



PUBLIC ASSESSMENT REPORT

Decentralised Procedure

**Teriparatid-ratiopharm 20 µg / 80ml,
Solution for injection**

Procedure Number

DE/H/4291/01/DC

DE/H/4292/01/DC

Active Substance

Teriparatide

Marketing Authorisation Holder:

Teva B.V. / Teva Generics

Revision: 08.05.2017

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Teriparatid-ratiopharm 20 µg / 80ml; Teriparatid-ratiopharm 20 µg / 80ml
Name of the drug substance (INN name):	Teriparatide
Pharmaco-therapeutic group (ATC Code):	H05AA02
Pharmaceutical form(s) and strength(s):	Solution for injection
Reference Number(s) for the Decentralised Procedure	DE/H/4291/01/DC ; DE/H/4292/01/DC
Reference Member State:	DE
Member States concerned:	DE/H/4291/01/DC: AT; CY; DK; EL; ES; FR; HR; HU; IE; IT; MT; NL; PT; SE; SI and UK DE/H/4292/01/DC: ES
Marketing Authorisation Holder	Teva B.V. (Teva Generics) Swensweg 5 NL-2031 GA HAARLEM

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety, and efficacy, the RMS considers that the application for Teriparatid-ratiopharm 20 µg / 80ml in the treatment of osteoporosis, is approvable

II. EXECUTIVE SUMMARY

II.1 Problem statement

The applicant has submitted a marketing authorisation application for Teriparatid-ratiopharm 20 mikrogramms / 80 microliters solution for injection. The legal basis for this decentralised procedure is Article 10(3) Hybrid Application. The reference product is Forsteo 20 µg / 80 microliters solution for injection in pre-filled pen authorised via the centralised procedure in 2003. It should be noted that the active substance teriparatide in the reference product is a biological product of recombinant origin whereas the active substance in the applicant's drug product is chemically synthesised.

II.2 About the product

Teriparatide 20 µg / 80 microlitres solution for injection is a clear, colorless solution, free from visible particles, packaged in a glass cartridge (2.4 ml nominal fill volume in 3 ml cartridge) closed with a plunger at one end and with a rubber disc and aluminum cap (combiseal) at the other end. The filled cartridge is assembled into a pen injector intended for multiple injections.

Mode of action

Teriparatide Teva contains synthetic human parathyroid hormone (1-34), which contains the biologically active region of the 84-amino acid parathyroid hormone. The amino terminus is critical for G-protein linked stimulation of adenylate cyclase that catalyses the formation of second messengers such as cyclic adenosine monophosphate (cAMP) that activated the desired biological effects by phosphorylation of critical intracellular proteins. Once-daily administration increases apposition of new bone on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity thus increasing bone density.

Claimed indication and recommendation for use

The proposed indications for Teriparatide Teva 20 µg / 80 microliters solution for injection in pre-filled pen are:

Teriparatide–Teva is indicated in adults.

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non- vertebral fractures but not hip fractures 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 proposed Posology is:

The recommended dose of Teriparatide Teva is 20 µg administered once daily.

The maximum total duration of treatment with Teriparatide Teva should be 24 months (see section 4.4). The 24-month course of Teriparatide Teva 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 Teva therapy, patients may be continued on other osteoporosis therapies.

The proposed indications and posology are consistent with the indications for the reference product Forsteo.

II.3 General comments on the submitted dossier

The clinical overview is in general adequate in its discussion of the efficacy, safety, pharmacokinetics, and pharmacodynamics of teriparatide, and with regards to the review of available literature.

The SPC and PL for the proposed product are in line with the reference product.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites .

A QP declaration from the drug product manufacturer for the ASMF holder is provided in Module 1.

The applicant states that the bioequivalence study submitted in support of this application was performed in compliance with Good Clinical Practice (GCP) and in accordance with ethical standards of clinical studies in humans.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Teriparatide the drug substance of the drug product applied for in this application is a synthetic peptide which consists of 34 natural amino acids. The amino acid sequence is: H-Ser-Val-Ser-Glu-Ile5-Gln-Leu-Met-His-Asn10-Leu-Gly-Lys-His-Leu15-Asn-Ser-Met-Glu-Arg20-Val-Glu-Trp-Leu-Arg25-Lys-Lys-Leu-Gln-Asp30-Val-His-Asn-Phe-OH. The drug substance is an acetate salt in the form of a lyophilized powder. The ASMF procedure is used.

