15 September 2022
EMA/897619/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Teriparatide SUN

International non-proprietary name: teriparatide

Procedure No. EMEA/H/C/005793/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Administrative information

| | |
|---|---|
| **Name of the medicinal product:** | Teriparatide SUN |
| **Applicant:** | Sun Pharmaceutical Industries Europe B.V.<br>Polarisavenue 87<br>2132JH Hoofddorp<br>NETHERLANDS |
| **Active substance:** | Teriparatide |
| **International Nonproprietary Name/Common Name:** | teriparatide |
| **Pharmaco-therapeutic group (ATC Code):** | PARATHYROID HORMONES AND ANALOGUES, Parathyroid hormones and analogues (H05AA02) |
| **Therapeutic indication(s):** | 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.<br><br>Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (see section 5.1). |
| **Pharmaceutical form(s):** | Solution for injection |
| **Strength(s):** | 20 µg/80 µl |
| **Route(s) of administration:** | Subcutaneous use |

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| **Packaging:** | cartridge (glass) in a pre-filled pen |
| **Package size(s):** | 1 pre-filled pen and 3 pre-filled pens |

# Table of contents

# List of abbreviations

| | |
|---|---|
| AA | Amino acid |
| ADA | Anti-drug antibody |
| AEs | Adverse Events |
| AEX | Anion exchange chromatography |
| ALT | Alanine transaminase |
| ANOVA | Analysis of variance |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| AUC | Area Under the Curve |
| $AUC_{0-t}$ | AUC from time 0 to last quantifiable concentration |
| $AUC_{0-\infty}$ | AUC from time 0 to infinity |
| $\%AUC_{0-t}$ | Percentage AUC(0-∞) extrapolated |
| BLQ | Below Limit of Quantitation |
| BMC | Bone Mineral Content |
| BMD | Bone Mineral Density |
| BMDD | Bone Mineralisation Density Distribution |
| BMI | Body Mass Index |
| BTM | Bone Turnover Markers |
| C | Celsius |
| cAMP | Cyclic Adenosine Mono Phosphate |
| CEX | Cation exchange chromatography |
| CFB | Change From Baseline |
| CFU/mL | Colony forming units/millilitre |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| CL/F | Clearance |
| CPP | Critical process parameter |
| CPV | Continued process verification |
| CQA | Critical quality attribute |
| $C_{max}$ | Maximum observed concentration |
| $C_{min}$ | Minimum observed concentration |
| CTX | C-terminal Telopeptide of type 1 collagen |

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|---|---|
| Da | Dalton(s) |
| DBP | Diastolic Blood Pressure |
| DLP | Data Lock Point |
| DNA | deoxyribonucleic acid |
| DP | Drug product |
| DS | Drug substance |
| DXA | Dual-energy X-ray Absorptiometry |
| EMA | European Medicines Agency |
| EU | European Union |
| EURD | European Union Reference Date |
| FDA | Food and Drug Administration |
| GC | Glucocorticoids |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| GH | Growth Hormone |
| IGF | Insulin Growth Factor |
| GMP | Good manufacturing practice |
| INN | international nonproprietary name |
| IPC | In-process control |
| i-PTH | Intact PTH |
| KPA | Key performance attribute |
| KPP | Key process parameter |
| L | Litre(s) |
| MAA | Marketing Authorisation Application |
| MD | Mean Difference |
| MeSH | Medical Subject Headings |
| MIA | Manufacture and importation authorisation |
| MO | Major Objection |
| MW | Molecular weight |
| NOR | Normal operating range |
| NVFx | Non-Vertebral Fractures |
| OC | Other concern |
| OD | Optical density |

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|---|---|
| OFAT | One factor at a time |
| ONJ | Osteonecrosis of the Jaw |
| OP | Osteoporosis |
| OR | Odds Ratio |
| PAR | Proven acceptable range |
| PD | Pharmacodynamics |
| PIMP | Procollagen type I N Propeptide |
| PK | Pharmacokinetics |
| PKA | Protein Kinase A |
| PKC | Protein Kinase C |
| PMO | Postmenopausal Osteoporosis |
| PP | Process parameter |
| PPA | Process performance attribute |
| PPQ | Process performance qualification |
| PSUR | Periodic Safety Assessment Report |
| PTH | Parathyroid Hormone |
| PTH1R | PTH Receptor 1 |
| PTHrP | Parathyroid-Hormone-related Protein (Peptide) |
| QALY | Quality Adjusted Life Years |
| QP | Qualified person |
| RCTs | Randomised Clinical Trials |
| RP-HPLC | Reverse phase high performance liquid chromatography |
| RT | Reference-test |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SE | Standard Error |
| RT | Reference-test |
| T2DM | Type 2 Diabetes Mellitus |
| TEAE | Treatment-Emergent Adverse Event |
| TP | Teriparatide |
| TR | Test-reference |
| ULOQ | Upper limit of quantitation |
| ULN | Upper limit of normal |

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|---|---|
| US | United States |
| VAS | Visual Analogue Scale |
| Vz/F | Apparent Volume of distribution |
| WBC | White blood cell |
| WCB | Working cell bank |
| WHO | World Health Organisation |
| µL | Microlitre |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Sun Pharmaceutical Industries Europe B.V. submitted on 31 December 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Teriparatide SUN, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 November 2020.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> *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).*

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Forsteo instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Forsteo, 20 µg/80 µl, Solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 10.06.2003
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/03/247/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Forsteo, 20 µg/80 µl, Solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.

- Date of authorisation: 10.06.2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/247/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Forsteo, 20 µg/80 µl, Solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 10.06.2003
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/03/247/001-002
- Bioavailability study number(s): TER15

## *1.3. Information on paediatric requirements*

Not applicable

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *1.5. Scientific advice*

The applicant did not seek Scientific advice from the CHMP.

## *1.6. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra Co-Rapporteur: Simona Badoi

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| The application was received by the EMA on | 31 December 2020 |
| The procedure started on | 21 January 2021 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 12 April 2021 |

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| The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 12 April 2021 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 26 April 2021 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 20 May 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 25 April 2022 |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on | 01 June 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 10 June 2022 |
| The CHMP agreed on a list of outstanding issues to be sent to the applicant on | 23 June 2022 |
| The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on | 16 August 2022 |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 26 August 2022 |
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | N/A |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Teriparatide SUN on | 15 September 2022 |

# 2. Scientific discussion

## *2.1. Introduction*

Osteoporosis, as defined by World Health Organization, is a systemic disease of the skeleton characterised by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue with consequent increased bone fragility that predisposes to fracture risk. Due to the silent progression of bone structure degeneration, osteoporosis diagnosis often follows a painful fracture event.

In 27 European Union (EU) countries, the prevalence of osteoporosis was estimated to be 6.6 % and 22.1 % in men and women, respectively, aged 50 years or more and 5.5 % in the general population. According to the National (US) Osteoporosis Foundation, up to 25% of men over the age of 50 years will experience a fracture due to osteoporosis, with approximately 80,000 suffering from a broken hip.

Osteoporosis is commonly experienced in postmenopausal women due to declining oestrogen-levels. However, osteoporosis can also occur in both sexes as a side effect of prolonged treatment with glucocorticoid medications. Glucocorticoid-induced osteoporosis may be responsible for up to 20% of all osteoporosis cases. Fractures, primarily hip fractures, decrease a patient's quality of life by increasing pain, medical costs, morbidity, and mortality.

