COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Teriparatide Ambio Pharma 20 microgram/80 microliter, solution for injection in pre-filled pen (teriparatide acetate hydrate)

NL/H/4934/001/DC

Date: 28 October 2022

This module reflects the scientific discussion for the approval of Teriparatide Ambio Pharma 20 microgram/80 microliter. The procedure was finalised at 26 January 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Teriparatide Ambio Pharma 20 microgram/80 microliter, solution for injection in pre-filled pen, from Ambio Pharma Europe.

The product is indicated in adults for:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture (see Section 5.1 of SmPC). 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 of SmPC).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product FORSTEO 20 microgram/microliter, solution for injection in pre-filled pen which has been registered through the Centralised Procedure on 10 June 2003 by Eli Lilly (original product) under marketing authorisation number EU/1/03/247.

The concerned member states (CMS) involved in this procedure were Germany, France, Italy, Norway, Sweden and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Teriparatide Ambio Pharma is a colourless, clear solution.

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

The solution is packed in glass cartridges within an injector pen (FixPen).

The excipients are glacial acetic acid (E260), sodium acetate – anhydrous (E262), mannitol (E421), metacresol, hydrochloric acid (for pH adjustment) (E507), sodium hydroxide (for pH adjustment) (E524) and water for injections.

II.2 Drug Substance

The active substance is teriparatide acetate hydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.) and the United States Pharmacopoeia (USP). The substance is of synthetic origin, whereas the European Pharmacopoeia describes the substance of recombinant DNA origin. The active substance is amorphous white to off-white powder. Enantiomeric purity is ensured by adequate controls of the starting materials and testing of the drug substance. The counter ion acetate is the same as for the substance described in the Ph.Eur. and USP.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The synthesis consists of synthesis of several intermediates from protected amino acids. The intermediates are coupled to Teriparatide and the substance is further purified. The specifications of the starting materials, reagents and solvents are considered acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph for rDNA teriparatide (although this monograph is not mandatory for the synthetic peptide) in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance has been provided for three commercial scaled batches stored at -20°C (36 months) and 5°C (six months) in accordance with applicable European guidelines demonstrating the stability of the active substance for one year. Stress studies have been performed at 25°C. -Based on the data submitted, a retest period could be granted of one year when stored below -15°C.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The formulation was based on information on the (US) reference product and reversed engineering. The pharmaceutical development of the product has been adequately performed. The QTPP has been defined, CQAs discussed, and risk assessment performed. The control strategy has been provided and

is considered adequate. The preservative efficacy of the metacresol has been shown, also at the lower shelf-life limit. The concentration of the preservative has been chosen based on the reference product which is acceptable. Data at the end of shelf-life also shows sufficient preservative efficacy.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process consists of bulk manufacture, sterile filtration followed by aseptic filling in glass cartridges. The product is manufactured using conventional manufacturing techniques but is considered non-standard. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with USP requirements and Ph.Eur. requirements, except nitrogen and water for injections which comply with USP requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH, osmolality, assay, degradation products, metacresol content, metacresol identity, residual solvents, particulate matter, uniformity of dosage units, sterility, bacterial endotoxins, container closure integrity, dosing accuracy of the pen-injector, extractable volume and USP <1 for injections. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site has been provided, demonstrating compliance with the specification. The risk evaluation for the potential presence of Nitrosamines is complete and the conclusion of no risk for nitrosamines can be agreed to.

Stability of drug product

Stability data on the product have been provided for three batches stored at 5°C (24 months) and 25°C/60% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. However, the product inside the pen-injector (with cap) is sufficiently protected against light degradation. On basis of the data submitted, a shelf life was granted of 24 months when stored in the refrigerator.

Stability data has been provided demonstrating that the product remains stable for 28 days after opening / first use. The product should also be stored at 5°C after opening / use.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Teriparatide Ambio Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Teriparatide Ambio Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of FORSTEO which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Teriparatide acetate hydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Teriparatide for Injection (250 microgram/mL) (AMBIO, INC., United States) is compared with the pharmacokinetic profile of the reference product FORSTEO (Teriparatide) 20 micrograms/80 microliters solution for injection (Eli Lilly, France).

Bioequivalence studies

Design

An open-label, randomized, single-dose, two-treatment, two-period, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 38 healthy adult subjects, aged 18-65 years. Each subject received a single dose (20 µg) of one of the two teriparatide acetate hydrate formulations in each period. The solution was administered via a single 0.08 mL subcutaneous injection to the subject's abdominal wall after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of four days.

Blood samples were collected at pre dose and 2, 5, 7, 10, 12, 15, 20, 25, 30, 45 minutes and 1.0, 1.25, 1.5, 2.0, 2.5 and 3 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Out of a total of 38, 37 subjects were eligible for pharmacokinetic analysis. One subject withdrew voluntarily.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of teriparatide acetate hydrate (20 µg) under fasted conditions.

Treatment	AUC_{0-t} (ng.h/ml) N=37	$AUC_{0-\infty}$ (ng.h/ml) N=35	C_{max} (ng/ml) N=37	t_{max} (h) N=37
Test (CV%)	124.5 ± 59.6 (48)	149.3 ± 55.8 (37)	138.5 ± 70.0 (51)	0.20 (0.12 – 0.75)

Reference (CV%)	120.7 ± 56.1 (46)	145.29 ± 55.0011 (38)	128.9790 ± 63.2446 (49)	0.33 (0.12 – 1.00)
***Ratio (90% CI)**	101.21 (94.04 – 108.93)	102.53 (96.29 – 109.17)	106.94 (101.02 – 113.21)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation
CI confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 80.00 – 125.00%. Based on the submitted bioequivalence study Teriparatide Ambio Pharma is considered bioequivalent with FORSTEO.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Teriparatide Ambio Pharma.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- None
Important potential risks	- None
Missing information	- None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product FORSTEO. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to FORSTEO (EU/1/03/247) and MOVYMIA (EU/1/16/1161). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Teriparatide Ambio Pharma 20 microgram/80 microliter, solution for injection in pre-filled pen has a proven chemical-pharmaceutical quality and is a generic form of FORSTEO 20 microgram/80 microliter, solution for injection in pre-filled pen. FORSTEO is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Teriparatide Ambio Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 January 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4934 /IB/001/G	- Change in the (invented) name of the medicinal product for Nationally Authorised Products. - Introduction of a summary of pharmacovigilance system for medicinal products for human use.	Yes	12-5-2022	Approved	N/A