Manufacture

The drug substance is synthesized according to the general solid-phase peptide synthesis (SPPS) process. The peptide is assembled from the C-terminal to the N-terminal. The peptide is assembled onto resin. Deblocking, coupling, and acetylation reactions are repeated with the appropriate amino acid derivative in the desired sequence to result in the crude protected peptide attached to the resin support. The crude peptide is cleaved from the resin support and the side chain protecting groups removed . The crude peptide is purified and isolated . The purified drug substance is appropriately labelled and packaged in amber glass bottles. A detailed description of the manufacturing process is provided in the restricted part of the ASMF.

Characterisation

The drug substance has been sufficiently characterised by state of the art techniques . The sequence of the peptide with 34 amino acids has been confirmed. Information on the three-dimensional structure of the drug substance has been provided.

The impurity profile of the drug substance has been adequately described. Stress testing has been performed and the resulting impurities have been characterised . Process-related impurities, elemental impurities and genotoxic impurities have been adequately addressed. The requirements for synthetic peptides described in the Ph. Eur. monograph ‘Substances for pharmaceutical use’ concerning the identification and qualification of impurities are fulfilled.

Control of Active Substance

The drug substance specification contains the relevant attributes for a synthetic peptide . The proposed acceptance criteria and limits are acceptable.

All analytical methods have been sufficiently described. The analytical methods have been validated according to the requirements described in ICH Q2. Validation data have been provided and the methods are suitable for their intended use. Batch analysis data for three batches have been provided. All batch analysis data are within the proposed specifications. A justification for each attribute of the specification has been provided.

Reference Standards and Container Closure System

Sufficient information on the primary reference standard and the container closure system has been provided. Information on working standards and their qualification has been provided.

Stability

Stability studies have been performed with three GMP batches and a re-test period has been set.

Drug Product

Teriparatide 20 µg / 80 microlitres solution for injection is a clear, colorless solution, free from visible particles, packaged in a glass cartridge (2.4 ml nominal fill volume in 3 ml cartridge) closed with a plunger at one end and with a rubber disc and aluminum cap (combiseal) at the other end. The filled cartridge is assembled into a pen injector (fixed combination).

Pharmaceutical Development

The aim of the pharmaceutical development was to develop a formulation being essentially similar to the reference product Forsteo®. The antimicrobial preservative was confirmed to be satisfactorily effective (requirement according to Ph. Eur. were met).

Forsteo® is a biological product derived from *E.coli* whereas the teriparatide drug substance for Teva’s teriparatide is manufactured synthetically. Thus, both drug substances are expected to have a different impurity profile based on the different manufacturing processes. Therefore, the Applicant performed a characterisation study of the synthetic teriparatide and an analytical comparability study with teriparatide Teva solution for injection and Forsteo®. The respective data were provided in the dossier section P.2 Pharmaceutical Development.

Characterisation of Teriparatide

Identity of teriparatide drug substance was confirmed. Purity of the drug substance has been addressed by orthogonal state-of-the-art analytical methods. From the data provided, it can be concluded that overall, the drug substance is highly pure. Potency was measured against the WHO reference standard purchased from NIBSC using a validated bioassay.

Comparability to Forsteo®

In addition to the drug substance characterisation data, the Applicant provided comparative analytical data of Forsteo® and Teriparatide Teva drug products to substantiate comparability of both. The data provided support the comparability of the test and the reference product.

Container Closure System

The selected container closure materials are overall considered appropriate.

Manufacturing Process

The drug product manufacturing process is a straightforward fill finish process comprising the compounding of the drug product solution, sterile filtration and filling into the cartridges. The cartridges are then assembled into the secondary packaging, i.e. the single-use pen.

Overall, the manufacturing process has been described in satisfactory detail. Process validation data have been provided substantiating that the process produces drug product of consistent quality. Batch analyses of the validation batches are included in the validation report. All acceptance criteria were met.

Hold time studies were performed addressing physicochemical and microbiological stability of the bulk solution.

The Applicant investigated comprehensively the suitability of the sterile filtration systems.

Control of Drug Product

The drug product specifications cover the attributes relevant for teriparatide solution for injection.