The diagnosis of osteoporosis is established by means of bone densitometry or by the presence of a fragility fracture. Any bone may be affected; although the skeletal sites most prone to fracture include proximal femur (hip), vertebrae (spine), and distal forearm (wrist). Osteoporotic fractures lead to pain and occasional disability.

Current pharmacological options for the treatment of osteoporosis in Europe include anti-resorptive agents (e.g. bisphosphonates, calcitonin and raloxifene), which reduce osteoclastic activity, strontium ranelate, which reduces osteoclastic activity and may have anabolic properties as well, and parathyroid hormone (PTH) analogues including teriparatide, which stimulate bone turnover with a positive bone balance thereby increasing bone mass. In addition, denosumab, an anti RANKL antibody that reduces osteoclast activity, is available.

The current application concerns a marketing authorisation for Teriparatide Sun, a proposed hybrid to the innovator product Forsteo (teriparatide).

The European Commission granted a marketing authorisation for Forsteo on 10 June 2003 and it is indicated for the:

- 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 nonvertebral 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).

Forsteo is available as a pre-filled pen of 2.4 mL, containing 600 micrograms of teriparatide corresponding to 250 micrograms per mL; each dose of 80 microlitres contains 20 micrograms of teriparatide. The recommended dose of Forsteo is 20 micrograms administered once daily, the maximum total duration of treatment should be 24 months, and the 24-month course should not be repeated over a patient's lifetime. Patients should receive supplemental calcium and vitamin D supplements if dietary intake is inadequate.

In the current application a marketing authorisation is requested for Teriparatide Sun 20 micrograms / 80 microliters solution for injection in a cartridge. Each pen contains 2.4 mL of solution enough for 28 doses to be administered subcutaneously.

The biologically active ingredient of Teriparatide Sun is teriparatide which is a key regulator of the concentrations of calcium, phosphate, and active vitamin D metabolites in blood and modulates cellular activity in bone resulting in bone remodelling and maintenance of the bone structure. Teriparatide is the biologically active 34-amino acid N-terminal fragment and analogue of the 84-amino acid native parathyroid hormone PTH (1-84). It belongs to the pharmacotherapeutic group of calcium homeostasis, parathyroid hormones and analogues, ATC-code H05AA02. Teriparatide Sun is a synthetic form of parathyroid hormone (PTH).

Physiological actions of parathyroid hormone include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors known as the PTH-1 receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as solution for injection in pre-filled pen containing teriparatide 20 micrograms/80 microliters as active substance.

Other ingredients are: mannitol, glacial acetic acid, sodium acetate anhydrous, metacresol, sodium hydroxide, hydrochloric acid and water for injection.

The product is available in siliconised type 1 glass 3 mL cartridge with a bromobutyl rubber plunger stopper and disc seal/cap ((polyisoprene/bromobutyl rubber laminate)/aluminium). The cartridge is assembled into a single, integral pen device. The pen consists of body-subassembly with button and dose set knob, cartridge holder and cap. Needles are not supplied with the product.

### 2.2.2. Active substance

Teriparatide is the subject of a monograph in the European Pharmacopoeia. The Active Substance Master File (ASMF) procedure is followed.

#### *2.2.2.1. General information*

Teriparatide is a tetratriacontapeptide in which the sequence of amino acids is the same as that of the 1-34 *N*-terminal fragment of endogeneous human parathyroid hormone (rhPTH). The chemical name of Teriparatide is *H*-Ser-Val-Ser-Glu-Ile$^{5}$-Gln-Leu-Met-His-Asn$^{10}$Leu-Gly-Lys-His-Leu$^{15}$-Asn-Ser-Met-Glu-Arg$^{20}$-Val-Glu-Trp-Leu-Arg$^{25}$-Lys-Lys-Leu-Gln-Asp$^{30}$-Val-His-Asn-Phe$^{34}$-OH corresponding to the molecular formula $C_{181}H_{291}N_{55}O_{51}S_2$. It has a relative molecular mass of 4117.7 g/mol and the following structure:

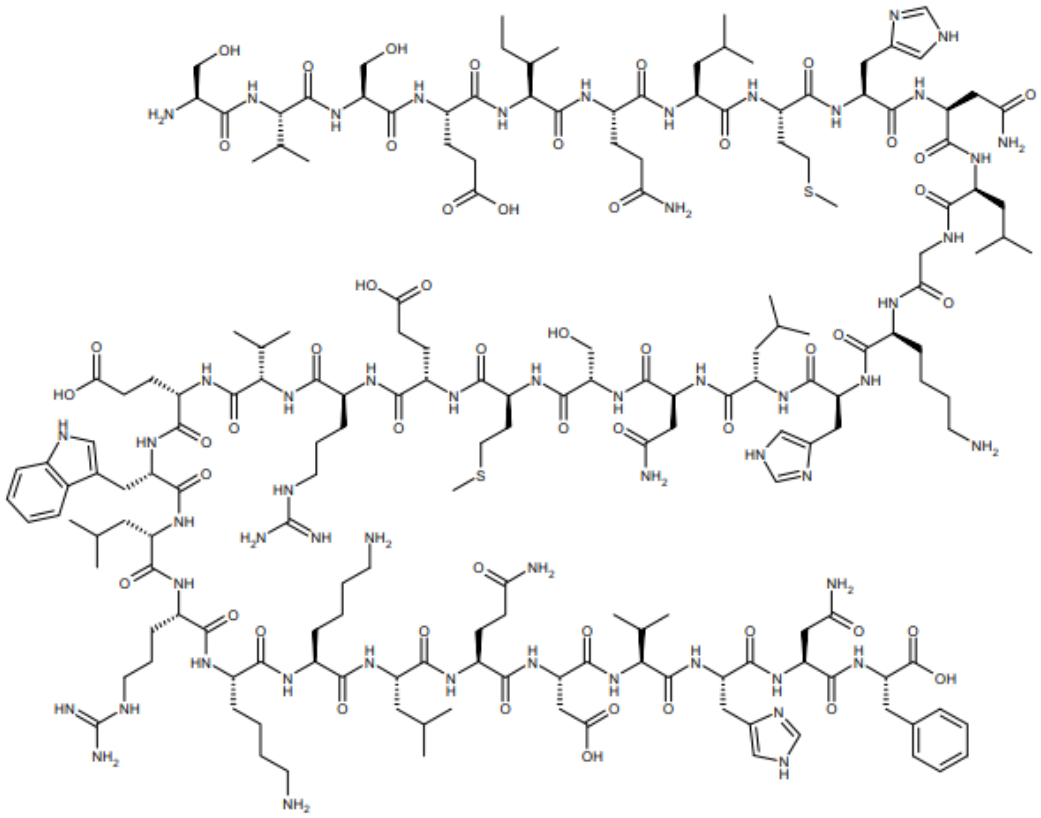


**Figure 1: active substance structure**

The active substance is a white or almost white, very hygroscopic powder. It is freely soluble in water and practically insoluble in acetonitrile or methanol

The primary chemical structure of teriparatide was elucidated by a combination of standard methods including IR spectroscopy, UV spectroscopy, NMR spectroscopy (both $^{1}H$ and $^{13}C$ NMR spectrum), Mass spectrometry with ionisation technique by electrospray (ESI+), and elemental analysis. The secondary and tertiary structure was confirmed by Peptide Mapping and Amino Acid Sequencing (AAS), *N*-Terminal amino acid sequence by Edman degradation using Protein sequencer, Circular Dichroism Spectroscopy, Intact Mass Analysis and Intrinsic Fluorescence. The biopotency of the active substance was analysed by *in-vitro* cell-based assay by tracking produced cyclic-AMP by cells exposed to teriparatide. The relative potency of teriparatide active substance was calculated by comparing the response with that of the reference product, Forsteo, using parallel line assay.

