ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Teriparatide SUN 20 micrograms/80 microliters solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 80 microliters contains 20 micrograms of teriparatide.
Each 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

Clear, colourless solution free from visible particles.
The pH is between 3.8 and 4.5. The osmolality is between 250 to 350 mOsmol.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Teriparatide SUN is indicated in adults.
Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture (see section 5.1). In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated.

Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (see section 5.1).

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 patients
Dose 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 available in patients with impaired hepatic function (see section 5.3). 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 established. Teriparatide SUN should not be used in paediatric patients (less than 18 years), or young adults with open epiphyses.

Method of administration

Teriparatide SUN should be administered once daily by subcutaneous injection in the thigh or abdomen.

Patients must be trained to use the proper injection techniques (see section 6.6). Please also refer to the pen user manual for instructions on the correct use of the pen at the end of the package leaflet.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- pregnancy and breast-feeding (see sections 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

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered medicinal product should be clearly recorded.

Serum and urine calcium

In normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been observed 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 incidence of hypercalciuria did not differ from that in the placebo-treated patients in clinical trials.

Urolithiasis
Teriparatide has not been 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

In short-term clinical trials with teriparatide, 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, 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, including premenopausal women, is limited (see section 5.1). 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

Studies in rats indicate an increased incidence of osteosarcoma with long-term administration of teriparatide (see section 5.3). Until further clinical data become available, the recommended treatment time of 24 months should not be exceeded.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per maximum daily dose, that is to say 'sodium- free'.

4.5 Interactions with other medicinal products and other forms of interaction

In a study of 15 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 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.

Teriparatide has been evaluated in pharmacodynamic interaction studies with hydrochlorothiazide. No clinically significant interactions were noted.

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.

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 SUN is contraindicated for use during pregnancy (see section 4.3).

Breast-feeding

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

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

Teriparatide SUN has no or negligible influence on the ability to drive and use machines. 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

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

Of patients in the teriparatide trials, 82.8 % of the teriparatide patients and 84.5 % of the placebo patients reported at least 1 adverse event.

The adverse reactions associated with the use of teriparatide in osteoporosis clinical trials and post-marketing exposure 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).

Table 1. Adverse reaction

MedDRA system organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Anaemia	Common
Immune system disorder	Anaphylaxis	Rare
Metabolism and nutrition disorders	Hypercholesterolaemia	Common
	Hypercalcaemia greater than 2.76 mmol/l, hyperuricemia	Uncommon
	Hypercalcaemia greater than 3.25 mmol/l	Rare
Psychiatric disorders	Depression	Common
Nervous system disorders	Dizziness, headache, sciatica, syncope	Common
Ear and labyrinth disorders	Vertigo	Common
Cardiac disorders	Palpitations	Common
	Tachycardia	Uncommon
Vascular disorders	Hypotension	Common

MedDRA system organ class	Adverse reaction	Frequency
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
	Emphysema	Uncommon
Gastrointestinal disorders	Nausea, vomiting, hiatus hernia, gastroesophageal reflux disease	Common
	Haemorrhoids	Uncommon
Skin and subcutaneous tissue disorders	Sweating increased	Common
Musculoskeletal and connective tissue disorders	Pain in limb	Very common
	Muscle cramps	Common
	Myalgia, arthralgia, back cramp/pain*	Uncommon
Renal and urinary disorders	Urinary incontinence, polyuria, micturition urgency, nephrolithiasis	Uncommon
	Renal failure/impairment	Rare
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	Common
	Injection site erythema, injection site reaction	Uncommon
	Possible allergic events soon after injection: acute dyspnoea, oro/facial oedema, generalised urticaria, chest pain, oedema (mainly peripheral)	Rare
Investigations	Weight increased, cardiac murmur, alkaline phosphatase increase	Uncommon

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

Description of selected adverse reactions

In 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 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.