The Applicant provided satisfactorily detailed method description of the analytical methods for release. Overall, the analytical methods were appropriately validated and it was demonstrated that the methods are suitable for their intended use.

Reference Standards

A teriparatide in-house working standard, supplied by Teva Pharmaceutical Industries Ltd. was used as the reference standard. The Certificate of analysis and the characterisation information of this standard are provided

The Certificates of analysis of working standards are provided.

Acceptance criteria and analytical methods used for qualification of the reference materials have been provided.

Container Closure

Specifications of the packaging materials being in contact with the medicinal product have been given. Certificates of Analysis from the packaging material suppliers demonstrate that the container materials are in compliance with the respective Ph. Eur. monographs for the materials and the containers. Compatibility of the materials with the drug product solution has been demonstrated during pharmaceutical development. The components of the pen injector are well described in the dossier. Technical drawings are provided in the CoA of the respective components

Stability

The stability protocol complies with ICH requirements. Not all of the specified parameters are tested at each time-point of the stability studies. As requested the detailed schedule for non-routine-tests during the stability testing has been provided and is considered acceptable.

Based on the data provided, the Applicant claims a shelf-life of 18 month at 2-8 °C which is considered acceptable.

Photostability studies were performed proving that the pen is able to protect the drug product solution adequately from light. In-use stability data support physicochemical stability of the solution after first opening for 28 days if stored at 2-8 °C. The product was sterile 28 days after first opening. The in-use conditions are overall adequately reflected in the SmPC. From the data provided in the photostability report it is concluded that the pen cap is needed to protect the drug product adequately from light. This is reflected in the SmPC by stating that the cap has to be closed after use.

A satisfactory post-approval stability commitment has been provided.

Descriptions of the pen-specific tests performed for stability testing are provided. These comply with the requirements as outlined in the relevant EN ISO regulations. The device testing during stability studies is considered appropriate for this fixed combination of drug and medical device.

III.2 Non-clinical aspects

The Application procedure refers to Article 10(3) hybrid application. In line with this type of procedure the Applicant submitted initially bibliographical data plus results from in-vitro experiments aimed at demonstrating the similarity between synthetically derived Teriparatide Teva and biotechnology derived Forsteo [EU]. During the course of the application procedure, the Applicant submitted results of an in-vivo comparability study in rats.

Pharmacology, pharmacokinetics and toxicology data have been derived from literature available up to mid-2015.

Pharmacodynamic, pharmacokinetic and toxicological properties of teriparatide are well known. As teriparatide is a widely used, well-known active substance, apart from the comparability studies, the Applicant has not provided additional studies. An Overview based mainly on literature review is, thus, appropriate.

Pharmacology

Primary Pharmacodynamics

Similarity Assessment in Cell-Based Functional Assays

A study was undertaken to assess the similarity between lots of Teva Teriparatide drug product (DP) and EU (Forsteo) Reference in two cell based assays, a cAMP Potency Assay and a PTH Receptor Internalization Bioassay. Test samples were run against the WHO teriparatide reference standard in every assay plate. Results from each plate are reported as relative potency.

The cAMP Potency Bioassay is validated. The relative potencies of all lots of Teva Teriparatide tested in the cAMP Potency Bioassay are within the ranges of relative potencies for Forsteo.

The PTH Receptor Internalization Bioassay had undergone performance assessment for precision, accuracy and specificity, among other parameters, demonstrating its suitability for use as a characterization assay. The median values for both products in this PTH Receptor Internalization Bioassay are very close to each other, the mean values differ slightly more.

Similarity Assessment in an in-vivo study in rats

In addition to initially requested documents regarding the cell-based functional assays, the Applicant submitted data of an in-vivo study with intravenous application in thyroparathyroidectomized rats on thyroid hormone therapy. The objective of this GLP conform study was to evaluate the pharmacological effect (calcium mobilization) in the rats compared to the European reference product. A pharmacokinetic evaluation was performed in addition.

Teva Teriparatide was noted to provide slightly greater pharmacological response than Forsteo with statistical significance for a few data points.

As the teriparatide plasma levels of Teva Teriparatide were slightly higher than those determined for Forsteo, it is concluded that the slight differences in the pharmacological response parallel the slight differences in teriparatide plasma levels.

