CBG MEB

Public Assessment Report

Scientific discussion

Paricalcitol Accord 2 microgram/ml and 5 microgram/ml solution for injection

(paricalcitol)

NL/H/3107/001-002/DC

Date: 12 October 2015

This module reflects the scientific discussion for the approval of Paricalcitol Accord 2 microgram/ml and 5 microgram/ml solution for injection. The procedure was finalised on 19 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Paricalcitol Accord 2 microgram/ml and 5 microgram/ml solution for injection from Accord Healthcare Ltd.

The product is indicated for the prevention and treatment of secondary hyperparathyroidism in patients with chronic renal failure undergoing haemodialysis.

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

This decentralised procedure concerns a generic application with reference to the innovator product Zemplar 2 microgram/ml and 5 microgram/ml solution for injection (NL License RVG 106105 and 31535) which have been registered in the Netherlands by AbbVie B.V. through MRP ES/H/0113/001;005 since 21 April 2005 (5 mcg/ml) and 14 June 2010 (2 mcg/ml).

The concerned member states (CMS) involved in this procedure were:

For the 2 mcg/ml: Italy, Malta, Portugal and Spain.
For the 5 mcg/ml: Austria, Czech Republic, Finland, Germany, Hungary, Italy, Malta, Portugal, Spain and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Paricalcitol Accord is a clear and colourless aqueous solution free from visible particles with pH 6.5 to 9.0 and osmolarity 11,077 mOsm/L.

The 2 mcg/ml formulation is supplied in clear glass vial containing 2 mcg/1 ml of paricalcitol.
The 5 mcg/ml product is supplied in clear glass ampoule containing 5 mcg/1 ml or 10 mcg/2 ml of paricalcitol, and in clear glass vial containing 5 mcg/1 ml or 10 mcg/2 ml of paricalcitol.

The excipients are anhydrous ethanol, propylene glycol and water for injections.

II.2 Drug Substance

The active substance is paricalcitol, an established active substance described in the United States Pharmacopoeia (USP). Paricalcitol is a white to almost white crystalline powder, insoluble in water at room temperature, but soluble in most polar solvents e.g., ether, methanol, ethanol. The compound is very lipophilic and very hygroscopic. The substance is dissolved in the excipients/water mixture, particle size and polymorphism are not considered of influence on the product characteristics.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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.

<u>Manufacturing process</u>

The manufacturing process has been described for both active substance manufacturers. No heavy metal catalysts are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The MAH has provided the specifications of the drug substance of each supplier. The specifications are the same for both suppliers except for loss on drying, residual solvents, specific optical rotation and chiral purity testing. Sufficient batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
Stability data on the active substance have been provided for the first manufacturer on three full-scale batches stored at -18 °C (60 months) and 25°C/60% RH (6 months). The re-test period of the ASMF holder is 60 months, when stored at or below -18 °C protected from light.
For the second ASMF holder stability data on the active substance have been provided for three full-scale batches and one mother liquor process batch, stored at -20 °C (36 months), 25°C/60% RH (36 months) and 40 °C/75% RH (6 months). The re-test period of 36 months, when stored at or below 25°C is acceptable. The substance should be protected from light, based on the available, incomplete photostability testing.

The MAH has confirmed that a re-test period of one year will be applied for the drug substance of each supplier.

II.3 Medicinal Product

Pharmaceutical development
The development studies were aimed at obtaining a product essentially similar to the innovator product. Comparative studies were performed. The proposed formulation contains a higher percentage of ethanol than the innovator product. It has been shown that the use of this formulation results in an acceptable drug product with regard to pH, osmolarity and rise in blood alcohol level after injection. The packaging is usual and suitable for the product at issue. Furthermore, terminal sterilization was selected to ensure sterility of the final product. As this is the preferred method for sterilization according to the guidelines, and it was demonstrated that the product did not deteriorate under the sterilization conditions, this is acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of preparation of a bulk solution, filtration, filling and sealing, and terminal sterilization. This is followed by leak testing and visual inspection, and labelling and packing. The product is manufactured using conventional manufacturing techniques.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented on a sufficient number of batches of each presentation, at the intended (smallest) commercial scale. This is sufficient.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identity, assay of paricalcitol, content of ethanol and propylene glycol, particulate matter, sterility, endotoxins, extractable volume, related compounds and clarity and colour of solution. The shelf-life limits are equal to the release limits, and in line with the USP paricalcitol injection monograph.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on a sufficient number of batches of each presentation, demonstrating compliance with the release specification.