The solid state properties of the active substance were measured by X-Ray diffraction and FT-IR spectroscopy. Polymorphism has not been observed. Teriparatide manufactured by SUN is an amorphous peptide. The amorphous structure of teriparatide is confirmed by X-Ray diffraction and FT-IR spectroscopic techniques.

Teriparatide is a 34-amino acid peptide. All chiral amino acids are of L configuration. The chiral purity, tested by GC-MS with a limit of NMT 99%, is included into the specification of each protected amino acid (used as starting material) as "critical material attribute". This is used to control the carryover of the other isomer of the desired amino acid leading to the formation of incorrect enantiomers during manufacture of teriparatide.

#### *2.2.2.2. Manufacture, characterisation and process controls*

Detailed information on the manufacturing of the active substance was provided in the restricted part of the ASMF and it was considered satisfactory.

Teriparatide is synthesised by linear stepwise solid-phase peptide chemistry using well defined starting materials with acceptable specifications. In a stepwise manner, all amino acids are incorporated as active esters following that procedure. After the coupling of the last amino acid the complete protected sequence on the resin is obtained. A subsequent acidolitic treatment which cleaves the peptide-resin bond and removes the side-chain protecting groups, yields the final teriparatide crude that is purified followed by freeze drying to obtain Pure Teriparatide. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Discussion on genotoxic impurities has been provided. The active substance manufacturer has evaluated probable impurities with regards to their mutagenic or genotoxic potential. No structural alerts have been identified with regards to key protected amino acids. Nitrosamine impurities have been discussed, however their formation is improbable, since no sodium nitrate or other nitrosating agents are used in the synthesis.

The active substance is packaged in HDPE bottle containing the product in tared transparent poly bag and seal with fastener, which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

#### *2.2.2.3. Specification*

The active substance specification, shown in Table 1, includes tests for description, solubility (USP, BP, Ph. Eur., IP), identification (Peptide mapping), identification (RP-HPLC), identification (Mass spectrophotometry), amino acid content (Ph. Eur.), impurities with molecular mass higher than that of teriparatide (SEC), related substances (HPLC), acetic acid/acetate (RP-HPLC), content of dimethyl formamide and dimethyl acetamide (RP-HPLC), water (Ph. Eur.), assay (RP-HPLC), peptide content (RP-HPLC), clarity (spectrometric), colour index (spectrometric), residual solvents (HS-GC), content of trifluoroacetic acid and triethylamine (IC), bacterial endotoxins (Ph. Eur.), microbial purity (Ph. Eur.).

The active substance specification covers all required parameters, in line with requirements of ICH Q1A guideline and relevant European Pharmacopoeia monographs. Limits for assay and impurities are justified. A justification for the proposed specification has been provided and is acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (four commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

#### *2.2.2.4. Stability*

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term

conditions (-20°C±5°C) and for up to 6 months under accelerated conditions (5°C±3°C) according to the ICH guidelines were provided.

The following parameters were tested: description, identification by HPLC, limit-impurities with molecular mass higher than that of teriparatide, related substances, acetic acid/acetate, water content, assay by HPLC, peptide content, clarity, colour index, bacterial endotoxins and bioburden test. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. No clear trends in assay and impurities profile can be seen.

Results on stress conditions (alkaline hydrolysis, acidic hydrolysis, oxidative stress, UV light, temperature stress) on one batch were also provided. It is concluded that the active substance is sensitive to acid, basic and oxidative hydrolysis, thermal degradation and light. The main degradation product in acidic degradation is impurity A. The main basic degradation was reported as unknown impurity. The oxidative degradation peaks corresponded to impurity F and impurity G. The substance is degraded by heat at 80°C and the main degradation product is impurity A.

Photostability testing following the ICH guideline Q1B was performed on one batch. It was concluded that the active substance is sensitive to light and should be protected from light. The main impurities were impurity F and impurity G.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of two years when stored in tight, light resistant container and temperature of -25°C -15°C.

## 2.2.3. Finished medicinal product

### *2.2.3.1. Description of the product and Pharmaceutical development*

The finished product is presented as solution for injection in pre-filled pen containing teriparatide 20 micrograms/80 microliters as active substance. The full quantitative and qualitative composition was provided. It is a clear, colorless, sterile solution, free from visible particulate matter.

The finished product is supplied in a siliconised type 1 glass 3 ml cartridge with a bromobutyl rubber plunger stopper and disc seal/cap ((polyisoprene/bromobutyl rubber laminate)/aluminium). The cartridge is assembled into a single, integral pen device. The pen consists of body-subassembly with button and dose set knob, cartridge holder and cap. Needles are not supplied with the product. The product information (SmPC and package leaflet) clearly defines the needle gauge types to use with the finished product (i.e. insulin pen injection needles).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur or USP standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The applicant developed Teriparatide SUN finished product to be generic of the European reference medicinal product Forsteo 20 micrograms/80 microliters solution for injection in pre-filled pen. The formulation is therefore based on that of the reference product.

A Quality Target Product Profile (QTPP) was provided. The finished product quality attributes included in QTPP are based on analysis of several batches of Forsteo reference product. Critical quality attributes (CQAs) are clearly listed, and adequate justification is provided for criticality of each CQAs. The applicant identifies the CQAs to be tracked in risk assessment.

The active substance is described with regard to the physicochemical characterisation and risk assessment of active substance attributes on finished product CQAs. The outcome of the assessment and the accompanying justification is provided in the pharmaceutical development report. Results comprehensively justified that the impact of variability in excipients (quality and level) on finished product's CQAs are very unlikely. Compatibility of the active substance with the excipients has been demonstrated.A comparability study of Teriparatide SUN solution for injection in pre-filled pen and the reference product - Forsteo 20 micrograms/80 microliters solution for injection in pre-filled pen was performed. During the procedure a multidisciplinary (quality/non-clinical) major objection (MO) was raised relating to the biological activity, as the level of detail on the *in vitro* potency analytical method and the number of batches tested was considered not sufficient to substantiate the claim that the biological activity of Teriparatide SUN product is comparable with Forsteo product. Two MOs on quality aspects were also raised. The first quality MO was raised on the comparability studies in general with respect to the number of batches of test and reference product chosen, the descriptions and validity of analytical methods and the statistical approaches used. The second quality MO was raised addressing the comparability of purity profiles and differences observed between Teriparatide SUN and Forsteo products.

The first MO was resolved by the inclusion of additional batches in comparability studies and providing detailed information and validation data of the potency assay. The method validation for bioassay has been performed in line with the ICH Q2 (R1) guidelines. It can be concluded that relative potency for Sun's Teriparatide (synthetic) solution for injection in pre-filled pen and Forsteo are comparable. To address the two quality MOs, multiple different batches of the medicinal product Forsteo were used to provide robust comparability data in order to generate a representative quality profile. The statistical analysis and statistical tests used are justified and take account of the EMA Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017). In conclusion, the three MOs raised on comparability studies were adequately addressed by the provision of additional data and information about the test methods. The comparability studies are comprehensive and fully characterise differences between the two products. Presented results confirm the applicant's claim of comparability between the SUN product to Forsteo medicinal product. CHMP concluded that the physicochemical and biological differences between the products (e.g. differences in impurity profiles following forced degradation studies), don't adversely affect the efficacy and safety profile of the Teriparatide SUN finished product.