Although the amount of data points obtained in the PTH Receptor Internalization Bioassay is limited and although the data points obtained do not match perfectly for Forsteo on the one hand side and Teriparatide Teva on the other hand side, and although the in-vivo calcium mobilization assay in rats showed slightly higher biological activity of Teva Teriparatide compared to the European Reference product, which is considered likely due to slightly higher plasma levels of Teva Teriparatide, taking into account the complete data set for both products including the results of the cAMP Potency Bioassay, the biological activity of both products is considered to be similar.

The formulation of Teriparatide Teva is similar to that of Forsteo and no toxicological concerns are raised regarding the excipients used in Teriparatide Teva.

No toxicological concerns are raised regarding impurities identified in Teriparatide Teva.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)

Although this is a Hybrid Application according to Article 10(3), since Teriparatide Teva is intended for generic-type substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary. Furthermore, as indicated in the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use peptides are due to their nature unlikely to result in a significant risk to the environment.

III.3 Clinical aspects

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

Pharmacokinetics and pharmacodynamics of teriparatide are well-characterised. The clinical overview is comprehensive and well written. It is therefore acceptable.

Pharmacokinetics

Distribution

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

Biotransformation

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.

Bioequivalence study

To support the application, the applicant has submitted one bioequivalence study (11336032): A Study to Evaluate the Relative Bioavailability of a Test Formulation of Teriparatide injection, 0.6 mg/2.4 mL (Teva) Compared to FORTEO® (teriparatide [rDNA origin] injection), 0.6 mg/2.4 mL (Lilly) and FORSTEO® (teriparatide [rDNA origin] injection), 0.6 mg/2.4 mL (Lilly) in Healthy Adult Subjects.

In this study Teva's teriparatide has been compared with Forsteo (EU product) and Forteo (US product). In this Assessment Report only the comparison with the EU product is considered. This procedure is acceptable. A statement on the application of appropriate GCP standards has been provided.

Methods

Study design

The study was conducted as Open-Label, Single-Dose, Randomized, Three-Treatment, Three-Period, Six-Sequence, Crossover Study; to compare bioavailability of the proposed Teriparatide Teva (A) with that of the reference product Forsteo (rDNA origin (C); Lilly Limited), in 72 healthy volunteers under fasting conditions. – The treatment group B received Forteo (teriparatide[rDNA origin] injection), 0.6mg/2.4 mL; Multi-dose prefilled delivery device (pen). This product is marketed in the US; the results from this group are not discussed in this Assessment Report.

The study was conducted by and at Novum Pharmaceutical Research Service, Huston, USA. The protocol and informed consent forms were approved by an institutional review board. The clinical part of the study was conducted between Period I: 4.2.2015, Period II: 7.2.2015, Period III: 10.2.2015.

The study report states that the study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Treatments were administered according to a three-treatment, three-period, six-sequence randomization schedule. The randomization was generated in blocks of six with each sequence occurring once in each block.

Sequence	Period I	Period II	Period III
1	A	B	C
2	B	A	C
3	C	A	B
4	A	C	B
5	B	C	A
6	C	B	A

Subjects fasted overnight for at least 10 hours before drug administration. A single dose of the assigned formulation was administered subcutaneously starting at 07:00.

Within 1 hour before dosing, each pen injector was weighed and the resulting weight recorded as the pre-dose weight. After dosing, it was re-weighed and the weight recorded as the post-dose weight. When the injected volume differed by than 10% the subject was excluded from that period and no blood samples were taken.

Blood samples were collected prior to and 2; 5; 10; 15; 20; 25; 30; 45 min and at 1; 1.25; 1.5; 2; 2.5; 3; 4 and 5 hours after each drug administration.

The study design is acceptable.

The maximum observed plasma concentrations of teriparatide, after subcutaneous administration, are normally seen within 0.5 to 2 hours (median 1 hour). The sampling scheme chosen is adequate around the period of C_{max} , to determine a reliable estimate of peak exposure.

The terminal half-life of teriparatide is generally in the range of 1 hour. The chosen washout period of 3 days is therefore considered adequate to allow elimination of the drug and to avoid any carry-over effects.

The period of sample collection (last sample at 5 hours) is adequate.

There was a high number of run failures that needed thorough explanation. A justification of the pertinent validation report was requested to ensure that all relevant validation parameters are in line with the ICH requirements for bioanalytical validation.

The reasons for the run failures have been satisfactorily explained in the applicant's response to the LoQ. The requested reports have been provided.