In a large 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 evidence of hypersensitivity reactions, allergic reactions, effects on serum calcium, or effects on Bone Mineral Density (BMD) response.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms

Teriparatide has been 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 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

In post-marketing spontaneous reports, there have been cases of medication error where the entire contents (up to 800 mcg) 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 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

5.1 Pharmacodynamic properties

Pharmaco-therapeutic 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 increases apposition of new bone on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity.

Clinical efficacy

Risk factors
Independent risk factors, for example, low BMD, age, the existence of previous fracture, family history of hip fractures, high bone turnover and low body mass index should be considered in order to identify women and men at increased risk of osteoporotic fractures who could benefit from treatment.

Premenopausal women with glucocorticoid-induced osteoporosis should be considered at high risk for fracture if they have a prevalent fracture or a combination of risk factors that place them at high risk for fracture (e.g., low bone density [e.g., T score ≤−2], sustained high dose glucocorticoid therapy [e.g., ≥7.5 mg/day for at least 6 months], high underlying disease activity, low sex steroid levels).

Postmenopausal osteoporosis
The pivotal study included 1637 postmenopausal women (mean age 69.5 years). At baseline, ninety percent of the patients had one or more vertebral fractures, and on average, vertebral BMD was 0.82 g/cm2 (equivalent to a T-score = - 2.6). All patients were offered 1 000 mg calcium per day and at least 400 IU vitamin D per day. Results from up to 24 months (median: 19 months) treatment with teriparatide demonstrate statistically significant fracture reduction (Table 1). To prevent one or more new vertebral fractures, 11 women had to be treated for a median of 19 months.

Table 2 Fracture incidence in postmenopausal women

	Placebo (N = 544) (%)	Teriparatide (N = 541) (%)	Relative risk (95% CI) vs. placebo
New vertebral fracture (≥1) [a]	14.3	5.0[b]	0.35 (0.22, 0.55)
Multiple vertebral fractures (≥2) [a]	4.9	1.1[b]	0.23 (0.09, 0.60)
Non-vertebral fragility fractures	5.5%	2.6%[d]	0.47 (0.25, 0.87)
Major non-vertebral fragility fractures[c] (hip, radius, humerus, ribs and pelvis)	3.9%	1.5%[d]	0.38 (0.17, 0.86)

Abbreviations: N = number of patients randomly assigned to each treatment group; CI = Confidence Interval.

[a] The incidence of vertebral fractures was assessed in 448 placebo and 444 teriperatide patients who had baseline and follow-up spine radiographs.
[b] p≤0.001 compared with placebo
[c] A significant reduction in the incidence of hip fractures has not been demonstrated
[d] p≤0.025 compared with placebo.

After 19 months (median) treatment, BMD had increased in the lumbar spine and total hip, respectively, by 9 % and 4 % compared with placebo (p<0.001).

Post-treatment management: Following treatment with teriparatide, 1262 postmenopausal women from the pivotal trial enrolled in a post-treatment follow-up study. The primary objective of the study was to collect safety data of teriparatide. During this observational period, other osteoporosis treatments were allowed and additional assessment of vertebral fractures was performed.

During a median of 18 months following discontinuation of teriparatide, 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 an open-label study, 503 postmenopausal women with severe osteoporosis and a fragility fracture within the previous 3 years (83 % had received previous osteoporosis therapy) were treated with teriparatide for up to 24 months. At 24 months, the mean increase from baseline in lumbar spine, total hip and femoral neck BMD was 10.5 %, 2.6 % and 3.9 % respectively. The mean increase in BMD from 18 to 24 months was 1.4 %, 1.2 %, and 1.6 % at the lumbar spine, total hip and femoral neck, respectively.