The use of meta-cresol preservative is justified in line with other approved teriparatide products and by antimicrobial effectiveness testing results. The applicant performs the test for antimicrobial efficacy according to Ph. Eur. 5.1.3. The preservative effectiveness was demonstrated in finished product samples (full scale commercial batches) where the preservative concentration is at or below its lower specification limit. In addition, one stability batch of the finished product was tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life. The preservative efficacy test was performed at the proposed special storage conditions (2-8°C). The efficacy of the antimicrobial preservative under simulated in-use finished product's conditions were established. Manufacturing process development data has been described in line with ICH Q8 guideline. The applicant properly justified the selected sterilisation method (sterile filtration). The primary packaging is a cartridge (siliconised glass) with a plunger (halobutyl rubber), disc seal (polyisoprene/bromobutyl rubber laminate)/aluminium assembled into a disposable pen. The packaging materials comply with Ph.Eur. and EC requirements. Extractables & leachables have been adequately investigated. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The results of container closure integrity testing (microbial ingress method) performed in accordance with Ph. Eur. methods on full scale commercial and available stability batches are presented. The result

of an in-use study support the compatibility between product and container / device. The applicant provided results of the in-use stability testing on additional two PPQ finished product batches at commercial scale. Microbial integrity and all functional parameters of the pen device (dose accuracy, glide force, break loose force) were confirmed to remain unaffected at the end of 28 days of daily use. Functionality studies (glide force, break loose force and dose accuracy) have been performed during development. It has been demonstrated that a reproducible and accurate dose of the product is delivered under testing conditions which simulate the use of the product under various environmental conditions.

#### *2.2.3.2. Manufacture of the product and process controls*

The manufacturing process consists of five main steps: thawing, mixing, sterile filtration, filling and automatic pen assembly. The process is considered to be a non-standard manufacturing process.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner, by a process validation study of 3 commercial scale (50 L) batches. Hold times and filling times have been defined and justified during process validation. Media fill studies demonstrate that sterility is maintained during the filling process.

A number of defects were noted during visual inspection, due to physical damage of fragile primary packaging, and tentative limits have been set during process validation. The applicant is recommended to update the dossier with acceptance criteria for number of individual rejections (visual inspection during finished product manufacturing process) once 10 commercial batches are available (REC1).Data on shipping validation of the finished product from the non-EU manufacturing site to the EU importation site was provided.

#### *2.2.3.3. Product specification*

The finished product specifications include appropriate tests for this kind of dosage form; description (visual), identification (HPLC, PDA-HPLC), pH (Ph. Eur.), osmolality (Ph. Eur.), extractable volume (Ph. Eur.), particulate contamination (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), assay-metacresol (HPLC), assay-teriparatide (HPLC), delivered dose accuracy (in house), related substances (USP, HPLC), pen device functionality tests (break-loose force, glide force) , and antimicrobial effectiveness testing.

The finished product is released on the market based on the above release specifications, through traditional final product release testing. The specification parameters and acceptance criteria are in line with ICH Q6A guideline and relevant Ph. Eur. monographs.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested during the review) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

As part of response to the questions on comparability studies and impurity profiles, additional batch data was provided (total: 6 batches). The applicant is recommended to provide batch analysis data from the next 10 commercial finished product batches when available (REC2). While the proposed limits for impurities are in line with Ph. Eur, and USP requirements and are considered acceptable, it was noted that batch data (release and stability) may support tighter limits. The applicant is recommended to revise finished product specification release and stability limits for impurities (both methods, any unspecified individual and total) once batch data for next 10 commercial finished product batches is available (REC3).

#### *2.2.3.4. Stability of the product*

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (2°C – 8°C) and for up to 6 months under accelerated conditions (25ºC / 60% RH) according to the ICH guidelines were provided. The batches of are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for according to the shelf-life specifications. The analytical procedures used are stability indicating. No significant changes have been observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based upon the results of photo-stability study, it is concluded that the selected primary pack and market pack of Teriparatide SUN provides adequate protection against light. However, being photo sensitive when exposed directly under photostability conditions as per ICH Guidelines Q1B, the product should be protected from light during manufacture, packaging and storage.

Based on available stability data, the proposed shelf-life of 2 years with the storage conditions (*Store in a refrigerator (2°C – 8°C) at all times. The pen should be returned to the refrigerator immediately after use. Do not freeze.*) as stated in the SmPC (section 6.3) are acceptable.

#### *2.2.3.5. Adventitious agents*

No excipients derived from animal or human origin have been used.

### 2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product Teriparatide SUN has been developed as a generic to the European reference medicinal product Forsteo 20 micrograms/80 microliters solution for injection in pre-filled pen. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The three MOs raised on comparability studies were adequately addressed by the provision of additional data and information about the test methods. The comparability studies are comprehensive and fully characterise differences between the test and reference products (e.g. differences in impurity profiles following forced degradation studies). CHMP concluded that the physicochemical and biological differences between the products do not adversely affect the efficacy and safety profile of the Teriparatide SUN finished product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit-risk balance of the product, these resulted in three recommendations to be addressed post-marketing (see list of recommendations below).

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to update the dossier with an acceptance criteria for number of individual rejections (visual inspection during finished product manufacturing process) once 10 commercial batches are available.
2. The applicant is recommended to provide batch analysis data from the next 10 finished product commercial batches once they are available.
3. The applicant is recommended to revise finished product specification release and stability limits for impurities (both methods, any unspecified individual and total) once batch data from the next 10 finished product commercial batches is available.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

## 2.3.2. Pharmacology

Teriparatide Sun is a synthetic form of parathyroid hormone (PTH). It has been developed as a hybrid to the reference product Forsteo (teriparatide; Eli Lilly Nederland BV), authorised in the EU.

The assessment of similarity of Teriparatide Sun is primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted.

No secondary pharmacology, PD drug-drug interaction or safety pharmacology studies have been performed. This is considered acceptable for a hybrid application.

## 2.3.3. Pharmacokinetics

Pharmacokinetics assessment was directly assessed in human. This is acceptable.

## 2.3.4. Toxicology

No single dose toxicity or repeat dose toxicity studies have been performed. No genotoxicity, reproductive toxicology or carcinogenicity studies have been performed. This is in line with the CHMP guidance for users of the centralised procedure for generics/hybrid applications (EMEA/CHMP/225411/2006) and is acceptable for a hybrid MAA. The proposed information in Section 5.3 of the SmPC is in line with that of the reference product.

## 2.3.5. Ecotoxicity/environmental risk assessment

In line with the "Guideline on the Environmental Risk Assessment for medicinal products for human use" (EMEA/CHMP/SWP/4447/00 Rev. 1), amino acid, peptides and proteins are unlikely to result in significant risk to the environment and no environmental risk assessment is required.

Contrary to the reference product, which is a single chain peptide and contains recombinant human parathyroid hormone which has an identical sequence to the 34 N-terminal amino acids of the 84-amino acid human parathyroid hormone, Teriparatide Sun is a synthetic form of PTH.

The applicant provided the calculation for Predicted Environmental Concentration (PEC, which is restricted to aquatic environment in Phase I) based on formula:

$$PEC_{Surfacewater} = \frac{\text{DOSEai} * \text{Fpen}}{\text{WASTEWinhab} * \text{DILUTION}}$$

Where, DOSEai = 20 mcg/inhabitant/day
The maximum dose of teriparatide solution for injection in pre-filled pen is considered as 20 mcg daily.
Fpen = 0.01 (Default value)
WASTEinhab = 200 L/inhabitant/day (Default value)
DILUTION = 10 (Default value)
PECsurface water = 0.02 x 0.01 / (200 x 10) = 0.0000001 mg/L = 0.0001 µg/L

As the PEC $_{\text{SURFACE WATER}}$ of 0.0001 µg/L for teriparatide is 100 times lower than the action limit of 0.01 µg/L, indicating no need to proceed to Phase II. It is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients and no further risk assessment is required.