Test and reference products

The test product Teriparatid-ratiopharm 20 µg / 80ml, solution for injection ; has been compared to Forsteo ® teriparatide (rDNA origin) injection 20 mcg/0.08 mL (Lilly France S.A.S.),.

The chosen reference product is sourced from the EU and appropriate.

The batch size of the batch used in the bioequivalence study is 1/10th of the anticipated commercial batch size. This is acceptable and as per the guidelines.

Population studied

A total of 72 healthy subjects were enrolled. According to the study report, there were 5 dropouts.

The population chosen is according to guidelines. Protocol deviations/violations have been sufficiently described in the study report.

Pharmacokinetic Variables

The pharmacokinetic parameters of this trial were C_{max} , T_{max} , AUC_T , AUC_{∞} , $AUC_{T/\infty}$, Kel and $T_{1/2el}$.

Pharmacokinetic variables chosen for assessment are adequate.

Statistical methods

The permitted reasons for exclusion have been pre-specified in the protocol. The trapezoidal rule was used to estimate area under the curve, and the terminal phase estimation was based on maximizing the coefficient of determination. SAS (Version 9.4) was used for all pharmacokinetic and statistical calculations. Bioequivalence was determined by a statistical comparison of the natural log-transformed data for the pharmacokinetic parameters, AUC_{0t} , AUC_{0inf} , and C_{max} and ln-transformed AUC_{0t} and C_{max} for Test A versus Reference C. The ANOVA was conducted separately for Test A versus Reference B analysis and for Test A versus Reference C analysis, using an incomplete block design and the Mixed Procedure in SAS.

As criterion for bioequivalence the ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} , AUC_T and AUC_{∞} were all to be within the 80 to 125% bioequivalence range.

The statistical methods have been described adequately, and are acceptable.

Bioanalytical Methods

The analysis of teriparatide experienced an unusually high number of run failures, which could not be attributed to the instrument.

For a final assessment to prove the validity of the obtained data set a review of the pertinent validation report of the applied analytical method (Quantitation of Teriparatide in Human Plasma via HPLC with MS/MS Detection) was requested.

Beside the ICH conforming validation items like specificity, suitability, linearity, accuracy, detection limit, quantitation limit, precision in terms of repeatability and intermediate precision and solutions stability with representative sample chromatograms the robustness and ruggedness of the method using different equipments was requested to be demonstrated with satisfying suitability parameters of method precision. – But it is acknowledged that the Incurred Sample Reproducibility is acceptable.

The applicant's response on the LoQ was given in two parts:

I. Detailed explanation of the failures in the original report

Analyses were conducted on the Waters Xevo TQ-S UPLC®-MS/MS platform. The Waters Xevo TQ-S system employs a work station (WS) which is comprised of a sample manager, two binary solvent managers and a column manager. The WS is not a standalone piece of equipment therefore any errors associated with the WS also cause the mass spectrometer to stop functioning. During the course of analyses the Waters Xevo TQ-S instruments experienced numerous issues that required Technical Service engineer interventions; service records are on file at PPD. The different failures were explained in detail in the "Response to Day 70/100 questions".

II. Reports and SOPs for reanalyzed samples were provided and found acceptable.

In Table 1 and 2 the results of the original analysis and reanalysis are compared.

All samples have been reanalysed. In both datasets – the original and the reanalysed one – bioequivalence between Test Product and Reference Product C could be demonstrated.

Results

Five drop-out subjects were not analysed. The reasons for drop-out are given in Table 1. They were regarded as not compromising the kinetic evaluations.

Table 1 Discontinued Subjects

Sub. No.	Reason for discontinuation	Comment
01		delivered dose (Period I, Test A) was calculated to be greater than $\pm 10\%$ of the theoretical dose of 0.08 grams
04		delivered dose (Period I, Test A) was calculated to be greater than $\pm 10\%$ of the theoretical dose of 0.08 grams
06		delivered dose (Period I, Test C) was calculated to be greater than $\pm 10\%$ of the theoretical dose of 0.08 grams
55	Non-compliance	Positive drug test
59	Non-compliance	Positive alcohol test
61	Voluntary withdrawal	This subject received Reference B in Period I and Reference C in Period II. Plasma samples were not analyzed as this subject did not complete the periods with the test product.

