Concerned Member State Comments on Day 70 Preliminary Assessment Report to be sent at Day 100 at the latest

1. This document is sent by:

CMS	FR
Contact point, project team leader (name) phone email	[redacted]
Assessors, if applicable (name e-mail, phone)	[redacted]
Date/Day of procedure	26/06/2019

2. This document concerns:

Name of the product in the RMS	Teriparatide 20 µg/80 µl Injektionslösung in einem vorgefüllten Injektor
Name of the active substance	Teriparatide
Applicant	Welding GmbH & Co.KG
Procedure number	DE/H/6160/001/DC
Deadline for comments	**26/06/2019**

3. Comments, general

3.1 Assessment of the RMS

We fully endorse the RMS assessment, and have no further comments ☐

We endorse the RMS assessment, but also have additional comments ☒

We do not fully endorse the RMS assessment, and have other comments ☐

3.2 Conclusions on the product

Our conclusion is that the product is

Approvable ☐

Approvable, provided that satisfactory responses are given to the list of questions and/or the SmPC/PL/labelling is changed according to the comments ☐

Non-approvable ☒

3.3. List of Questions/Proposed conditions for marketing authorisation

We have grounds of potential serious risks to public health on the following part of the assessment report not already raised by the RMS

Quality ☒

Non-Clinical ☐

Clinical ☐

SmPC ☐

PL ☐

Labelling ☐

We have additional points for clarification on the following part of the assessment report

Quality ☒

Non-Clinical ☐

Clinical ☐

SmPC ☒

PL ☒

Labelling ☒

Module 1 – Application related comments (including product name) ☒

4. Potential serious risk to public health

Quality

Potential serious risk to public health not already raised by the RMS FR propose to complete the MO2 with these additional points: - the satisfactory number of reference product batches should cover the shelf-life of the product to establish a scientifically justified database for comparison of test and reference product, in particular with reference to purity and impurities.

- Only one biological assay was performed in the comparability study which is not acceptable. Therefore, a qualified SPR- (Surface plasmon resonance) based assay for comparative binding analysis between Forsteo and the synthetic peptide should be included in the comparability exercise.
Rationale

Non-clinical

Potential serious risk to public health not already raised by the RMS
Rationale

Clinical

Potential serious risk to public health not already raised by the RMS
Rationale

SmPC

Potential serious risk to public health not already raised by the RMS
Rationale

PL

Potential serious risk to public health not already raised by the RMS
Rationale

Labelling

Potential serious risk to public health not already raised by the RMS
Rationale

5. Additional points for clarification

Quality

Points for clarification not already raised by the RMS

Drug Substance

Regarding the Applicant's Part of ASMF

3.2.S.1

1. According to the process described in section 3.2.S.2.2, the final product is obtained in its acetate form. The section 3.2.S.1 should be revised to include data on the acetate form as only the free base is described. The stoichiometry of the counter ion acetate should be specified.
2. In addition, the specific optical rotation should be described in the general properties.

3.2.S.2.3 (AP)

3. The suppliers of a given protected amino acid should be clearly identified as only a joint list of vendors has been submitted. Regarding their origin, only one certificate of origin has been enclosed for Fmoc-L-Val-OH outsourced by [redacted]. This is not sufficient. A declaration of origin from each supplier of each amino acid derivative should be provided in order to certify the absence use of materials of human or animal origin in its process.
4. The proposed specifications for each protected amino acid are not acceptable. They should include additional tests such as appearance, assay and specific optical rotation in order to confirm the correct chiral configuration (except for Fmoc-Gly-OH). The proposed acceptance criteria for purity (≥ 97 % for Fmoc-Asn-OH and Fmoc-Lys(Boc)-OH and ≥ 98 % for the other amino acids) are too wide and should be tightened based on actual values. Furthermore, the chemical purity should include suitable limits for identified and unidentified impurities. The proposed limit for enantiomeric purity (≥ 99.5 %) is also too wide and should be tightened based on actual values. Additional chiral impurities such as Fmoc-L-allo-Ile-OH and Fmoc-D-allo-Ile-OH should also be considered for Fmoc-Ile-OH. Batch analyses should be provided for each source of protected amino acid. The section 3.2.S.2.3 should be revised accordingly.

3.2.S.3.2

5. Some amino-acid derivatives are prone to epimerisation during the activation step or cleavage step. Therefore, diastereoisomers of Teriparatide should be considered as potential "peptide backbone modification" impurities, unless otherwise justified.

3.2.S.4.1

6. Unless otherwise justified, identification by peptide sequencing should be part of the identification tests.
7. A lower limit based on experimental data should be set for acetic acid in line with the expected stoichiometry.
8. With the exception of Gly, Ile and Phe, the proposed limits for amino acid analysis are considered too wide and should be tightened based on batch results.
9. The drug substance stereochemical integrity should be confirmed during release and stability testing.
10. Acceptance criteria for water content (≤ 10.0 % w/w) are considered too wide and should be tightened based on batch results at release and available stability data at long term conditions.