## 2.3.6. Discussion on non-clinical aspects

The assessment of similarity of Teriparatide Sun is primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted.

No secondary pharmacology, PD drug-drug interaction or safety pharmacology studies have been performed. This is considered acceptable for a hybrid application.

## 2.3.7. Conclusion on the non-clinical aspects

Teriparatide Sun is considered approvable from a non-clinical point of view.

# *2.4. Clinical aspects*

## 2.4.1. Introduction

This is an application for teriparatide 20 mcg/80 microliters solution for injection in pre-filled pen (2.4 ml). To support the MAA the applicant conducted a bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of teriparatide based on published literature. The SmPC is in line with the SmPC of the reference product.

***GCP aspect***

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**Tabular overview of clinical studies**

To support the application, the applicant has submitted one bioequivalence study.

**Table 1: Tabular overview of study TER-15**

| Type of study | Study Identifier | Location of study report | Objective of the study | Study Design and Type of Control | Test Products(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| BE (Fast) | TER15 | Module 5, Section 5.3.1.2 | To assess the bioequivalence between Teriparatide (synthetic) solution for injection in prefilled pen, 20µg/80µl, Subcutaneous Injection of Sun Pharmaceutical Industries Limited and FORSTEO® (Teriparatide) solution for injection in pre-filled pen, 20 mcg/80 microliters, Subcutaneous Injection of Eli Lilly and to monitor the safety in healthy, adult, human subjects under fasting conditions. | A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study, under fasting condition | Teriparatide (synthetic) solution for injection in prefilled pen<br><br>20 mcg/80 microliters, Subcutaneous Injection | Enrolled: 36 and Completed : 35 | Healthy, adult, human male subjects | Single-Dose | Completed; Abbreviated |

## 2.4.2. Clinical pharmacology

### *2.4.2.1. Pharmacokinetics*

***Study TER-15: Single dose two-way crossover bioequivalence study on Teriparatide (Synthetic) solution for injection in pre-filled pen, 20 mcg/80 microliters in healthy adult human subjects under fasting condition.***

***Methods***

- **Study design**

A randomised, open label, two-treatment, two period, two sequence, single dose, crossover, bioequivalence study in 36 healthy adult human subjects under fasting condition was conducted.

- **Test and reference products**

TERIPARATIDE SUN 20µg/80µl manufactured by Sun Pharmaceutical Ind. Ltd, Halol (batch No. JKUEX0206A; exp. date 10/2021) has been compared to FORSTEO 20µg/80µl manufactured by Eli Lilly Itallia S.P.A (batch No: D096836H; exp. date 04/2021).

- **Population(s) studied**

Thirty-six (36) healthy, adult subjects were enrolled in the study. One subject dropped out from the study.

- **Analytical methods**

Method validation of Teriparatide in human plasma was carried out as per Method Validation MV_TPD_362. This method validation was performed on API 5500 (PKD/997) system.
*Analytical Method:* Ultra High Performance Liquid chromatography Tandem Mass Spectrometry (LC/MS/MS) with Positive & Negative MRM Mode, Biological Matrix – Human K2 EDTA plasma

*Extraction Technique*: Solid Phase Extraction

The pre-study validation of the analytical methods is satisfactory and demonstrated adequate precision and accuracy (both intra- and inter-run) within the calibration range 5.13pg/mL to 996.87pg/mL, and showed adequate selectivity, sensitivity, no matrix effect and no-carry-over effect.

The method was linear over the declared range with correlation coefficient ≥0.9900. Back-calculated calibration standard concentrations met the criteria of the Guideline on Bioanalytical Method Validation.

The results of intra-day inter-day accuracy and precision were acceptable demonstrating the reliability of the assay.

Selectivity of the bioanalytical method was evaluated using six (6) different sources of K2EDTA human plasma, two (2) lot of lipemic and two (2) lot of haemolysed human plasma. The selectivity test met SOP acceptance criteria.

Assessment of the matrix effect on Teriparatide determination (without concomitant and with concomitant drugs) was performed at two (2) QC levels with 10 sources of blank human plasma (6 lot of normal plasma, two (2) lot of lipemic and two (2) lot of haemolysed human plasma) as matrix factors and IS-normalised matrix factors. The mean IS-normalised matrix factors were 1.03228 (4.3%CV) and 1.00731 (1.2%CV) at low and high level, respectively (without concomitant) and 1.00183 (5.9%CV) and 1.01551 (1.9%CV) at low and high level, respectively (with concomitant

drugs). The precision for IS normalised matrix factor at LQC-A and HQC was found ≤ 15% in line with requirement of the Guideline on the Bioanalytical Method Validation.

The LLOQ of the bioanalytical method 5.13 pg/mL was below 1/20 of the Cmax (arithmetic means for Teriparatide: test 106.545 pg/mL, reference 108.076 pg/mL) and was adequate to detect any relevant carry-over effect between the treatment periods.

In addition, in July 2020, a partial method validation was performed on instrument of API series (PKD/757 & PKD/756) systems with different make LC and instrument model to quantify this analyte. This was presented in the partial method validation report No. PMV_TPD_362. The validation parameters included in the partial method validation are: accuracy and precision of the batches, selectivity, the matrix factor and injector carry over.

In the partial method validation, a higher LLOQ was determined 5.42 pg/mL, which is higher than 1/20 of the $C_{max}$. The arguments provided that the % difference between LLOQ used the partial validation method with respect to 5% of Cmax are 1.7% Higher [i.e. (5.42/5.33 X 100)-100] for the Test product and 0.3% Higher [i.e. (5.42/5.40 X 100)-100] for the Reference product and that are non-significant and have no impact on Study Samples Analysis if we evaluate the data for carry over are agreed. In addition, it is noted the Cmax was not observed in any subject at the first sample time point and pre-dose concentration has not been detected in any subject.

Only analytical runs from the first 11 subjects were analysed with the API 5500 (PKD/997) system used for the validation of the analytical method and rest of the analytical runs from the subjects included in study were analysed with the instrument of API series (PKD/757 & PKD/756) systems used in the partial validation.

The applicant clarified that both these instruments are of the same series API instrument i.e. API 5500 series (same make and model as that of Method Validation). Due to large sample size, higher analysis run time and to complete the study sample analysis on priority, two additional systems of same series, were used after performing the required partial method validation activities (PMV_TPD_362 as per SOP022172, Version 1.0, ”Partial Bioanalytical Method Validation”.

***Results***

The pharmacokinetic (PK) analysis population had 35 male subjects and included all subjects who completed the PK sampling for both treatment periods, who did not have any deviations that could affect the PK profile, and who had sufficient concentration data points to accurately estimate the PK profiles for both treatments. Groups were sufficiently balanced with regard to demographic and other baseline characteristics.

Arithmetic mean plasma concentration-time profiles and PK parameters of teriparatide were comparable between the 2 products investigated.

Analysis of Variance

A summary of results from the Analysis of Variance for $AUC_{0-t}$ , $AUC_{0-inf}$ and $C_{max}$ for Teriparatide are summarised in the table below.

**Table 2: Summary of results**

| SUMMARY OF RESULTS | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TERIPARATIDE (N = 35) | | | | | | | | |
| Pharmacokinetic Parameters | | | | | | | | |
| Parameters | Teriparatide (Synthetic) solution for injection in pre-filled pen, 20 mcg/80 microliters Test (T) | | | | Forsteo (Teriparatide) solution for injection in pre-filled pen, 20 mcg/80 microliters Reference (R) | | | |
| | Mean | ± | SD | CV% | Mean | ± | SD | CV% |
| $AUC_{0-t}$ (pg.h/mL) | 90.9647 | ± | 43.1873 | 47.48 | 90.0378 | ± | 42.9399 | 47.69 |
| $AUC_{0-inf}$ (pg.h/mL) | 96.9075 | ± | 42.5494 | 43.91 | 95.8201 | ± | 43.0253 | 44.90 |
| $C_{max}$ (pg/mL) | 106.545 | ± | 48.252 | 45.29 | 108.076 | ± | 61.866 | 57.24 |
| $T_{max}$ (h) | 0.2129 | ± | 0.1096 | 51.49 | 0.2509 | ± | 0.1339 | 53.38 |
| $T_{max}$* (h) | 0.167 (0.083 - 0.500) | - | - | - | 0.250 (0.083 - 0.667) | - | - | - |
| $K_{el}$ ($h^{-1}$) | 1.36551 | ± | 0.32189 | 23.57 | 1.46040 | ± | 0.49285 | 33.75 |
| $t_{1/2}$ (h) | 0.5421 | ± | 0.1603 | 29.57 | 0.5317 | ± | 0.1902 | 35.77 |
| % AUC Extrapolation | 7.466 | ± | 5.240 | 70.18 | 7.170 | ± | 4.096 | 57.13 |

The ratios of least squares means (LSM) of primary pharmacokinetic parameters observed in Test versus Reference formulation and their 90% CIs did not show significant differences in the rate and extent of absorption of Teriparatide between treatment groups.

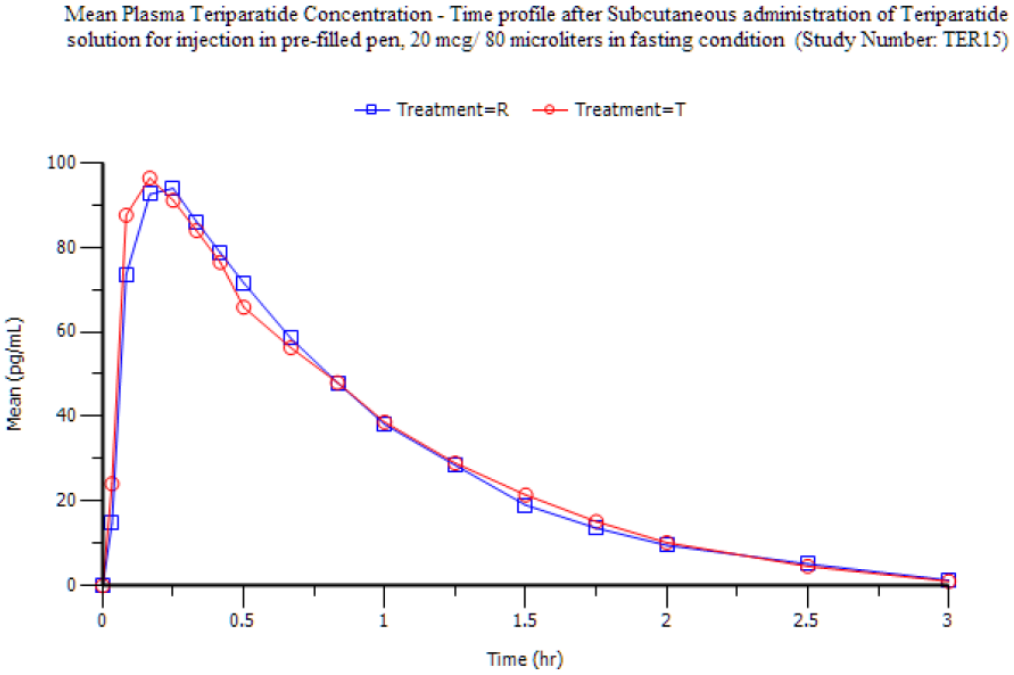
The point estimates of Test/Reference GMR (%) and their 90% CIs of the primary pharmacokinetic parameters were 102.87% (95.06% - 111.32%) for $AUC_{0-inf}$, 102.49% (94% - 111.74%) for $AUC_{0-t}$ and 101.74% (94.49% - 109.54%) for $C_{max}$ and were within EMA bioequivalence limits (80.00% - 125.00%). The intra-subject CV was 21.60% for $AUC_{0-t}$, 19.69% for $AUC_{0-inf}$ and 18.41% for $C_{max}$.

**Table 3: Summary of statistical analysis of teriparatide**

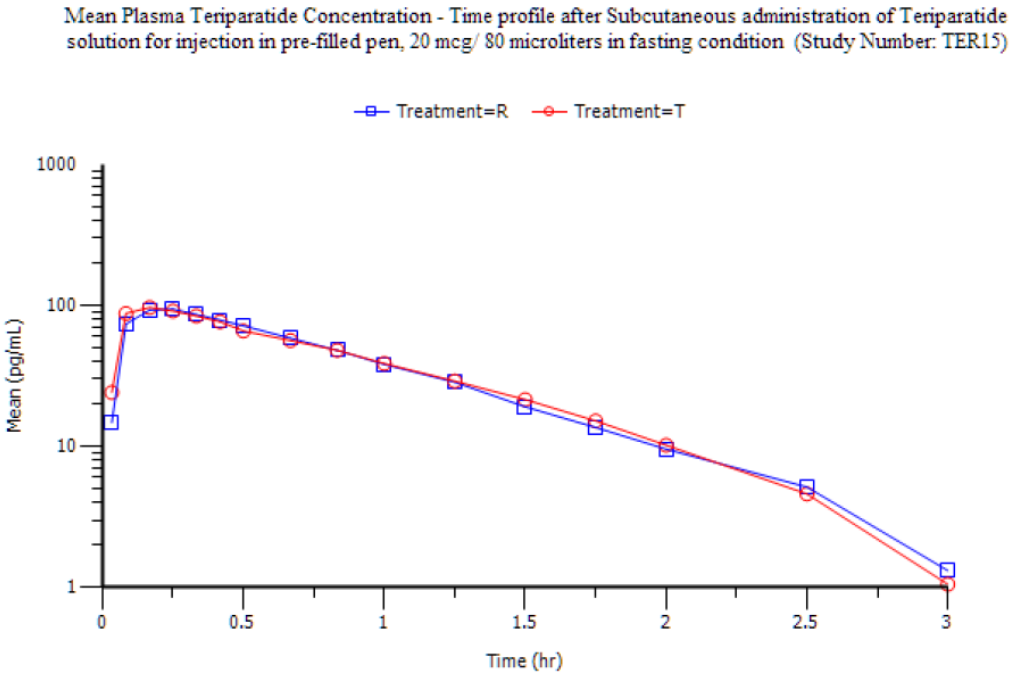
| SUMMARY OF STATISTICAL ANALYSIS OF TERIPARATIDE (N = 35) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ln- Transformed Data | | | | | | | |
| PK Variables | Least Squares Means | | Least Squares Geometric Means[3] | | Ratio of Least-Squares Geometric Means[1] % | 90% Geometric C.I.[2] | Intra-Subject CV % |
| | Test | Reference | Test | Reference | | | |
| $AUC_{0-t}$ | 4.41 | 4.38 | 82.02 | 80.03 | 102.49 | 94.00 to 111.74 | 21.60 |
| $AUC_{0-inf}$ | 4.49 | 4.46 | 88.80 | 86.32 | 102.87 | 95.06 to 111.32 | 19.69 |
| $C_{max}$ | 4.57 | 4.55 | 96.56 | 94.91 | 101.74 | 94.49 to 109.54 | 18.41 |

**Figure 2: Teriparatide mean plasma concentration – time profile**

Linear Plot of Mean Plasma Concentration-Time profile of Teriparatide (N = 35) :




Semi Logarithmic Plot of Mean Plasma Concentration-Time profile of Teriparatide (N = 35):



Teriparatide was rapidly absorbed following both test and reference product administration with a median $t_{max}$ of 10 minutes for Teriparatide Sun and 15 minutes for Forsteo.

