CBG MEB

Public Assessment Report

Scientific discussion

Sevelameercarbonaat Aurobindo 2.4 g, powder for oral suspension

(sevelamer carbonate)

NL Licence RVG: 119580

Date: 16 April 2018

This module reflects the scientific discussion for the approval of Sevelameer-carbonaat Aurobindo 2.4 g, powder for oral suspension. The marketing authorisation was granted on 16 February 2017. 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
CKD	Chronic Kidney Disease
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
GI	Gastro-intestinal
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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Sevelameercarbonaat Aurobindo 2.4 g, powder for oral suspension from Aurobindo Pharma B.V.

Sevelamer carbonate is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
Sevelamer carbonate is also indicated for the control of hyperphosphataemia in patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/L.
Sevelamer carbonate should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

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

This national procedure concerns a hybrid application claiming similarity with the innovator product Renvela (sevelamer carbonate) 2.4 g powder for oral suspension which has been registered in the EEA by Genzyme Europe B.V. through centralised procedure EU/1/09/521/006-007 since 10 June 2009. Renagel 403 mg capsules (sevelamer hydrochloride) is used as the original product for establishing the expiry date of the data protection period for sevelamer. Renagel 403 mg is registered through the centralised procedure since 28 January 2000. The formulations with both salts of sevelamer can be used as reference product since they are registered under a global marketing authorisation.

Sevelameercarbonaat Aurobindo 2.4 g powder for oral suspension is a line-extension (i.e. addition of a new pharmaceutical form) to Sevelameercarbonaat Aurobindo 800 mg film-coated tablets already authorised in the Netherlands under NL RVG 118019.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid medicinal product, as bioequivalence cannot be demonstrated through bioavailability studies. Sevelamer is not soluble in water, but it swells in an aqueous environment. After oral intake, the cross-linked polymer swells in the gastro-intestinal (GI) fluid and binds phosphate during its transit through the GI tract. Because sevelamer is not absorbed in the GI tract, a conventional bioequivalence study is not possible.

Scientific advice was sought in the Netherlands in 2013. The MAH was advised on the dossier requirements. The MEB indicated that equivalence to the reference product could be demonstrated based on *in vitro* studies.

II. QUALITY ASPECTS

II.1 Introduction

Sevelameercarbonaat Aurobindo 2.4 g is an off-white to yellow powder.

The powder is packed in PET/Al/LDPE sachets. The product should be dispersed in 60 ml of water prior to administration.

The excipients are: microcrystalline cellulose, carmellose sodium, sucralose, lemon flavour, orange flavour, the iron oxide yellow (E172).

II.2 Drug Substance

The active substance is sevelamer carbonate, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white, non-crystalline powder. Sevelamer

carbonate is a cross-linked polymer of varying size and is insoluble in water or organic solvents. The drug substance is amorphous.

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 starting materials for the synthesis of sevelamer carbonate have been sufficiently defined. The manufacturing process have been described in sufficient detail.

Quality control of drug substance
The drug substance specification has been adequately justified. The validation of analytical procedures is found acceptable. Adequate certificates of analysis are provided on three production scale batches.

Stability of drug substance
Stability studies have been performed with the drug substance. The proposed retest period of 24 months with no special precautions for storage is considered acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described and the functions of the excipients explained. Since sevelamer carbonate is not soluble in any aqueous media, the phosphate binding capacity is used as a measure of the content of the active substance. Equivalence with the reference product Renvela has been demonstrated based on *in-vitro* equivalence studies: an equilibrium binding study and a kinetics study. The studies performed are in line with the scientific advice that was given by the MEB. The assessment of the in vitro studies is discussed in section IV.2 of this report.

Manufacturing process
The manufacturing process, a dry blending process, has been described in sufficient detail, including the relevant process parameters. It is considered a standard process. The process has been validated on three batches. The validation performed is found sufficient.

Control of excipients
All excipients comply with the Ph. Eur. except for lemon flavour and orange flavour, which comply with EC No. 872/2012 and iron oxide yellow, which complies with USP-NF and EC No. 231/2012. These specifications are acceptable.

Quality control of drug product
The proposed finished product specifications are justified. The specification includes the parameters appearance, identification, potency of sevelamer carbonate, impurities, uniformity of mass and microbial contamination. Validation of the analytical methods have been presented and are found sufficient. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
Stability data on the product have been provided for 3 batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No significant changes were seen. All results are within the specification limits. A photostability study has been carried out, demonstrating that the finished product in the primary packaging is not sensitive to light.
A shelf-life of 24 months with the storage condition "no special precautions for storage" has been granted.

