PROFESSIONAL INFORMATION

S4

1. NAME OF THE MEDICINE

FORTEO, 250 μg/ml, Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of FORTEO contains 250 μg of teriparatide (rDNA origin).

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

Colourless, clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

FORTEO 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 FORTEO is 20 μg administered once daily by subcutaneous injection in the thigh or abdomen.

The maximum total duration of treatment with FORTEO should be 24 months (see section 4.4 and 5.1).

The 24-month course of FORTEO should not be repeated over a patient's lifetime.

FORTEO 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 FORTEO.

Special populations

Patients with renal impairment

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

Patients with hepatic impairment

No data are available in patients with impaired hepatic function (see section 5.3). Therefore, FORTEO should be used with caution.

Paediatric population and young adults with open epiphyses

The safety and efficacy of FORTEO in children and adolescents less than 18 years has not been established. FORTEO 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).

4.3 Contraindications

- FORTEO 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 other than primary 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 FORTEO.
- Pregnancy: Safety in pregnancy has not been established (see section 4.6).
- Lactation*:* The safety of FORTEO has not been established in breastfeeding women (see section 4.6).

4.4 Special warnings and precautions for use

Hypercalcaemia: FORTEO has not been studied in patients with pre-existing hypercalcaemia. These patients should be excluded from treatment with FORTEO because of the possibility of exacerbating hypercalcaemia. Hypercalcaemia should be excluded before treatment with FORTEO. 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 FORTEO. Patients with skeletal malignancies or bone metastases should also be excluded from treatment with FORTEO (see section 4.3).

Children: FORTEO has not been studied in paediatric populations. FORTEO should not be used in paediatric patients or young adults with open epiphyses.

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

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

Carcinogenesis: Rats treated with near-lifetime daily FORTEO injections had dose-dependent exaggerated bone formation and increased incidence of osteosarcoma. Teriparatide did not increase the incidence of neoplasms in other tissues. A 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 identified; the NOEL is 3 times the exposure in patients given a 20 µg dose based upon AUC. Until further clinical data become available, the recommended treatment duration of 24 months should not be exceeded.

Mutagenesis: FORTEO was not 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 observed in FORTEO 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Serum Calcium: FORTEO 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 FORTEO injection to allow waning of the effects of the administered teriparatide.

***Urinary Calcium*:** FORTEO may cause small increases in urinary calcium excretion, but the incidence of hypercalciuria did not differ from that in the placebo-treated patients in clinical trials.

Digoxin: In a study of 15 healthy subjects administered digoxin daily to steady state, a single FORTEO dose did not alter the cardiac effect of digoxin. However, sporadic case reports have suggested that hypercalcaemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, FORTEO should be used with caution in patients taking digitalis.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have been conducted with teriparatide. No teratogenic effects were observed (see section 5.3).

The effect of FORTEO treatment on human foetal development has not been studied. FORTEO should not be administered to pregnant women (see section 4.3).

Lactation

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

Fertility

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

4.7 Effects on ability to drive and use machines

FORTEO 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 FORTEO are nausea, pain in limb, headache and dizziness.

Adverse Reactions are classified according to the system organ class and frequency using the following frequency conversion: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1 000, <1/100); rare (≥ 1/10 000, < 1/1 000) and very rare (<1/10 000)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Anaemia
Immune System Disorder	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Hypercholesterolaemia
	Uncommon	Hypercalcaemia greater than 2.76 mmol/L, hyperuricemia
	Rare	Hypercalcaemia greater than 3.25 mmol/L
Psychiatric disorders	Common	Depression
Nervous system disorders	Common	Dizziness, headache, sciatica, syncope
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
Vascular disorders	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Emphysema
Gastrointestinal disorders	Common	Nausea, vomiting, hiatus hernia, gastroesophageal reflux disease
	Uncommon	Haemorrhoids

Skin and subcutaneous tissue disorders	Common	Increased sweating
Musculoskeletal and connective tissue disorders	Very common	Pain in limb
	Common	Muscle cramps
	Uncommon	Myalgia, arthralgia, back cramp/pain*
Renal and urinary disorders	Uncommon	Urinary incontinence, polyuria, micturition urgency, nephrolithiasis
	Rare	Renal failure/impairment
General disorders and administration site conditions	Common	Fatigue, chest pain, asthenia, mild and transient injection site events, including pain, swelling, erythema, localised bruising, pruritis and minor bleeding at injection site.
	Uncommon	Injection site erythema, injection site reaction
	Rare	Possible allergic events soon after injection: acute dyspnoea, oro/facial oedema, generalised urticaria, chest pain, oedema (mainly peripheral).
Investigations	Uncommon	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 large clinical trial, antibodies that cross-reacted with teriparatide were detected in 2.8 % of women receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any

suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Alternately, report suspected adverse reactions to the company at ade_za@lilly.com.

4.9. Overdose

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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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 (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. 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 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 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

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 half-life of teriparatide is approximately 1 hour when administered subcutaneously.

Patient Characteristics:

Geriatrics: No differences in teriparatide pharmacokinetics were detected 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 identified 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 evaluated in patients with significant 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.

Heart Failure: No clinically relevant pharmacokinetic, blood pressure, pulse rate, or other safety differences were identified 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 genotoxic in a standard battery of tests. It produced no teratogenic effects in rats, mice or rabbits. There were no important effects observed 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 observed 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).

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 observed in ovariectomised monkeys treated for 18 months or during a 3-year follow-up period after treatment cessation. In addition, no osteosarcomas have been observed in clinical trials or during the post treatment follow-up study.

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

Sodium acetate (anhydrous)

Mannitol

Metacresol

Water for injection.

6.2. Incompatibilities

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

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 FORTEO if it has been frozen.

The FORTEO 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

FORTEO is supplied as a sterile, colourless, clear, isotonic solution in a 2,4 ml cartridge contained in a prefilled delivery device (pen).

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Limited

1st Floor, Golden Oak House

Ballyoaks Office Park,

35 Ballyclare Drive

Bryanston, 2191

8. REGISTRATION NUMBER(S)

36/21.4/0334

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 March 2003

10. DATE OF REVISION OF THE TEXT

17 March 2022