Microbiological attributes
Tests for sterility and endotoxins are performed on the drug product. The results show compliance to the requirements and the tests have been validated. The product is a sterile product, filtered and sterilised in the final container, and is tested for sterility and endotoxins.

Stability of drug product
Stability data on 21 commercial scale batches of the drug product presentations have been provided. These batches were stored at 25°C/60% RH, up to 24 months, and 40°C/75%RH up to 6 months. The conditions used in the stability studies are in accordance with the Guideline on stability testing (CPMP/QWP/122/02, rev 1 corr) regarding finished products packaged in impermeable containers. All batches comply with the proposed set of specifications, at all temperatures tested. The proposed shelf-life of 24 months for the drug product is acceptable based on the data provided.
A photostability study was performed, according to ICH requirements. Samples were direct exposed, or packaged in secondary packaging or wrapped in aluminium foil (control). The product is sensitive to light but in the secondary packaging it is protected. Hence the product should be kept in the carton until 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 Paricalcitol Accord 2 microgram/ml and 5 microgram/ml solution for injection have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to validate additional batches at commercial scale.
- The stability studies will be continued for each batch and storage condition up to 36 months at 25 °C and 6 months at 40 °C.
- The first three commercial batches will be subjected to 6 months accelerated stability study at 40 °C/75% RH and long term stability study at 25 °C/60% RH until end of approved shelf-life.
- A minimum of one batch will be tested in a long term stability study at 25°C/60% RH each year of manufacture for each pack of paricalcitol injection.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Paricalcitol Accord 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 Zemplar, 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

Paricalcitol 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.

IV.2 Pharmacokinetics

Paricalcitol Accord 2 microgram/ml and 5 microgram/ml solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The use of the solvents ethanol and propylene glycol are based on the use by the innovator, although at different concentrations. The levels however are considered safe and common, as stated in the Handbook of Pharmaceutical Excipients. The applicant has also calculated the rise in Blood Alcohol Concentration (theoretical worst case scenario) due to ethanol in the formulation when administered up to 40 mcg paricalcitol by using 2 mcg/ml strength. This leads to a rise in 13.15 mg/100 ml, well below concentrations with clinical effect as stated in literature. Hence the increased amount of ethanol in the proposed formulation compared to the innovator product is considered acceptable. It may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current formulations can be used instead of the reference products.

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 Paricalcitol Accord solution for injection.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypercalcemia • Rise in serum phosphate concentrations • Decrease in eGFR due to an increase in serum creatinine (no effect on true GFR) • Allergic reactions, including anaphylaxis and angioedema • CYP3A4 drug-drug interactions
Important potential risks	• Major adverse cardiovascular events
Missing information	• Use in hepatic impairment patients • Use in paediatric population • Use in pregnancy and lactation

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 Zemplar. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A bridging statement has been provided to waive the readability testing on the proposed package leaflet (PL) of Paricalcitol Accord 2 micrograms/ml and 5 micrograms/ml based on the readability test report on the PL of Zemplar solution for injection [Parent PL-1] and Zolendronic Acid Accord 4 mg/5 ml concentrate for solution for infusion [Parent PL-2].
The key information for safe use in the Paricalcitol Accord leaflet is same as that of approved Parent PL-1. Hence consultation with target patient groups has been not conducted. Bridging to Parent PIL-2 is applied for the design, layout and format used by the MAH.
The Member States agree to the conclusions presented in the bridging statement; separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paricalcitol Accord 2 microgram/ml and 5 microgram/ml solution for injection have a proven chemical-pharmaceutical quality and are generic forms of Zemplar 2 microgram/ml and 5 microgram/ml solution for injection. Zemplar is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paricalcitol Accord solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 January 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached