 2 years duration) confirmed that the occurrence of osteosarcoma was dependent upon dose and duration of treatment. A no-observed-effect level (NOEL) was reported; the NOEL is 3 times the exposure in patients given a 20 µg dose based upon AUC. Until further reported clinical data become available, the recommended treatment duration of 24 months should not be exceeded.

Mutagenesis:

Teriparatide was found in reported studies to not be genotoxic in any of the following test systems: The Ames test for bacterial mutagenesis with and without metabolic activation, the mouse

lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells and the *in vivo* micronucleus test in mice.

The relevance of these findings to humans is not known: Osteosarcoma has not been reported in teriparatide clinical studies. Chronic elevation of blood PTH levels as occurs clinically in primary or secondary hyperparathyroidism is not associated with an increased risk of osteosarcoma.

Renal impairment:

Caution should be exercised in patients with moderate renal impairment.

**4.5 Interaction with other medicines and other forms of interaction**

Teriparatide has been evaluated in reported pharmacodynamic interaction studies with hydrochlorothiazide, furosemide, atenolol and extended release preparations of diltiazem, nifedipine, felodipine, nisoldipine. No clinically significant interactions were reported.

Co-administration of raloxifene or hormone replacement therapy with teriparatide did not alter the effects of teriparatide on serum or urine calcium or on clinical adverse events.

Serum Calcium:

**TERATYDE** can induce small, transient increases in serum calcium. If serum calcium is to be assessed, blood samples should be obtained at least 16 hours after the most recent **TERATYDE** injection to allow waning of the effects of the administered teriparatide.

Urinary Calcium:

Teriparatide may cause small increases in urinary calcium excretion, but the incidence of hypercalciuria did not differ om that in the placebo-treated patients in reported clinical trials.

Digoxin:

In a reported study of healthy subjects administered digoxin daily to steady state, a single teriparatide dose did not alter the cardiac effect of digoxin. However, sporadic case reports have reported that hypercalcaemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, teriparatide should be used with caution in patients taking digitalis.

**4.6 Fertility, pregnancy and lactation**

Women of childbearing potential / Contraception in females:

Women of childbearing potential should use effective methods of contraception during use of **TERATYDE**. If pregnancy occurs, **TERATYDE** should be discontinued.

Pregnancy:

Animal reproduction studies have shown no teratogenic effects with teriparatide. (see section 5.3). The effect of **TERATYDE** treatment on human foetal development has not been reported. Teriparatide should not be administered to pregnant women (see section 4.3).

Breastfeeding:

There have been no reported studies to determine if teriparatide is secreted into breast milk. Teriparatide should not be administered to nursing women (see section 4.3).

Fertility:

Reported studies in rabbits have shown reproductive toxicity (see section 5.3). The effect of teriparatide on human foetal development has not been reported. The potential risk for humans is unknown.

### 4.7 Effects on ability to drive and use machines

**TERATYDE** may cause orthostatic hypotension or dizziness. These patients should refrain from driving or the use of machines until symptoms have subsided.

### 4.8 Undesirable effects

The most commonly reported adverse reactions in patients treated with **TERATYDE** are nausea, pain in limb, headache and dizziness.

| System organ class | Frequent | Less frequent |
|---|---|---|
| **Blood and lymphatic system disorders** | Anaemia | - |
| **Immune System Disorder** | - | Anaphylaxis |
| **Metabolism and nutrition disorders** | Hypercholesterolaemia | Hypercalcaemia greater than 2.76 mmol/L, hyperuricemia, |
| **Psychiatric disorders** | Depression | - |
| **Nervous system disorders** | Dizziness, headache, sciatica, syncope | - |
| **Ear and labyrinth disorders** | Vertigo | - |
| **Cardiac disorders** | Palpitations | Tachycardia |
| **Vascular disorders** | Hypotension | - |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnoea | Emphysema |