A 24-month, randomised, double-blind, comparator-controlled Phase 4 study included 1,360 postmenopausal women with established osteoporosis. 680 subjects were randomised to teriparatide and 680 subjects were randomised to oral risedronate 35 mg/week. At baseline, the women had a mean age of 72.1 years and a median of 2 prevalent vertebral fractures; 57.9 % of patients had received previous bisphosphonate therapy and 18.8 % took concomitant glucocorticoids during the study. 1,013 (74.5 %) patients completed the 24-month follow-up. The mean (median) cumulative dose of glucocorticoid was 474.3 (66.2) mg in the teriparatide arm and 898.0 (100.0) mg in the risedronate arm. The mean (median) vitamin D intake for the teriparatide arm was 1433 IU/day (1400 IU/day) and for the risedronate arm was 1191 IU/day (900 IU/day). For those subjects who had baseline and follow-up spine radiographs, the incidence of new vertebral fractures was 28/516 (5.4 %) in teriparatide- and 64/533 (12.0 %) in risedronate-treated patients, relative risk (95 % CI) = 0.44 (0.29-0.68), P<0.0001. The cumulative incidence of pooled clinical fractures (clinical vertebral and non vertebral fractures) was 4.8 % in teriparatide and 9.8 % in risedronate-treated patients, hazard ratio (95 % CI) = 0.48 (0.32-0.74), P=0.0009.

Male osteoporosis
437 patients (mean age 58.7 years) were enrolled in a clinical trial for men with hypogonadal (defined as low morning free testosterone or an elevated FSH or LH) or idiopathic osteoporosis. Baseline spinal and femoral neck bone mineral density mean T-scores were -2.2 and -2.1, respectively. At baseline, 35 % of patients had a vertebral fracture and 59 % had a non-vertebral fracture.

All patients were offered 1 000 mg calcium per day and at least 400 IU vitamin D per day. Lumbar spine BMD significantly increased by 3 months. After 12 months, BMD had increased in the lumbar spine and total hip by 5 % and 1 %, respectively, compared with placebo. However, no significant effect on fracture rates was demonstrated.

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 the 18-month primary phase of a 36 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 were offered 1 000 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 primary phase. At the 18 month 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 %) ($p<0.05$). In patients treated with teriparatide, lumbar spine, total hip and femoral neck BMD increased between 18 and 24 months by an additional 1.7 %, 0.9 %, and 0.4 %, respectively.

At 36 months, analysis of spinal X-rays from 169 alendronate patients and 173 teriparatide patients showed that 13 patients in the alendronate group (7.7 %) had experienced a new vertebral fracture compared with 3 patients in the teriparatide group (1.7 %) ($p=0.01$). In addition, 15 of 214 patients in the alendronate group (7.0 %) had experienced a non-vertebral fracture compared with 16 of 214 patients in the teriparatide group (7.5 %) ($p=0.84$).

In premenopausal women, the increase in BMD from baseline to 18 month 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.

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.

Biostransformation

No metabolism or excretion studies have been performed with 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 detected with regard to age (range 31 to 85 years). Dosage adjustment based on age 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 1 000 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.

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 (E260)
Anhydrous sodium acetate (E262)
Mannitol (E421)
Metacresol
Hydrochloric acid (for pH adjustment) (E507)
Sodium hydroxide (for pH adjustment) (E524)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

After first opening
Chemical, physical and microbiological in-use stability has been demonstrated for 28 days at 2°C-8°C. Once opened, the medicinal product may be stored for a maximum of 28 days at 2°C to 8°C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

For storage conditions after first opening of the medicinal product, see section 6.3.

Before first opening
The product might be stored at 25°C for 24 hours.

6.5 Nature and contents of container

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

Teriparatide SUN is available in pack sizes of 1 pre-filled pen or 3 pre-filled pens. Each pre-filled pen contains 28 doses of 20 micrograms (per 80 microliters).

Not all pack sizes may be marketed

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. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

EU/1/22/1697/001
EU/1/22/1697/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands

Terapia S.A.
Strada Fabricii Nr. 124
Cluj-Napoca, 400632
Romania

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

Teriparatide SUN 20 micrograms/80 microliters solution for injection in pre-filled pen
teriparatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid (E260), anhydrous sodium acetate (E262), mannitol (E421), metacresol, hydrochloric acid (for pH adjustment) (E507), sodium hydroxide (for pH adjustment) (E524) and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen (28 doses)
3 pre-filled pens (3 x 28 doses)

Each pen contains 28 doses of 20 micrograms (per 80 microliters)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The pen should be discarded 28 days after the first use.