**Table 4: Results of the primary PK parameters**

| | |
|---|---|
| **$AUC_{0-inf}$** | |
| Teriparatide Sun | 96.9075 |
| Forsteo | 95.8201 |
| 90% CI | [95.06-111.32] |
| GMR | 102.87% |
| | |
| **$AUC_{0-t}$** | |
| Teriparatide SUN | 90.9647 |
| Forsteo | 90.0378 |
| 90% CI | [94.00-111.74] |
| GMR | 102.49% |
| | |
| **$C_{max}$** | |
| Teriparatide SUN | 106.545 |
| Forsteo | 108.076 |
| 90% CI | [94.49-109.54] |
| GMR | 101.74% |

*Secondary endpoints:*

The mean T1/2 of the test product was 0.2129h (~13 minutes) and of the reference product was 0.2509 (~15 minutes). The numerical difference of ~2 minutes is considered as non-relevant.

From the above results of Teriparatide, it can be concluded that the AUC0-t, AUC0-inf and Cmax results were within the acceptable limits of 80.00% to 125.00% for concluding bioequivalence.

Hence the Test (T) and Reference (R) formulations can be declared as bioequivalent when administered under fasting condition.

#### *2.4.2.2. Pharmacodynamics*

No new pharmacodynamic studies were presented and no such studies are required for this application.

## 2.4.3. Clinical efficacy

In a large, well designed clinical trials, teriparatide was effective in reducing fracture risk, increasing BMD values (particularly at the lumbar spine) and increasing bone turnover marker levels in male idiopathic or hypogonadal osteoporosis, and in postmenopausal and glucocorticoid-induced osteoporosis. The applicant has not provided data from dedicated studies to inform on the efficacy of teriparatide. Information on the efficacy of teriparatide is based on the documentation of the reference medicinal product Forsteo. This is considered acceptable for a hybrid product provided that bioequivalence has been established.

## 2.4.4. Clinical safety

The safety profile of teriparatide is well characterised. Contraindications, warnings and precautions for use, undesirable effects as well as use in special populations are sufficiently described for Forsteo. The therapeutic indications, posology and route of administration proposed for Teriparatide Sun are

identical to those for Forsteo, to which similarity is claimed by the applicant. Safety information of teriparatide are primarily based on the documentation of the reference medicinal product Forsteo.

Data from the only pivotal PK study TER15 are presented in the applicant's safety analysis. This study investigated the PK similarity, safety, and tolerability of Teriparatide Sun and reference medicinal product, Forsteo following a single dose of teriparatide (20 micrograms).

In the pivotal study safety was evaluated by vital signs measurement, adverse event monitoring, serum calcium test (prior to period I admission), injection site monitoring, visual analogue scale, clinical laboratory tests biochemistry (AST, ALT, BUN, Creatinine), urinalysis and haematology at end of study (for the subjects who were dosed at least once with the investigational products), physical examinations and adverse events reported during the conduct of study.

The applicant has not provided data from dedicated clinical studies to inform on the efficacy and safety of teriparatide. In general this is considered acceptable for a hybrid product.

- **Patient exposure**

The Safety Population included all subjects who received the study drug, i.e. test and/or reference product.

All 36 subjects enrolled in the study were randomised and 35 subjects completed the study.

The Safety Population included 36 subjects and they were all subjects who received the study drug, i.e. test and/or reference product.

**Table 5: patient exposure**

| Periods | No. of subjects who received test (T) Product | No. of subjects who received reference (R) Product |
|---|---|---|
| I | 18 | 18 |
| II | 18 | 17 |

- **Adverse events**

There were only four AEs reported in 3 subjects. All adverse events were experienced by the subjects after administration of the Reference product. Out of 4 AE, 3 were laboratory findings. The adverse events were mild to moderate in severity. 2 of the AE were considered possibly related to the treatment (urticaria rash at both hands and low haemoglobin) and 2 were considered unlikely related (low lymphocytes and urine glucose present).

No new or unexpected findings were identified during the study. The available data do not indicate important differences in the safety profiles between test and reference products, however, it should be noted that the study was open-label. Moreover, interpretation of data is limited due to the single treatment and limited number of subjects exposed.

**Table 6: Adverse events**

| Treatment (T & R) | No. of events associated with the respective treatment | Adverse events/Medical event |
|---|---|---|
| R | 1 | Urticarial Rash at both hands |
| | 1 | Low Hemoglobin |
| | 1 | Low Lymphocytes |
| | 1 | Urine Glucose Present |

- **Serious adverse events and deaths**

No serious adverse event or deaths were reported during the conduct of this study.

- **Laboratory findings**

There were no serious laboratory findings identified during the study.

- **Safety in special populations**

N/A

- **Immunological events**

No antibody measurement has been included in the pivotal trial. However, since Teriparatide SUN has been shown to be comparable to EU reference product Forsteo with respect to formulation, pharmaceutical equivalence, structural characterisation, purity profile, and potency, differences in immunogenicity should not be expected.

- **Safety related to drug-drug interactions and other interactions**

N/A

- **Discontinuation due to AES**

One subjects did not complete the study. The reason was: Not Contactable.

## 2.4.5. Discussion on clinical aspects

One pivotal PK study was provided, Study TER 15, which was designed as an open label, randomised, two-treatment, two-sequence, two-period, crossover study with the primary objective to assess the bioequivalence of proposed Teriparatide Sun (test product), for subcutaneous injection after single dose administration of 20 µg versus FORSTEO (reference product) 20 µg in healthy male subjects under fasting conditions. The number of subjects was 28 planned, 36 enrolled and 35 analysed for PK endpoints.

The design including the chosen reference product and a wash-out period of 4 days and the chosen study population are considered acceptable. Groups were sufficiently balanced with regard to demographic and other baseline characteristics.

The study objectives and the chosen endpoints are in general adequate for the assessment of bioequivalence between test and reference product. The method used for the determination of

teriparatide in human $K_2$EDTA plasma was ultra-high performance liquid chromatographic method tandem mass spectrometric detection. The applicant has provided an adequate method description protocol/study plan detailing preparation of all samples and calibration curves and acceptance criteria. In general, the method has been performed and validated in line with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009/Rev. 1). The acceptance criteria to determine validity of routine assay runs are in line with the aforementioned guideline.

The ratios of the least-squares geometric means (90% geometric confidence intervals) of the Test to Reference product were 102.49% (94.00 to 111.74) for AUC0-t, 102.87% (95.06 to 111.32) for AUC0-inf and 101.74% (94.49 to 109.54) for Cmax. Secondary endpoints: The mean T1/2 of the test product was 0.2129h (~13 minutes) and of the reference product was 0.2509 (~15 minutes). The numerical difference of ~2 minutes is considered as non-relevant.