| | | |
|---|---|---|
| **Gastrointestinal disorders** | Nausea, vomiting, hiatus hernia, gastroesophageal reflux disease | Haemorrhoids |
| **Skin and subcutaneous tissue disorders** | Increased sweating | - |
| **Musculoskeletal and connective tissue disorders** | Pain in limb<br>Muscle cramps | Myalgia, arthralgia, back cramp/pain* |
| **Renal and urinary disorders** | - | Urinary incontinence, polyuria, micturition urgency, nephrolithiasis, Renal failure/impairment |
| **General disorders and administration site conditions** | Fatigue, chest pain, asthenia, mild and transient injection site events, including pain, swelling, erythema, localised bruising, pruritis and minor bleeding at injection site. | Injection site erythema, injection site reaction<br>Possible allergic events soon after injection: acute dyspnoea, oro/facial oedema, generalised urticaria, chest pain, oedema (mainly peripheral). |
| **Investigations** | - | Weight increased, cardiac murmur, alkaline phosphatase increase |

*Serious cases of back cramp or pain have been reported within minutes of the injection.

Description of selected adverse reactions

In a reported clinical trial, antibodies that cross-reacted with teriparatide were detected in 2.,8 % of women receiving teriparatide. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy.

There was no reported evidence of hypersensitivity reactions, allergic reactions, effects on serum calcium, or effects on Bone Mineral Density (BMD) response.

In reported clinical trials, the following reactions were reported at a ≥ 1 % difference in frequency from placebo: vertigo, nausea, pain in limb, dizziness, depression, dyspnoea.

Teriparatide increases serum uric acid concentrations. In reported clinical trials, 2,8 % of teriparatide patients had serum uric acid concentrations above the upper limit of normal compared with 0,7 % of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of PATRAM is important. It allows continued monitoring of the benefit/risk balance of PATRAM. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or Tel: +27(0) 12 643 2000

**4.9 Overdose**

**Signs and symptoms**

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

**Overdose management**

There is no specific antidote for **TERATYDE**. Treatment of suspected overdose should include transitory discontinuation of **TERATYDE**, monitoring of serum calcium, and implementation of appropriate supportive measures, such as hydration.

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

Category and class: A 21.4 Parathyroid preparations

Pharmaco-therapeutic group: Calcium homeostasis, parathyroid hormones and analogues,

ATC code: H05 AA02.

Teriparatide stimulates new bone formation to increase bone mass.

Teriparatide (rhPTH(1-34)) is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone and is manufactured using recombinant DNA technology.

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 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. The biological actions of PTH are mediated through binding to PTH-specific cell-surface receptors.

Teriparatide binds to these receptors with the same affinity as PTH and has the same actions in bone and kidney as PTH. Like endogenous PTH, 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 increases apposition of new bone on trabecular and cortical (endosteal and periosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In 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.

The efficacy of teriparatide in men and women receiving sustained systemic glucocorticoid therapy (equivalent to 5 mg or greater of prednisone for at least 3 months) was reported in an 18-

month, randomised, double-blind, comparator-controlled study. Twenty-seven percent of patients had one or more vertebral fractures at baseline. All patients received 1000 mg calcium per day and 800 IU vitamin D per day. At endpoint (18 months), teriparatide significantly increased lumbar spine BMD, BMD at the total hip, as well as at the femoral neck.

In Fracture Prevention Trial, a reported phase 3 study, the planned duration of treatment with teriparatide versus placebo was 36 months, but due to rat toxicology findings of osteosarcoma the duration of treatment was shortened. Therefore, the reported Fracture Prevention Trial analysed the effects of a median 19 months of teriparatide versus placebo and the maximum duration of teriparatide treatment was 24 months.

**5.2 Pharmacokinetic properties**

Distribution

After subcutaneous (SC) injection, teriparatide has an absolute bioavailability of 95 %. Following a subcutaneous injection of a 20 µg dose, peak molar concentrations of teriparatide briefly exceed the upper limit of normal for endogenous PTH by 4- to 5-fold for about 30 minutes and decline to non-quantifiable concentrations within 3 hours.

The volume of distribution is approximately 1.7 L/kg. No metabolism or excretion studies have been reported with teriparatide but the peripheral metabolism of parathyroid hormone is believed to occur predominantly in liver and kidney. The half-life of teriparatide is approximately 1 hour when administered subcutaneously.

Biotransformation

No metabolism or excretion studies have been performed with teriparatide, but the peripheral metabolism of parathyroidhormone is believed to occur predominantly in liver and kidney.

Elimination

Teriparatide is eliminated through hepatic and extra-hepatic clearance (approximately 62 L/hr in women and 94 L/hr in men).

**Patient Characteristics:**

*Elderly patients*:

No differences in teriparatide pharmacokinetics were reported with regard to age (range 31 to 85 years). Dosage adjustment based on age is not required.

*Gender:*

Systemic exposure to teriparatide is approximately 20 % to 30 % lower in men than in women. There were, however, no gender differences with respect to safety, tolerability or pharmacodynamic responses. Dosage adjustment based upon gender is not required.

*Renal Impairment:*

No clinically relevant pharmacokinetic or safety differences were reported in patients with mild, moderate or severe chronic renal insufficiency who were administered a single dose of teriparatide and therefore dosage adjustment, based on renal function, is not required. Patients with renal impairment had reduced calcaemic and calciuric responses to teriparatide. Long-term safety and efficacy have not been reported in patients with significant renal impairment.

No pharmacokinetic differences were reported in patients with creatinine clearance (CrCl) 30 to 72 mL/minute administered a single dose of teriparatide. In patients with severe renal impairment (CrCl<30 mL/minute), the AUC and T1/2 of teriparatide were increased by 73 % and 77 %, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been reported in patients undergoing dialysis for chronic renal failure.

*Heart Failure:*

No clinically relevant pharmacokinetic, blood pressure, pulse rate, or other safety differences were reported in patients with stable heart failure (New York Heart Association Class I to III and additional evidence of cardiac dysfunction) after the administration of two 20 µg doses of teriparatide. Dosage adjustment based on the presence of mild or moderate heart failure is not required.

**5.3 Preclinical safety data**

Teriparatide was not reported to be genotoxic in a standard battery of tests. It produced no teratogenic effects in rats, mice or rabbits. There were no important effects reported in pregnant rats or mice administered teriparatide at daily doses of 30 to 1000 µg/kg. However, fetal resorption and reduced litter size occurred in pregnant rabbits administered daily doses of 3 to 100 µg/kg. The embryotoxicity reported in rabbits may be related to their much greater sensitivity to the effects of PTH on blood ionised calcium compared with rodents (see section 4.6).

It was reported that rats treated with near-life time daily injections had dose-dependent exaggerated bone formation and increased incidence of osteosarcoma most probably due to an epigenetic mechanism. Teriparatide 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 tumours were reported in ovariectomised monkeys treated for 18 months or during a 3-year follow-up period after treatment cessation. In addition, no osteosarcomas have been reported in clinical trials or during the post treatment follow-up study.

Reported animal studies have shown that severely reduced hepatic blood flow decreases exposure of PTH to the principal cleavage system (Kupffer cells) and consequently clearance of PTH (1-84).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

- Glacial acetic acid
- Hydrochloric acid (for pH-adjustment)
- Mannitol
- Metacresol
- Nitrogen
- Sodium acetate (anhydrous)
- Sodium hydroxide (for pH-adjustment)
- Water for injection

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 Months

### 6.4 Special precautions for storage

Store in a refrigerator between 2 °C and 8 °C.

Do not freeze. Do not use **TERATYDE** if it has been frozen.

The **TERATYDE** prefilled delivery device should be discarded 28 days after the first injection from the device, even if there is solution left in the pen.

### 6.5 Nature and contents of container

2,4 ml solution in a cartridge (siliconised Type I glass) with a plunger (halobutyl rubber), disc seal (polyisoprene/bromobutyl rubber laminate) / aluminium assembled into a disposable pen.

**TERATYDE** is available in pack sizes of 1's. Each pen contains 28 doses of 20 micrograms (per 80 microlitres).

### 6.6 Special precautions for disposal

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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## 8. REGISTRATION NUMBER(S)

**TERATYDE:** 58/21.4/0003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 July 2025

## 10. DATE OF REVISON OF THE TEXT

22 July 2025