Date of first use:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
The product might be stored before first opening at 25°C for 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe BV
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/16/1697/001
EU/1/22/16/1697/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

teriparatide sun

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Teriparatide SUN 20 micrograms/80 microliters solution for injection
teriparatide

Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 ml

6. OTHER

SUN Pharma logo

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Teriparatide SUN 20 micrograms/80 microliters solution for injection in pre-filled pen
teriparatide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Teriparatide SUN is and what it is used for
2. What you need to know before you use Teriparatide SUN
3. How to use Teriparatide SUN
4. Possible side effects
5. How to store Teriparatide SUN
6. Content of the pack and other information

1. What Teriparatide SUN is and what it is used for

Teriparatide SUN contains the active substance teriparatide that is used to make the bones stronger, and to reduce the risk of fractures by stimulating bone formation.

Teriparatide SUN is used to treat osteoporosis in adults. Osteoporosis is a disease that causes your bones to become thin and fragile. This disease is especially common in women after the menopause, but it can also occur in men. Osteoporosis is also common in patients receiving corticosteroids.

2. What you need to know before you use Teriparatide SUN

Do not use Teriparatide SUN
- if you are allergic to teriparatide or any of the other ingredients of this medicine (listed in section 6)
- if you suffer from high calcium levels (pre-existing hypercalcaemia)
- if you suffer from serious kidney problems
- if you have ever been diagnosed with bone cancer or other cancers that have spread (metastasised) to your bones
- if you have certain bone diseases. If you have a bone disease, tell your doctor
- if you have unexplained high levels of alkaline phosphatase in your blood, which means you might have Paget's disease of bone (disease with abnormal bone changes). If you are not sure, ask your doctor
- if you have had radiation therapy involving your bones
- if you are pregnant or breast-feeding.

Warnings and precautions
Teriparatide SUN may cause an increase in the amount of calcium in your blood or urine.
Talk to your doctor or pharmacist before or while using Teriparatide SUN
- if you have continuing nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs there is too much calcium in your blood
- if you suffer from kidney stones or have a history of kidney stones

- if you suffer from kidney problems (moderate renal impairment).

Some patients get dizzy or get a fast heartbeat after the first few doses. For the first doses, inject Teriparatide SUN where you can sit or lie down right away if you get dizzy.
The recommended treatment time of 24 months should not be exceeded.

Teriparatide SUN should not be used in growing adults.

Children and adolescents
Teriparatide SUN should not be used in children and adolescents (less than 18 years).

Other medicines and Teriparatide SUN
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, because occasionally they may interact (e.g. digoxin/digitalis, a medicine used to treat heart disease).

Pregnancy and breast-feeding
Do not use Teriparatide SUN if you are pregnant, think you may be pregnant, or if you are breast-feeding.
If you are a woman of child-bearing potential, you should use effective methods of contraception during use of Teriparatide SUN. If you become pregnant, Teriparatide SUN should be discontinued. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Some patients may feel dizzy after injecting Teriparatide SUN. If you feel dizzy you should not drive or use machines until you feel better.

Teriparatide SUN contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

3. How to use Teriparatide SUN

Always use this medicine exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 20 micrograms given once daily by injection under the skin (subcutaneous injection) in the thigh or abdomen. To help you remember to take your medicine, inject it at about the same time each day.

Inject Teriparatide SUN each day for as long as your doctor prescribes it for you. The total duration of treatment with Teriparatide SUN should not exceed 24 months. You should not receive more than one treatment course of 24 months over your lifetime.
Teriparatide SUN can be injected at meal times.

Carefully read how to use the pre-filled pen at the end of this package leaflet.

Injection needles are not included with the pen. Pen needles of 31 Gauge, 5 mm length can be used.