The results presented show that the criteria used to assess bioequivalence between the Test and

Reference formulations have been fulfilled. The 90% confidence interval for the C_{max} (92.38-106.83), AUC_T (99.04-113.96) and AUC_{∞} (102.51-116) were in the acceptance range of 80 to 125%.

No period or sequence effects have been reported with this study.

No pre-dose levels of teriparatide were detected in any subject, in either period of the study. The C_{max} noted is within the validated range of the bio-analytical assay.

The overall pharmacokinetic parameters' results are summarised in the table 2 and 3 below.

Table 2 Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range)

Pharmacokinetic parameter	Arithmetic Means \pm SD (%CV)			
	Test Product A N= 67		Reference Product C N=66	
Dataset	original	reanalysed	original	reanalysed
AUC_{0-t} (pg·h/mL)	117.7 \pm 49.5 (42.1)	102.3 \pm 43.8 (42.9)	111.8 \pm 51.4 (46.0)	96.2 \pm 45.9 (47.7)
AUC_{0-inf} (pg·h/mL)	133.3 \pm 50.5 (37.9)	116.2 \pm 44.4 (38.2)	125.3 \pm 54.3 (43.3)	109.5 \pm 46.3 (46.3)
C_{max} (pg/mL)	122.6 \pm 58.41 (47.7)	111.3 \pm 51.2 (46.0)	122.9 \pm 54.5 (44.3)	109.6 \pm 45.8 (41.8)
T_{max} (hr)	0.26 \pm 0.12 (45.5)	0.25 \pm 0.11 (42.7)	0.28 \pm 0.13 (45.1)	0.27 \pm 0.12 (44.6)

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
 $AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
 C_{max} Maximum plasma concentration
 T_{max} Time until C_{max} is reached

Table 3 Bioequivalence Evaluation of Teriparatide in 11336032 – Test A versus Reference C; Pharmacokinetic parameter for the original and reanalyzed datasets

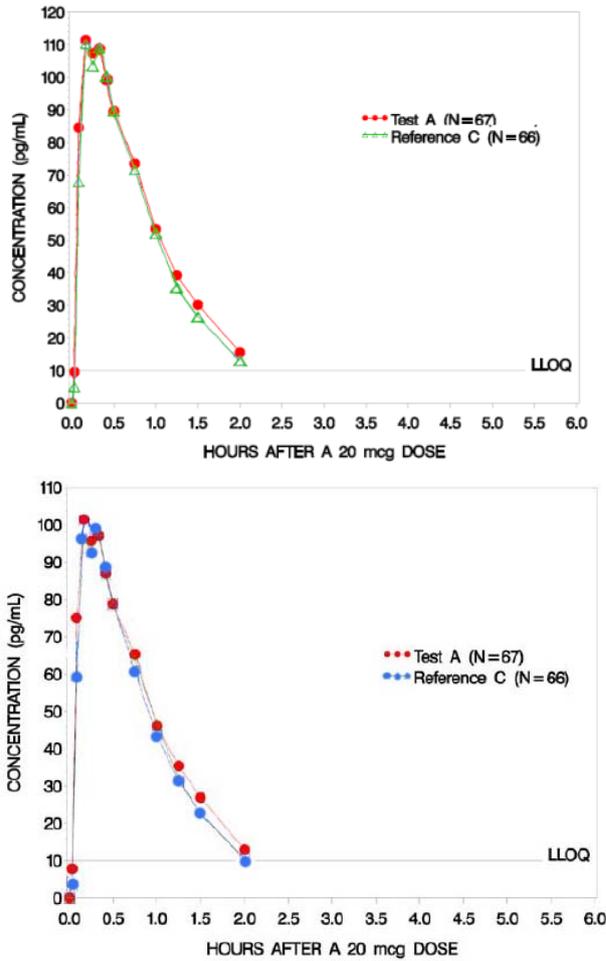
Pharmacokinetic parameter	Dataset	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
AUC_{0-t} (pg·h/mL)	original	106.24	99.04 - 113.96	24.5
	reanalysed	109.6	101.9 – 117.8	25.1
AUC_{0-inf} (pg·h/mL)	original	109.40	102.51 - 116.74	21.4
	reanalysed	108.2	102.4 – 115.49	20.2
C_{max} (pg/mL)	original	99.35	92.38 - 106.83	25.3
	reanalysed	103.09	95.92 – 110.79	24.9

