TERISUN
(Teriparatide Solution for injection 250 micrograms per mL)

1. NAME OF THE MEDICINAL PRODUCT

Terisun 250mcg/ml Solution for Injection, 2.4ml Pre-Filled Pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose contains 20 micrograms of teriparatide in 80 microliters.

One pre-filled pen of 2.4 mL contains 600 micrograms of teriparatide (corresponding to 250 micrograms per mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Teriparatide Solution for injection 250 micrograms per mL is a clear colorless solution free from visible particulate matter, filled in plunger stoppered glass cartridge.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Teriparatide is indicated in adults.

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non- vertebral fractures but not hip fractures have been reported.

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

Posology
The recommended dose of teriparatide is 20 micrograms administered once daily.

The maximum total duration of treatment with teriparatide should be 24 months (see Section 4.4). The 24-month course of teriparatide should not be repeated over a patient's lifetime.

Patients should receive supplemental calcium and vitamin D supplements if dietary intake is inadequate.

Following cessation of teriparatide therapy, patients may be continued on other osteoporosis therapies.

Special populations

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

Renal impairment
Teriparatide must not be used in patients with severe renal impairment (see Section 4.3). In patients with moderate renal impairment, teriparatide should be used with caution. No special caution is required for patients with mild renal impairment.

Hepatic impairment
No data are reported in patients with impaired hepatic function. Therefore, teriparatide should be used with caution.

Paediatric population and young adults with open epiphyses
The safety and efficacy of teriparatide in children and adolescents less than 18 years has not been reported. Teriparatide should not be used in paediatric patients (less than 18 years), or young adults with open epiphyses.

Method of administration
Teriparatide should be administered once daily by subcutaneous injection in the thigh or abdomen.

Patients must be trained to use the proper injection techniques. A medication guide is also available to instruct patients on the correct use of the pen.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the formulation listed in Section 6.1.
- Pregnancy and breast-feeding (see Section 4.4 and 4.6)
- Pre-existing hypercalcaemia
- Severe renal impairment
- Metabolic bone diseases (including hyperparathyroidism and Paget's disease of the bone) other than primary osteoporosis or glucorticoid-induced osteoporosis.
- Unexplained elevations of alkaline phosphatase
- Prior external beam or implant radiation therapy to the skeleton
- Patients with skeletal malignancies or bone metastases should be excluded from treatment with teriparatide.

4.4 Special warnings and precautions for use

Teriparatide Solution for injection is not interchangeable or automatically substitutable with any other formulations containing teriparatide.

Serum and urine calcium

In normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been reported following teriparatide injection. Serum calcium concentrations reach a maximum between 4 and 6 hours and return to baseline by 16 to 24 hours after each dose of teriparatide. Therefore, if blood samples for serum calcium measurements are taken, this should be done at least 16 hours after the most recent teriparatide injection. Routine calcium monitoring during therapy is not required.

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

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

Orthostatic hypotension
Isolated episodes of transient orthostatic hypotension were reported with teriparatide. Typically, an event has been reported to begin within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. Transient orthostatic hypotension has been reported to occur within the first several doses, and was relieved by placing subjects in a reclining position, and did not preclude continued treatment.

Renal impairment
Caution should be exercised in patients with moderate renal impairment.

Younger adult population
Experience in the younger adult population (>18 to 29 years), including premenopausal women, is limited. Treatment should only be initiated if the benefit clearly outweighs risks in this population.

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

Duration of treatment
An increased incidence of osteosarcoma with long-term administration of teriparatide has been reported in rats. The recommended treatment time of 24 months should not be exceeded.

Effects on ability to drive and use machines
Teriparatide has no or negligible influence on the ability to drive and use machines. Transient, orthostatic hypotension or dizziness was reported in some patients. These patients should refrain from driving or the use of machines until symptoms have subsided.

Excipient
This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Single dose of teriparatide has been reported did not alter the cardiac effect of digoxin in healthy subjects administered digoxin daily to steady state. However, reported sporadic cases have suggested that hypercalcaemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, teriparatide should be used with caution in patients taking digitalis.

No clinically significant pharmacodynamic interactions have been reported between teriparatide and hydrochlorothiazide.

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

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 teriparatide. If pregnancy occurs, teriparatide should be discontinued.

Pregnancy
Teriparatide is contraindicated for use during pregnancy (see Section 4.3).