You should use your Teriparatide SUN injection shortly after you take the pen out of the refrigerator as described in **Pen User Manual** at the end of this package leaflet. For instructions for use video, please scan the QR code included in the Pen User Manual or use the link: https://www.pharmaqr.info/tptemaen. Put the pen back into the refrigerator immediately after you have used it. Use a new injection needle of 31 Gauge, 5 mm length for each injection and dispose of it after each use. Never store your pen with the needle attached. Never share your Teriparatide SUN pen with others.

Your doctor may advise you to use Teriparatide SUN with calcium and vitamin D. Your doctor will tell you how much you should take each day.

Teriparatide SUN can be given with or without food.

If you use more Teriparatide SUN than you should
If, by mistake, you have used more Teriparatide SUN than you should, contact your doctor or pharmacist. The effects of overdose that might be expected include nausea, vomiting, dizziness, and headache.

If you forget or cannot take Teriparatide SUN at your usual time, use it as soon as possible on that day. Do not use a double dose to make up for a forgotten dose. Do not use more than one injection in the same day. Do not try to make up for a missed dose.

If you stop taking Teriparatide SUN
If you are considering stopping Teriparatide SUN treatment, please discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with Teriparatide SUN.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects are pain in limb (frequency is very common, may affect more than 1 in 10 people) and feeling sick, headache and dizziness (frequency is common, may affect up to 1 in 10 people). If you become dizzy (light-headed) after your injection, you should sit or lie down until you feel better. If you do not feel better, you should call a doctor before you continue treatment. Cases of fainting have been reported in association with teriparatide use.

If you experience discomfort such as redness of the skin, pain, swelling, itching, bruising or minor bleeding around the area of the injection (frequency is common), this should clear up in a few days or weeks. Otherwise, tell your doctor as soon as possible.

Some patients may have experienced allergic reactions soon after injection, consisting of breathlessness, swelling of the face, rash and chest pain (frequency is rare, may affect up to 1 in 1,000 people). In rare cases, serious and potentially life-threatening allergic reactions including anaphylaxis can occur.

Other side effects include

Common (may affect up to 1 in 10 people)
- increase in blood cholesterol levels
- depression
- neuralgic pain in the leg
- feeling faint
- irregular heart beats
- breathlessness
- increased sweating
- muscle cramps
- loss of energy
- tiredness
- chest pain
- low blood pressure
- heartburn (painful or burning sensation just below the breast bone)

- being sick (vomiting)
- a hernia of the tube that carries food to your stomach
- low haemoglobin or red blood cell count (anaemia)

Uncommon (may affect up to 1 in 100 people)
- increased heart rate
- abnormal heart sound
- shortness of breath
- haemorrhoids (piles)
- accidental loss or leakage of urine
- increased need to pass water
- weight increase
- kidney stones
- pain in the muscles and pain in the joints. Some patients have experienced severe back cramps or pain which lead to hospitalisation
- increase in blood calcium level
- increase in blood uric acid level
- increase in an enzyme called alkaline phosphatase.

Rare (may affect up to 1 in 1,000 people)
- reduced kidney function, including renal failure
- swelling, mainly in the hands, feet and legs.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Teriparatide SUN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and pen after EXP. The expiry date refers to the last day of that month.

Teriparatide SUN might be stored before the first opening at 25°C for 24 hours.

Teriparatide SUN should be stored in a refrigerator (2°C to 8°C) at all times. You can use Teriparatide SUN for up to 28 days after the first injection, as long as the pen is stored in a refrigerator (2°C to 8°C).

Do not freeze Teriparatide SUN. Avoid placing the pens close to the ice compartment of the refrigerator to prevent freezing. Do not use Teriparatide SUN if it is, or has been, frozen.

Each pen should be properly disposed of after 28 days, even if it is not completely empty.

Teriparatide SUN contains a clear and colourless solution. Do not use Teriparatide SUN if solid particles appear or if the solution is cloudy or coloured.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Teriparatide SUN contains

- The active substance is teriparatide. Each dose of 80 microliters contains 20 micrograms of teriparatide.
  Each pre-filled pen of 2.4 ml contains 600 micrograms of teriparatide (corresponding to 250 micrograms per ml.
- The other ingredients are glacial acetic acid (E260), anhydrous sodium acetate (E262), mannitol (E421), metacresol, and water for injections. In addition, hydrochloric acid (E507) and/or sodium hydroxide (E524) solution may have been added for pH adjustment. (See section 2 Teriparatide SUN contains sodium)

What Teriparatide SUN looks like and contents of the pack
Teriparatide SUN is a clear and colourless solution. It is supplied in a cartridge contained in a disposable pre-filled pen. Each pen contains 2.4 ml of solution enough for 28 doses.

It is available in packs of 1 pre-filled pen or 3 pre-filled pens.

Not all package sizes may be marketed.

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The Netherlands

Manufacturers
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The Netherlands

Terapia S.A.
Str. Fabricii nr. 124
Cluj-Napoca, 400632
Romania

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien/България/Česká republika/
Danmark/Eesti/Ελλάδα/Hrvatska/Ísland/Κύπρος/
Latvija/Lietuva/Luxembourg/Luxemburg/Magyarország/
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Ολλανδία/Nīderlande/Nyderlandai/Pays-Bas/Niederlande/
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website:
http://www.ema.europa.eu

PEN USER MANUAL

Teriparatide SUN 20 micrograms/80 microliters solution for injection in pre-filled pen

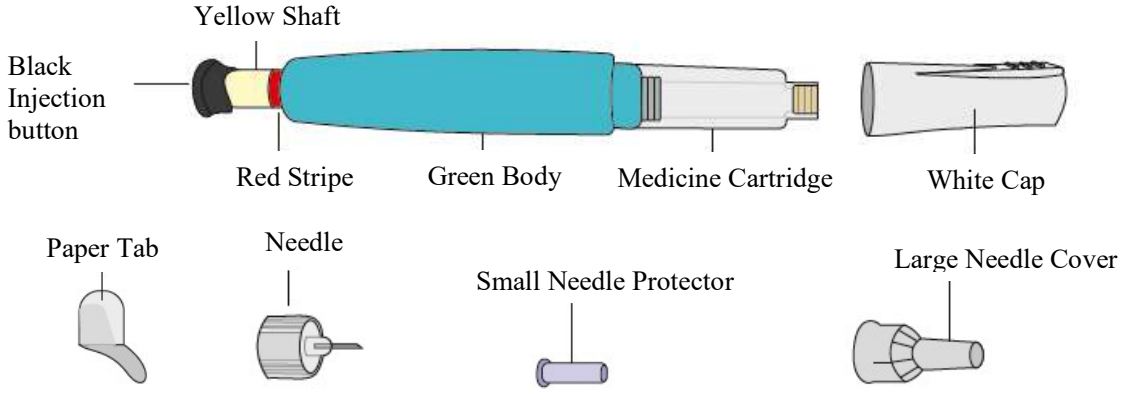
Instructions for use

Before you use your new pen, please read the section *Instructions for use* completely. Follow the directions carefully when using the pen. Also read the package leaflet provided.
For instructions for use video, please scan the QR code or use the link:
https://www.pharmaqr.info/tptemaen.

Do not share your pen or your needles as this may risk transmission of infectious agents.

Your pen contains 28 days of medicine.

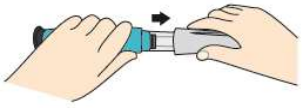
Teriparatide SUN Parts*



*Needles not included. The needle of 31 Gauge, 5 mm length can be used. Ask your doctor or pharmacist which needle gauge and length are best for you.

Always wash your hands before every injection. Prepare the injection site as directed by your doctor or pharmacist.