Table 4 Numerical Difference of AUC_{0-t} , AUC_{0-inf} and C_{max} of the original and reanalysed dataset

Product	Test	Reference C		Test	Reference C	
Dataset	original	original	Δ	reanalysed	reanalysed	Δ
AUC_{0-t} (pg·h/mL)	117.70	111.80	5.90	102.30	96.20	6.10
AUC_{0-inf} (pg·h/mL)	133.30	125.30	8.00	116.20	109.50	6.70
C_{max} (pg/mL)	122.60	122.90	-0.30	111.30	109.60	1.70

The values for AUC_{0-t} , AUC_{0-inf} and C_{max} are numerically lower in the re-analyses but the differences (Δ) between Test Product A and reference Product C are maintained (Table 4).

Figure 1: Teriparatide mean plasma concentration. First based on original dataset; second: based on reanalysed dataset



The results presented show that the criteria used to assess bioequivalence between the Test and Reference formulations have been fulfilled. The 90% confidence interval for the C_{max} , AUC_{0-T} and $AUC_{0-\infty}$ were in the acceptance range of 80 to 125% for both, the original and the reanalysed data.

Clinical safety

Eighteen (18) adverse events (7 Test A, 6 Reference B, 5 Reference C) were reported by 15 of the 72 subjects who participated in this study. Twelve (12) of the reported adverse events were considered “mild”; 10 resolved spontaneously by the end of the study. There were no serious adverse events or deaths reported. No subject was withdrawn from the study for safety reasons.

Body System/Adverse Event	Bioequivalence Study	
	Test A N (%)	Reference C N (%)
General disorders and administration site conditions		
Injection site erythema	1 (1.43%)	1 (1.47%)
Investigations		
Blood bilirubin increased	1 (1.43%)	1 (1.47%)
Blood pressure decreased	1 (1.43%)	0 (0.00%)
Blood pressure increased	1 (1.43%)	0 (0.00%)
Blood triglycerides increased	2 (2.86%)	1 (1.47%)
White blood cell count increased	1 (1.43%)	0 (0.00%)
Nervous system disorders		
Dizziness	0 (0.00%)	0 (0.00%)
Headache	0 (0.00%)	1 (1.47%)
Reproductive system and breast disorders		
Premenstrual cramps	0 (0.00%)	1 (1.47%)
Total N%	7 (10.00%)	5 (7.35%)

Based on the analytical comparability of this well-characterised, small, non-glycosylated polypeptide and the fact that the impurity profile does not raise concerns, immunogenicity of the applied products is expected to be similar to the reference product. Therefore, clinical immunogenicity data are not required.

Legal Status

Subject to medical prescription

User Testing

The user testing is considered acceptable.

Summary Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

The Applicant submitted a revised RMP (version 1.2; data lock point: 31 January 2016, date of final sign-off: August 2016), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to the following medicinal product:

- [Teriparatide] 20 micrograms/80 microliters solution for injection in pre-filled pen.

The following summary of the safety concerns is included in the RMP:

Summary of safety concerns	
Important identified risks	• Hypercalcemia

Summary of safety concerns	
	<ul style="list-style-type: none"> • Orthostatic hypotension
Important potential risks	<ul style="list-style-type: none"> • Osteosarcoma • Non-uraemic calciphylaxis
Missing information	<ul style="list-style-type: none"> • None

Proposed pharmacovigilance activities:

- Routine pharmacovigilance.

Proposed risk minimisation measures:

- Routine risk minimisation.

The proposed RMP is in line with the EU-RMP format for hybrid medicinal products. The included summary of the safety concerns is deemed acceptable. The proposed routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

The Applicant has adequately answered all questions previously raised.

The proposed RMP is deemed overall acceptable.

The future 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 RMS;
- 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.
-

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date

Include final proposal for a common renewal date (i.e. in general 5 years after the finalisation of the procedure).

IV. BENEFIT RISK ASSESSMENT

Teriparatid-ratiopharm 20 µg / 80ml, the product applied for was shown to be analytically and functionally comparable to the EU reference product Forsteo. In addition, bioequivalence has been demonstrated and no safety or immunogenicity concerns arose from the data.

The benefit-risk ratio of Teriparatid-ratiopharm 20 µg / 80ml is considered positive.