Public Assessment Report

Scientific discussion

Porontazin 1 and 2 microgram, soft capsules (paricalcitol)

NL/H/2946/001-002/DC

Date: 21 August 2014

This module reflects the scientific discussion for the approval of Porontazin soft capsules. The procedure was finalised on 14 March 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 9-11.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation Porontazin 1 and 2 microgram, soft capsules from Regiomedica GmbH.

The product is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency (chronic kidney disease Stages 3 and 4) patients and chronic renal failure (chronic kidney disease Stage 5) patients on haemodialysis or peritoneal dialysis.

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 5 mcg/ml solution for injection, which has been registered in Spain by Abbvie Farmaceutica S.L.U since 9 August 2002. In the Netherlands, Zemplar 1 and 2 microgram, soft capsules (NL License RVG 100436-100437) have been registered since 22 January 2008 through MRP ES/H/0113/002-003.

The concerned member state (CMS) involved in this procedure was Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Porontazin 1 microgram is a white to off-white, oval, soft-gelatin capsule containing a clear oily liquid, containing 1 microgram of paricalcitol.
Porontazin 2 microgram is a red, oval, soft-gelatin capsule containing a clear oily liquid, containing 2 microgram of paricalcitol.

The capsules are packed in PVC/PVDC/Aluminium blisters.

The excipients are:
Capsule contents: medium chain triglycerides, **e**thanol 96%, butylhydroxytoluene (E321)
Capsule shell: gelatin (E441), purified water, glycerol (E422), titanium dioxide (E171), 2 mg only - iron oxide red (E172)

The ratio between the amount of each excipient to the amount of active substance is the same for both strengths.

II.2 Drug Substance

The active substance is paricalcitol, an established active substance described in the Pharmacopoeia of the United States (USP). It is a white to almost white, very hygroscopic powder, which is insoluble in water at room temperature, but soluble in most polar solvents, *e.g.* ether, methanol and ethanol.
The manufacturer produces a crystalline powder described as polymorphic form I.

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 manufacturing process has been described in sufficient detail. The starting materials, reagents and solvents have been adequately specified.

Quality control of drug substance
The MAH's testing is based on the test parameters from the USP monograph on paricalcitol. Batch analysis results ware presented for 2 batches, demonstrating compliance with the drug substance specification.

Stability of drug substance
Three batches of drug substance have been stored at -18°C for 60 months and at 25°C/60% RH for 6 months. All (long-term and accelerated) stability results were in accordance with the set drug substance specification. The substance was shown to be light sensitive. The applicable re-test period is 5 years if stored in a well-closed container, protected from light, at or below -18°C.

II.3 Medicinal Product

Pharmaceutical development
. The formulation is strongly based on that of the innovator product. An adequate description of the development of the dissolution method has been given. The proposed dissolution method is quite similar to the recommended dissolution method in FDA Dissolution Data Base for paricalcitol capsules. In view of the provided dissolution results for the test and reference bio-batches the proposed dissolution specification of NLT 75% (Q) after 45 min is considered acceptable.
A comparison of the innovator product from the member states has been performed. The innovator product was registered throughout the EU using one Mutual Recognition Procedure for both strengths, therefore, the innovator product marketed in the EU is expected to be identical. The bioequivalence study was conducted with the 2 microgram strength sourced from the EU.
The comparative dissolution studies between test- and reference bio-batches, between various reference products, an between the 1 & 2 microgram capsule strengths of the proposed product demonstrated similar release profiles. The information and data about the pharmaceutical development are considered adequate and sufficient.

Manufacturing process
The description of the manufacturing process is sufficiently detailed. The manufacturing steps are 1) manufacture of the gelatin mass, 2) manufacture of the capsule fill, 3) encapsulation, 4) drying process, and 5) packaging. The applied in-process controls are considered to be adequate.
Three commercial-scale batches of each strength have been validated.
The manufacturing process is a non-standard process, producing soft capsules with a very low drug substance content. Although the paricalcitol contents are low in the capsules (1 µg and 2 µg), the process is not very critical, as paricalcitol is easily dissolved in a solution. This was confirmed by content uniformity testing on both the 1 µg and 2 µg capsules with acceptable content uniformity variability.

Control of excipients
The excipients glycerol, titanium dioxide, gelatin, medium chain triglycerides, butylhydroxytoluene (BHT), ethanol and purified water meet the requirements of the corresponding Ph. Eur. monograph.
For iron oxide red Regulation (EU) 231/2012 is applied. These specifications are acceptable.

Quality control of drug product
The specifications are adequate to control the relevant parameters for the dosage form and include tests for description, identification (paricalcitol, butylhydroxytoluene, iron oxide, titanium dioxide), assay (paricalcitol and butylhydroxytoluene), uniformity of dosage units – mass variation, related substances, dissolution and microbial contamination.
The descriptions of the analytical methods are considered adequate, and the validations sufficient. Batch analysis results for 3 batches of each strength have been provided. All results met the set specifications.

Stability of drug product
Three batches of each strength have been placed on stability for 24 months at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH. There are no mass balance concerns when the product is stored according to the proposed storage conditions of "store below 30°C" in stability studies conducted to date. The related substances method is therefore considered to be suitable.
For the accelerated studies several 3- and 6 months assay results are out of specification. At 30°C/65% RH (up to 12 months) and 25°C/60% RH (up to 18 months) all results including assay were meeting the requirements. The out-of spec results at 40°C/75% RH justify the restriction of the storage condition to 'Not above 30°C'. The MAH demonstrated that the 24 month results at 25°C/60% RH

meet the stability assay specification. Photostability has been shown. Based on this additional data, a shelf life of 24 months with a storage condition of “Do not store above 30 °C” can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The excipient glycerol is of synthetic origin, and herewith there is no TSE issue. For gelatine valid TSE Certificate of Suitability has been provided. For the production of ethanol the manufacturer uses milk from healthy cows. Therefore there is no TSE issue. The ethanol is a fermentation product, produced by fermentation of lactose in casein whey. A statement from the supplier is provided confirming that this excipient is manufactured according to the Ph. Eur. monograph on Fermentation Products, as well as outlining the process and confirming that no additional specifications relating to impurities are required. The ethanol at issue is in accordance with the Ph. Eur. monograph for Ethanol (96 per cent).

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Porontazin 1 and 2 microgram, soft capsules have 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 Porontazin 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 soft capsules, which is available on the European market. Reference is made tot 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.

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

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Porontazin 2 microgram (Regiomedica GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Zemplar 2 microgram soft capsules (Abbott, UK).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The results of the bioequivalence study with the 2 microgram strength are also valid for the 1 microgram strength, since the following conditions are met for Paricalcitol capsules:

- Both pharmaceutical products are manufactured by the same manufacturer and process.
- The qualitative composition of the different strengths is the same.
- The ratio between the amount of each excipient to the amount of active substance is the same for both strengths, since it is the same capsule fill for both strengths.
- The dissolution profiles are similar between the additional strength and the strength of the batch used in the bioequivalence study.
- The pharmacokinetics of paricalcitol are linear over the therapeutic dose range, as confirmed in the innovator product SmPC.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 22 healthy subjects (6 males and 16 females), aged 20-64 years. Each subject received a single dose of 8 micrograms of one of the 2 paricalcitol formulations, administered as 4 capsules of 2 microgram. The capsules were orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence for paricalcitol is considered adequate. Paricalcitol can be taken with or without food, according to the SmPC.

In order to reach detectable levels of paricalcitol, 4 capsules of paricalcitol 2 microgram were administered. This will give a C_{max} of approximately 300 pg/ml. Considering the lower limit of quantitation (LLOQ) of the applied analytical method of about 10 pg/ml, plasma concentrations after a 8 µg dose are sufficiently high to have a reliable estimation of the pharmacokinetics. Furthermore, paricalcitol shows linear pharmacokinetics over the 0.06 – 0.48 µg/kg dose range. The weight range of the included subjects was 51 – 78.5 kg, and taken into account the lowest administered µg/kg dose of 0.06 mg/kg this would range from 3 – 4.7 µg. The applied 8 µg dose is considered 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

All subjects completed the study and were analysed and included in the pharmacokinetic and statistical analysis.