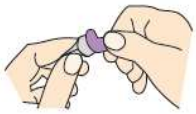
Step 1 Pull off white cap



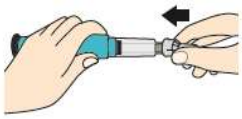
Remove the white cap by pulling it straight off the pen

Step 2 Attach a new needle

Large needle protector

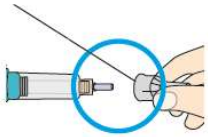


a) Pull off paper tab



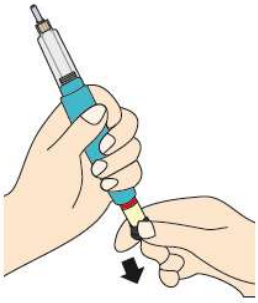
b) Push needle **straight** onto medicine cartridge.

c) Screw on needle clockwise firmly attached.



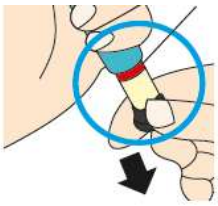
d) Pull off large needle cover and **save it.**

Step 3 Set dose



e) **Pull** out black injection button **until it stops.**

Red stripe



f) **Check** to make sure red stripe shows.

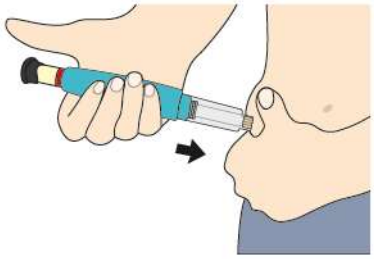
Small needle protector

g) Pull off small needle protector and throw away.

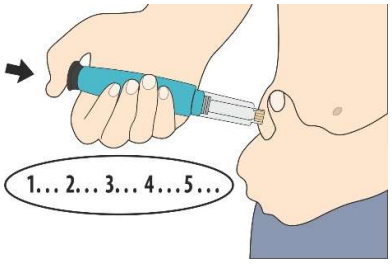
If you cannot pull out the black injection button see *Troubleshooting Problem E.*

Note: After removal of inner needle protector, you may see drop(s) of medicine coming out of the needle.
It is normal and will not affect your dose.

Step 4 Inject dose



h) Gently hold a fold of skin from thigh or abdomen and insert needle straight into skin.



i) **Push in** black injection button until it stops. Hold it in and **count to 5 s-l-o-w-l-y.** Then pull the needle from skin.

IMPORTANT

Step 5 Confirm dose

j)

After completing the injection

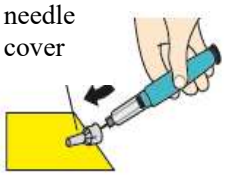
Once the needle is removed from the skin, **check** to make sure the black injection button is all the way in. If the yellow shaft does not show, you have completed the injection steps correctly.

k)

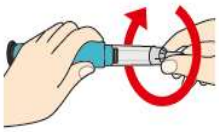
You should **NOT** see any of the yellow shaft. If you do and have already injected, do not inject yourself a second time on the same day. Instead, **you MUST reset Teriparatide SUN** (See Troubleshooting Problem A).

Step 6 Remove needle

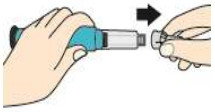
Large needle cover



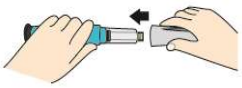
l) Put large needle cover on needle.



m) Unscrew the needle anti-clockwise all the way by giving the large needle cover 3 to 5 complete turns.



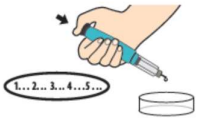
n) Pull off needle and throw away as directed by your doctor or pharmacist.



o) Push white cap back on. Place Teriparatide SUN in the refrigerator immediately after use.

The directions regarding needle handling are not intended to replace local, healthcare professional or institutional policies.

