Scientific Advice given by Member States

Teriparatide 20 µg / 80 µl solution for injection in pre-filled pen
Procedure No.:

1. Written response received from RMS Germany on August 12, 2015 following Scientific Advise meeting held on March 18, 2015 is copied below.
   Main outcome of meeting is that if full comparative analytical characterization is provided, equivalence of reference product Forsteo and Teriparatide 20 µg/80 µl formulation can be assumed and a BE waiver can be granted taking into account the parental administration of product.
   RMS position is also confirmed during discussion at CMD(h) meeting in June 2015.

BfArM

Written Response

Applicant:	Welding GmbH & Co. KG
Active Agent:	Teriparatide
Topic:	Regulatory Advice
Date of Application:	18th March 2015

Background

Welding GmbH & Co KG (Hamburg), together with its partners and , collectively called the Applicant, developed a Teriparatide 20µg/80µl solution for injection ("BGW formulation or "Teriparatide BGW formulation"), essentially similar to the reference drug product Forsteo®. Both formulations are aqueous solutions intended for subcutaneous administration and have the same qualitative and quantitative composition in terms of drug substance (API) , being the only difference the origin of the API used in both formulations: Teriparatide API used in the reference product (Forsteo®) is obtained by recombinant technology, while the API used in is produced by chemical synthesis.

On 15.01.2014, the Applicant submitted a first Scientific Advice to the BfArM requesting general information on whether based on the rationale provided the medicinal product may be submitted as a generic application.

In the written response (dated 11.02.2014) the BfArM considered a hybrid application according to Art 10(3) as an option as this would allow providing additionally required data and rationale without submission of a full dossier.

To address the suggestions and requirements provided with that response, the Applicant generated additional data to demonstrate that both products are comparable in terms of safety and efficacy. For this purpose, the Applicant fully characterized the API and the BGW formulation impurity profile and compared it to that of the reference drug product, performed a risk assessment to evaluate a potential immunogenicity different from that of the reference drug product and performed an in vitro pharmacodynamic equivalence test.

This additional information is presented hereafter to address the points raised after the first scientific advice.

Question 1

Does BfArM agree that Teriparatide BGW formulation and Forsteo are essentially similar?

Please see attached justification and documentation.

BfArM Response:

Based on the data provided, BWG formulation and the formulation of Forsteo appear essentially similar. However, it is out of the scope of this scientific advice to pre-assess whether or not Forsteo and BGW formulation are essentially similar and a final conclusion can only be drawn based on the full data package provided for MAA.

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BfArM

Question 2

Does BfArM agree that Forsteo and Teriparatide BGW formulation can be regarded as similar with respect to safety without conducting further studies?

BfArM Response:

As peptides and proteins are not deemed to bear considerable risks for genotoxicity, it is agreed that the main issue regarding potential safety profiles of synthetically versus biotechnologically manufactured teriparatide is related to potential differences in immunogenicity caused by the altered impurity profile. However, as outlined by the Company, the amount of impurities is relatively low (albeit "new" impurities are contained in the synthetic peptide) and - based on the knowledge gained about teriparatide so far – the immunogenicity of teriparatide is relatively low and anti-drug-antibodies did not show any clinical effect. The data shown in the Company's position to Q1 did not reveal significant differences in secondary structure. Taken together, the Company's position can be agreed; however, as outlined above, any pre-assessment is out of scope of the scientific advice and a final conclusion will be drawn upon review of the MAA.

Question 3

Does BfArM agree that Teriparatide BGW formulation and Forsteo are bioequivalent and therefore that a MA can be granted based on full comparative analytical characterisation and that BE can be waived?

BfArM Response:

The topic was discussed in the CMDh meeting in June; in the following the publicly available minutes are cited (http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Agendas_and_Minutes/Minutes/2015_06_CMDh_Minutes.pdf):

"*The CMDh discussed under which legal basis an application for a synthetic peptide can be submitted, claiming equivalence to a reference product containing the same peptide manufactured using recombinant technology and which can be well characterised. In the past, Art. 10(3) was recommended for such applications.*

Some MSs preferred to get these applications under Art. 10(3), but it was agreed that Art. 10(1) applications also have to be accepted and should not be invalidated. The approval of the MAA is subject to assessment of the submitted data. The similarity assessment of the active substances will be part of the assessment. If similarity cannot be proven during assessment, the application will have to be rejected. No change of the legal basis can occur during the procedure. […]"

If an application according to 10(1) is intended and the data package is sufficient, waiving the BE study could be acceptable taking into account the parenteral administration.

Bonn, 12th Aug. 2015

2. As stated above, this topic was also discussed during CMD(h) meeting in June 2015. Respective excerpt of Meeting Minutes is copied below.
   Main outcome of CMD(h) meeting is that an application for a product acc. to art. 10(3) [generic application] is possible in case generic product contains a chemically synthetized peptide while reference product contains a peptide from recombinant origin.

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

19 June 2015
EMA/CMDh/454372/2015
Procedure Management and Business Support Division

Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)

Draft minutes from the meeting on 22-24 June 2015, (Version 5)

Chair: Peter Bachmann – Vice-Chair: Christer Backman

22 June 2015, 13:00 – 18:00, room 3E
23 June 2015, 09:00 – 17:00, room 3E
24 June 2015, 09:00 – 15:00, room 3E

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4.5. Generic/hybrid applications for products containing a single synthetic peptide / DE

Appropriate legal basis in case the synthetic peptide is highly similar to the recombinant product and fulfills the requirements for substances for pharmaceutical use

The CMDh discussed under which legal basis an application for a synthetic peptide can be submitted, claiming equivalence to a reference product containing the same peptide manufactured using recombinant technology and which can be well characterised. In the past, Art. 10(3) was recommended for such applications.
Some MSs preferred to get these applications under Art. 10(3), but it was agreed that Art. 10(1) applications also have to be accepted and should not be invalidated. The approval of the MAA is subject to assessment of the submitted data. The similarity assessment of the active substances will be part of the assessment. If similarity cannot be proven during assessment, the application will have to be rejected. No change of the legal basis can occur during the procedure.
The RMS of a recently submitted procedure was asked to circulate the AR to the CMDh once ready.
The CMDh further discussed and agreed that a BE study using two reference medicinal products, from the US and from the EU, is acceptable. However, only the results related to the EU product can be taken into account for the assessment.