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

Treatment N=22	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3161 ± 607	3404 ± 642	285 ± 61	2.17 (1.5 – 4.5)	10.7 ± 2.3
Reference	3189 ± 512	3449 ± 553	284 ± 49	2.33 (1.0 – 5.0)	10.9 ± 2.8
***Ratio (90% CI)**	0.98 (0.94 – 1.03)	0.98 (0.94 – 1.03)	0.99 (0.91 – 1.09)	--	--
CV (%)	8.7	8.6	17.7	--	--

$AUC_{0-\infty}$	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

**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 0.80 – 1.25. Based on the submitted bioequivalence study, Porontazin 2 microgram is considered bioequivalent with Zemplar 2 microgram soft capsules.

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 Porontazin soft capsules.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypercalcemia • Decrease in eGFR due to an increase in serum creatinine (no effect on true GFR) • Allergic reactions, including anaphylaxis and angioedema • CYP3A drug-drug interactions
Important potential risks	• Major adverse cardiovascular events • Initiation of dialysis
Missing information	• Safety in paediatric patients

The RMP is in line with the innovator's. The MAH will apply routine pharmacovigilance measures for the risks listed above. No additional pharmacovigilance activities are required.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zemplar soft capsules. 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

The package leaflet (PL) of Porontazin 1 microgram has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. Bridging is applied for the 2 microgram strength, for which a justification has been submitted. The language used for the purpose of user testing the PL was English. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each.

A total of 14 questions were asked in random order which sufficiently addressed the key safety messages. Another three questions have been asked to determine the test person's overall impression of the PL.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The overall impression of the participants was positive.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Porontazin 1 and 2 microgram soft capsules have a proven chemical-pharmaceutical quality and are generic forms of Zemplar soft capsules. Zemplar 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Porontazin 1 and 2 microgram with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 March 2014.

There were no post-approval commitments made during the procedure.

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

Summary Public Assessment Report

Generics

Porontazin 1 and 2 microgram, soft capsules (paricalcitol)

NL/H/2946/001-002/DC

Date: 21 August 2014

Summary Public Assessment Report

Generics

Porontazin 1 and 2 microgram, soft capsules

Active substance: paricalcitol

This is a summary of the public assessment report (PAR) for Porontazin 1 and 2 microgram, soft capsules. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Porontazin.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Porontazin and what is it used for?
Porontazin is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Zemplar 1 and 2 microgram, soft capsules.

The active substance paricalcitol is a synthetic form of active vitamin D. In patients with kidney disease (Stages 3, 4 and 5) the body cannot produce enough vitamin D. Low levels of active vitamin D may lead to high levels of parathyroid hormone, which can cause bone problems.

How is this medicine used?
The medicine can only be obtained with a prescription. The prescribing doctor will use the results of laboratory tests to determine the right dose.

The usual dose is:
- Chronic kidney disease Stages 3 and 4 - one capsule every day, or every other day, up to three times a week.
- Chronic kidney disease Stage 5 - one capsule every other day, up to three times a week.

How does this medicine work?
Active vitamin D is required for the normal function of many tissues in the body, including the parathyroid gland and bones. In people who have normal kidney function, this active form of vitamin D is naturally produced by the kidneys. In kidney failure, however, the production of active vitamin D is markedly reduced. If the body is unable to produce enough active vitamin D, this medicine can be used as a source of it. Porontazin is a synthetic form of vitamin D that can replace the natural, active form.

How has this medicine been studied?
Because Porontazin is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Zemplar. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of this medicine?
Because Porontazin is a generic medicine and is bioequivalent to the reference medicine Zemplar, its benefits and risks are taken as being the same as the reference medicine.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, Porontazin has been shown to have comparable quality and to be bioequivalent to Zemplar. Therefore, the view was that, as for Zemplar, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Porontazin, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about this medicine
In the Netherlands, the marketing authorisation for Porontazin 1 and 2 microgram, soft capsules was granted on 10 April 2014.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human.
For more information about treatment with Porontazin, read the package leaflet (http://mri.medagencies.org/download/NL_H_2946_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in August 2014.