Troubleshooting

Problem	Solution
A. The yellow shaft is still showing after I push in the black injection button. How do I reset my Teriparatide SUN?  	To reset the Teriparatide SUN, follow the steps below. 1) The recommended dose is 20 micrograms given once daily. If you have already injected, DO NOT inject yourself a second time on the same day. 2) Remove the needle. 3) Attach a new needle, pull off the large needle cover and save it. 4) Pull out the black injection button until it stops. Check to make sure the red stripe shows. (See step 3) 5) Pull off the small needle protector and throw away. 6) Point the needle down into an empty container. Push in the black injection button until it stops. Hold it in and count to 5 s-l-o-w-l-y. You may see a small stream or drop of fluid. **When you have finished, the black injection button should be all the way in.** 7) If you still see the yellow shaft showing, please contact your doctor or pharmacist 8) Put the large needle cover on needle. Unscrew the needle all the way by giving the needle cover 3 to 5 complete turns. Pull off needle cover and throw away as directed by your doctor or pharmacist. Push the white cap back on, and place Teriparatide SUN in the refrigerator. (See step 6) You can prevent this problem by **always using a NEW needle for each injection, and by pushing the black injection button all the way in and counting to 5 s-l-o-w-l-y.**
B. How do I know if my Teriparatide SUN works?	The Teriparatide SUN is designed to inject the full dose every time it is used according to the directions in the section *How to use.* The black injection button will be all the way in to show that the full dose has been injected from the Teriparatide SUN. Remember to use a new needle every time you inject to be sure your Teriparatide SUN will work properly.
C. I see an air bubble in my Teriparatide SUN.	A small air bubble will not affect your dose nor will it harm you. You can continue to take your dose as usual.

D. I cannot get the needle off.	➡	1) Put the large needle cover on the needle. (See step 6) 2) Use the large needle cover to unscrew the needle. 3) Unscrew the needle all the way by giving the large needle cover 3 to 5 complete turns. 4) If you still cannot get the needle off, ask someone to help you.

E. What should I do if I cannot pull out the black injection button?	➡	**Change to a new Teriparatide SUN to take your dose as directed by your doctor or pharmacist.** This indicates that you have now used all the medicine that can be injected accurately even though you may still see some medicine left in the cartridge.

Cleaning and Storage

Cleaning Your Teriparatide SUN

- Wipe the outside of the Teriparatide SUN with a damp cloth.
- Do not place the Teriparatide SUN in water, or wash or clean it with any liquid.

Storing Your Teriparatide SUN

- Refrigerate the Teriparatide SUN immediately after every use. Read and follow the instructions in the *Information for the Patient leaflet* on how to store your pen.
- Do not store the Teriparatide SUN with a needle attached as this may cause air bubbles to form in the cartridge.
- Store the Teriparatide SUN with the white cap on.
- If the medicine has been frozen, throw the pre-filled pen away and use a new Teriparatide SUN.
- If the Teriparatide SUN has been left out of the refrigerator, do not throw the pen away. Place the pen back in the refrigerator and contact your doctor or pharmacist.

Disposal of Pen Needles and Pre-filled pen

Disposal of Pen Needles and Teriparatide SUN pre-filled pen

- Before disposing of the Teriparatide SUN pre-filled pen, be sure to remove the pen needle.
- Put used needles in a sharps container or a hard plastic container with a secure lid. Do not throw needles directly into your household waste.
- Do not recycle the filled sharps container.
- Ask your healthcare professional about options to dispose of the pen and the sharps container properly.
- The directions regarding needle handling are not intended to replace local, healthcare professional or institutional policies.
- Dispose of the pre-filled pen 28 days after first use.

Other Important Notes

- The Teriparatide SUN contains 28 days of medicine.
- Do not transfer the medicine into a syringe.
- Write down your first injection date on a calendar.
- Check the Teriparatide SUN label to make sure you have the correct medicine and that it has not expired.
- During injection, you may hear one or more clicks – this is a normal pre-filled pen operation.
- The Teriparatide SUN is not recommended for use by the blind or visually impaired persons without the assistance of a person trained in the proper use of the pre-filled pen.