Breast-feeding
Teriparatide is contraindicated for use during breast-feeding. It is not reported whether teriparatide is excreted in human milk.

Fertility
Reproductive toxicity has been reported in rabbits. The effect of teriparatide on human foetal development has not been reported. The potential risk for humans is unknown.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions in patients treated with teriparatide are nausea, pain in limb, headache and dizziness.

Tabulated list of adverse reactions
The adverse reactions reported with the use of teriparatide are summarised in the table below. 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).

Organ class system	**Very common**	**Common**	**Uncommon**	**Rare**
Blood and lymphatic system disorders		Anaemia		

Immune system disorders				Anaphylaxis
Metabolism and nutrition disorders		Hypercholesterolaemia	Hypercalcaemia greater than 2.76 mmol/L, hyperuricemia	Hypercalcaemia greater than 3.25 mmol/L
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, gastro-oesophageal reflux disease	Haemorrhoids	
Skin and subcutaneous tissue disorders		Sweating increased		
Musculoskeletal and connective tissue disorders	Pain in limb	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 condition		Fatigue, chest pain, asthenia, mild and transient injection site events, including pain, swelling, erythema, localised bruising, pruritus and minor	Injection site erythema, injection site reaction	Possible allergic events soon after injection: acute dyspnoea, oro/facial oedema, generalised urticaria, chest pain, oedema (mainly peripheral)

		bleeding at injection site		
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
The following reactions have been reported at a ≥1 % difference in frequency: vertigo, nausea, pain in limb, dizziness, depression, dyspnoea.

Teriparatide increases serum uric acid concentrations. In 2.8% of teriparatide patients the serum uric acid concentrations has been reported above the upper limit of normal compared with 0.7% of placebo patients. However, the hyperuricemia has not been reported to result in an increase in gout, arthralgia, or urolithiasis.

Antibodies that cross-reacted with teriparatide have been reported 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.

4.9 Overdose

Signs and symptoms
Teriparatide has been reportedly administered in single doses of up to 100 micrograms and in repeated doses of up to 60 micrograms/day for 6 weeks.

The effects of overdose that has been reported include delayed hypercalcaemia and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache can also occur.

Overdose experience based on post-marketing spontaneous reports
In post-marketing spontaneous reports, there have been cases of medication error where the entire contents (up to 800 micrograms) of the teriparatide pen have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events has been reported 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium homeostasis, parathyroid hormones and analogues, ATC code: H05AA02.

Mechanism of Action
Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Teriparatide (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 re-absorption of calcium and excretion of phosphate by the kidney.

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

5.2 Pharmacokinetic properties

Distribution
The volume of distribution is approximately 1.7 L/kg. The half-life of teriparatide is approximately 1 hour when administered subcutaneously, which reflects the time required for absorption from the injection site.

Biotransformation
There are no reported data on metabolism or excretion of teriparatide, but the peripheral metabolism of parathyroid hormone 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).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol Ph. Eur, Glacial acetic acid Ph. Eur, Sodium acetate anhydrous USP, Metacresol Ph. Eur, Sodium hydroxide Ph. Eur, Hydrochloric acid Ph. Eur, Water for Injection Ph. Eur

6.2 Incompatibilities

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

6.3 Shelf life

Observe 'Expiry Date' imprinted on outer carton.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) at all times. The pre-filled pen should be returned to the refrigerator immediately after use. Do not freeze. Do not store the pre-filled pen with the needle attached.

6.5 Nature and contents of container

2.4 mL solution in cartridge (siliconised glass) with a plunger (bromobutyl rubber), disc seal (polyisoprene/bromobutyl rubber laminate)/aluminium assembled into a disposable pen.

Teriparatide is available in pack sizes of 1 pre-filled pen. Each pen contains 28 doses of 20 micrograms (per 80 microliters).

6.6 Special precautions for disposal and other handling

Handling
Teriparatide SUN is supplied in a pre-filled pen. Each pen should be used by only one patient. A new, sterile needle of 31 Gauge, 5 mm length must be used for every injection. No needles are supplied with the medicinal product. After each injection, Teriparatide SUN pre-filled pen should be returned to the refrigerator immediately after use.

Do not store the pre-filled pen with the needle attached. Teriparatide SUN should not be used if the solution is cloudy, coloured or contains particles.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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