Since 90% CIs of $AUC_{0\text{-}inf}$, $C_{max}$ and $AUC_{0\text{-}t}$ were in pre-defined limits of 80%-125% it is agreed that PK similarity of Teriparatide Sun and Forsteo has been shown.

No primary pharmacology studies have been conducted by the applicant. Moreover, no pharmacodynamic parameters related to serum calcium levels were evaluated in Study TER-15, which is acceptable.

The applicant did not perform a Human Factor Study to test the usability of Sun Pharma's proposed drug device combination product; instead, a comparative usability/task analysis was performed. The rationale provided by the applicant is considered acceptable.

The "Guideline on the clinical investigation of the pharmacokinetics of the therapeutic proteins (CHMP/EWP/89249/2004)", recommends that the relationship between drug concentration and pharmacodynamic response (PK/PD) should be evaluated. The applicant performed PK/PD modelling and simulation exercise based on the literature data and results obtained from the BE study, which showed that the predicted serum calcium levels following single subcutaneous injection of synthetic Teriparatide (Test formulation) and Forsteo (Reference formulation) formulations of Teriparatide are comparable.

Sun's Teriparatide (synthetic) solution for injection in pre-filled pen shows similarities with EU reference product Forsteo with respect to all aspects considering formulation, pharmaceutical equivalence, analytical, structural and functional characterisation, purity profile and potency. Thus, Teriparatide SUN is assumed to have similar immunogenicity as the EU reference product Forsteo.

The applicant has not conducted any dedicated efficacy/safety study with teriparatide. Data regarding safety are mainly based on the documentation of the reference medicinal product Forsteo and literature references. In addition safety data from the open-label, pivotal single-dose PK study has been provided. In general this is considered acceptable for a hybrid product. However, interpretation of available data is limited due to the open-label design, single treatment and limited number of subjects exposed. Nevertheless, no new or unexpected findings were identified during the study. Both treatments were well tolerated. There were only four AEs reported in 3 subjects. All adverse events were mild or moderate and all were experienced by the subjects exposed to the reference product.

Out of 4 AE, 3 were laboratory findings. The adverse events were mild to moderate in severity. 2 of the AE were considered possibly related to the treatment (urticaria rash at both hands and low haemoglobin) and 2 were considered unlikely related (low lymphocytes and urine glucose present).

No new or unexpected findings were identified during the study.

The available data do not indicate differences in the safety profiles between test and reference products.

Since Teriparatide SUN has been shown to be comparable to the EU reference product Forsteo with respect to formulation, pharmaceutical equivalence, structural characterisation, purity profile, and potency, differences in immunogenicity should not be expected.

### 2.4.6. Conclusions on clinical aspects

Based on the provided bioequivalence study Teriparatide Sun is considered bioequivalent with Forsteo.

## *2.5. Risk Management Plan*

### 2.5.1. Safety concerns

None.

### 2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

### 2.5.3. Risk minimisation measures

None.

### 2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 01 is acceptable.

## *2.6. Pharmacovigilance*

### 2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.6.2. Periodic Safety Update Reports submission requirements

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.

## *2.7. Product information*

### 2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on

the readability of the label and package leaflet of medicinal products for human use.

# 3. Benefit-risk balance

## *3.1. Bioequivalence assessment - comparability exercise and indications claimed*

Teriparatide Sun was developed as a hybrid product to Forsteo, containing 20µg/80µL of recombinantly produced teriparatide. Teriparatide drug product is presented as a clear, colourless solution free from particulate matter, filled in plunger stopped glass cartridge assembled in pen injector, which is having white coloured cap, green coloured body cover and black covered injection button.

Each pen contains 2.4 mL of solution (250 micrograms per mL) enough for 28 doses to be administered subcutaneously.

The therapeutic indications, posology, and route of administration proposed for Teriparatide SUN are identical to those for Forsteo. Forsteo is currently authorised for the following therapeutic indications in the EU:

- 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 has been demonstrated.
- Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

The recommended dose of Forsteo is 20 micrograms administered once daily, the maximum total duration of treatment should be 24 months, and the 24-month course should not be repeated over a patient's lifetime. Patients should receive supplemental calcium and vitamin D supplements if dietary intake is inadequate.

The applicant performed an analytical comparability study to evaluate quality differences of Teriparatide Sun and Forsteo on the quality level.

For confirmation of the clinical similarity data from a pivotal 2-way comparative PK study between Teriparatide SUN and the EU reference product Forsteo have been provided.

A comparability quality exercise has been performed between Teriparatide Sun six drug product batches, six EU Forsteo batches.

## *3.2. Results supporting bioequivalence*

A panel of standard and state-of-the-art analytical methods is presented for assessment of comparability and overall the proposed analytical comparability strategy seems suitable to fully investigate differences between the proposed Teriparatide SUN product and EU-approved Forsteo. Relevant physico-chemical and biological quality attributes are included. The provided results confirm the applicant's claim of comparability between Teriparatide SUN and Forsteo. The applicant justified that the observed minor differences between both products do not have any impact on the safety and efficacy of Teriparatide SUN.

Since 90% CIs of $AUC_{0\text{-}inf}$, $C_{max}$ and $AUC_{0\text{-}t}$ were in pre-defined limits of 80%-125% it is agreed that PK similarity of Teriparatide Sun and Forsteo has been shown.

## 3.3. Uncertainties and limitations about bioequivalence

From the quality point of view comparability is demonstrated.

There are no identified uncertainties and limitations from the non-clinical and clinical perspective.

## 3.4. Discussion on bioequivalence

The analytical comparability exercises conducted to investigate differences between Teriparatide SUN and the EU-sourced product Forsteo are comprehensive and sufficient in order to fully characterise differences between the products. Differences that were found between Teriparatide SUN and the Forsteo in HPLC analysis were discussed and justified. Presented results allow for a firm conclusion that the physicochemical and biological differences between the products do not adversely affect the efficacy and safety profile of Teriparatide SUN. The claimed analytical comparability between Teriparatide SUN and the product Forsteo has been demonstrated.

## 3.5. Extrapolation of safety and efficacy

Since bioequivalence for Teriparatide SUN to the reference product Forsteo can be considered established, extrapolation of safety and efficacy is acceptable.

## 3.6. Additional considerations

N/A

## 3.7. Conclusions on bioequivalence and benefit risk balance

This application concerns a hybrid version of teriparatide, solution for injection 20µg/80µl. The reference product Forsteo is indicated in adults for the 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 has been demonstrated.

Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance, and the applicant's clinical overview on these aspects based on information from published literature was considered sufficient.

The bioequivalence study TER 15 forms the pivotal bases and was an open label, randomised, two-treatment, two-sequence, two-period, crossover study to compare the pharmacokinetics, tolerability and safety after a single dose administration of both Test and Reference formulations of Teriparatide in 36 healthy male volunteers under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The cross over design was chosen to evaluate PK comparability of Teriparatide SUN and Forsteo, and is considered acceptable.

Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Teriparatide Sun met the protocol-defined criteria for bioequivalence when compared with Forsteo. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A bridge was established between the data for the test formulation and the data for the reference formulation based by means of studies (e.g. bioavailability, pharmacokinetic or clinical studies) and/or through a scientific rationale/justification.

Based on the review of the submitted data, comparability of Teriparatide SUN to reference product Forsteo has been concluded. A positive benefit/risk ratio comparable to the reference product can therefore be concluded.

# 4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Teriparatide SUN is favourable in the following indication:

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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to medical prescription.

***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.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.