Regarding the specifications applied by the drug product manufacturer

3.2.S.4.1 Dpm

11. The questions raised on the specification applied by the active substance manufacturer should also be considered by the drug product manufacturer.

Drug Product

3.2.P.2.

12. Data on three-dimensional structure of the synthetic teriparatide molecule should be provided and compared to that of the recombinant teriparatide molecule.
13. For the comparison of the impurity profile between the recombinant and the synthetic Teriparatide molecules in table 5, the molecular mass of each reported peak should be assigned.
14. Elucidation of the amino acid composition e.g. by amino acid analysis and peptide map should be included in the comparability exercise.
15. In the stress stability study, only one condition was investigated. Others conditions should be studied (e.g. oxidative, low and high pH,…). The impurities profile should be quantified to complete the outcome of the results.

3.2.P.5.1

16. Unless otherwise justified, oxidised species (Met8, Met18) should be specified and suitable limits should be set at release and shelf-life.
17. Since this peptide is claimed is to be similar to the biological product Forsteo and it has a biological activity, the specification should be included in the drug product specification.

Rationale

Non-clinical

Points for clarification not already raised by the RMS

Rationale

Clinical

Points for clarification not already raised by the RMS

Rationale

SmPC

Points for clarification not already raised by the RMS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 80 microliter**S** contains 20 microgram**S** of teriparatide.

…

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

For the full list of excipients, see section 6.1

6. PHARMACEUTICAL PARTICULARS

6.3 Shelf life and 6.4 Special precautions for storage =>not yet granted as RMS J70 opinion

Rationale

PL

Points for clarification not already raised by the RMS

5. How to store [INVENTED NAME]

=>not yet granted as RMS J70 opinion

Rationale

Labelling

Points for clarification not already raised by the RMS

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each ml contains 250 micrograms of teriparatide.
To add : Each dose of 80 microliters contains 20 micrograms of teriparatide

4. PHARMACEUTICAL FORM AND CONTENTS
Solution for injection.
1 pen of 2.4 ml solution. 3 pens of 2.4 ml solution each.
Each pen contains 28 doses of 20 micrograms (per 80 microliters) of teriparatide.

8. EXPIRY DATE and 9. SPECIAL STORAGE CONDITIONS
=>not yet granted as RMS J70 opinion

14. GENERAL CLASSIFICATION FOR SUPPLY
~~Medicinal product subject to medical prescription~~.=>To be completed nationally

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
[INVENTED NAME]
20 microgram**S**/80 microliter**S**, solution for injection in pre-filled pen
Teriparatide
Subcutaneous use.

6. OTHER
Store in refrigerator. Do not freeze. =>not yet granted as RMS J70 opinion
~~For subcutaneous use.~~
Pen contains medicine for 28 injections.
Prepare pen for first injection, see User Manual

Rationale

Module I – Application related comments (including product name)[1]

Points for clarification not already raised by the RMS

1) The product name TERIWEL is not acceptable in France as it is too close to TORISEL from PFIZER EUROPE MA EEIG.

[1] Please note that for 10.1 and 10.3 applications with a centrally authorised product as reference product, the product name in RMS and all CMS must be the same. It is therefore important that comments on the product name are sent early in the procedure in order to reach agreement before day 210/90.

The product name should be choosen to avoid confusions with others drug products. 2) The name of the responsible for placing the product on the French market (so called “exploitant” in France) should be specified and copy of the manufacturing authorization should be provided. The declaration of the “exploitant” should be sent with the summary of the PV System. 3) It should be confirmed whether the rubber stopper contains latex and the product information should be updated as necessary according to Volume 3B Guideline on Excipients in the label and package leaflet 4) Copy of the CE marking should be provided for pen
Rationale

Practical information to the applicant

Response document:

Please note that any response document submitted by email should be sent to the following email addresses:

To be added in case of paper submission:
4 hard copies should also be sent to the following address:
ANSM, 143/147 boulevard Anatole France, 93285 Saint-Denis Cedex, FRANCE

National translation

We kindly remind the MAH that, in case of positive outcome, the **adequate French translation** of the approved SPC, package leaflet and labelling should be sent not later than 5 days after the finalisation of the procedure.

In order to optimise national notifications, please follow A**NSM recommendations**
http://ansm.sante.fr/Activites/Autorisations-de-Mise-sur-le-Marche-AMM/Demande-initiale-d-AMM/(offset)/1

If any, the letter of commitments should also be translated and provided.

In order to optimise national notifications, both French and English electronic versions of the final approved SPC, package leaflet and labelling in Word format / Template 10 should be sent to ueurop@ansm.sante.fr