The powder for oral suspension should be dispersed in 60 ml of water prior to administration. The reconstituted suspension must be administered within 30 minutes. The results of the appearance check upon reconstitution demonstrate that the sediment is readily dispersible upon stirring, both upon dispersion of the powder as well as 30 minutes after emptying the sachet.

Specific measures for 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 MEB considers that Sevelameercarbonaat Aurobindo 2.4 g, powder for oral suspension 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)

No new studies have been performed. Sevelamer carbonate is already used in existing marketed products and no significant increase in environmental exposure is anticipated following approval of this hybrid formulation.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Renvela, 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sevelamer carbonate 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 MEB agrees that no further clinical studies are required.

In support of this hybrid application, the MAH has submitted two *in-vitro* equivalence studies were conducted to test equivalence between sevelamer carbonate and Renvela at pH 4 and pH 7, with and without acid pre-treatment. The MAH justified that there is no need to perform a pharmacodynamic (PD) study with safety and efficacy objectives.

IV.2 Pharmacokinetics

In conventional bioequivalence studies the bioavailability of two or more formulations of the same active ingredient is measured in human subjects to support the claim of similar efficacy and safety.

There is no European guideline that describes how *in vitro* studies for sevelamer should be designed and/or performed. However, the FDA has described the design of an *in vitro* equivalence study in 'The Draft Guidance on Sevelamer Carbonate'. In this guidance, it was proposed to test phosphate binding

of test and reference product at 2 different pH levels, 4 and 7, with and without acid pre-treatment. The *in vitro* test is considered the most sensitive test for comparing the phosphate binding. With an *in vitro* test the naturally occurring variability, which is inherent to doing studies in human subjects, has been eliminated. Therefore, the outcome of the *in vitro* study is more precise in comparing the pharmaceutical quality against the originator product with respect to therapeutic efficacy than an *in vivo* test.

Equilibrium binding study
Eight incubation vessels were prepared for both test and reference product. The study was performed using phosphate concentrations of 1.0, 2.5, 5.0, 7.5, 10.0, 15.0, 30.0, and 40.0 mM under pH = 4.0 and 7.0 conditions with acid pre-treatment (AP) and without acid pre-treatment (NAP), and following incubation in dissolution vessels in a water bath maintained at 37 °C and using a stirring speed of 100 rpm. The phosphate concentrations were determined by ion chromatography following 2 hours of incubation. For the acid pre-treatment, the content of each sachet was treated with 80 mL of 0.45 M HCl and left at 37 ºC for 4 hours before incubation.

Twelve sachets containing powder for oral suspension of the test and 12 sachets containing powder for oral suspension of the reference product were tested. The Langmuir binding constants k1 (binding affinity constant) and k2 (binding capacity constant) were determined. The test/reference ratio was calculated for k1 and k2. The primary outcome for equivalence was the 90% confidence interval (CI) for k2. An acceptance range of 80% to 120% was applied. The k1 data was for information purposes only.

The test formulation Sevelamercarbonaat Aurobindo 2.4 g powder for oral suspension was found to be equivalent to the reference formulation Renvela 2.4 g powder for oral suspension, since the 90% CI for test/reference ratio was within the acceptance range. Similar results were obtained with and without acid pre-treatment.

Kinetic study
The kinetic binding study was performed to support the pivotal equilibrium binding study. In the kinetic study, a constant phosphate concentration was incubated with the content of a sachet of either the test or the reference product and subsequently samples were taken at various times. Measurements were performed at pH 4.0 and 7.0, with AP and NAP and at two phosphate concentrations: 1.0 and 40 mM. Incubation times were 5, 15, 30, 45, 60, 90 and 120 minutes, and incubation took place at 37°C.
The phosphate concentrations were determined by in chromatography. For the AP, the content of each sachet with 2.4 g sevelamer powder for oral suspension was treated with 80 mL of 0.45 M HCl and left at 37ºC for 4 hours before incubation. The experiment was conducted in 12 fold. The test/reference ratio was compared for all time points, but not subjected to the 90% CI interval criteria.

The study demonstrated the kinetics during the incubation and provided evidence that equilibrium was reached before the 2 hour sampling point. The test/reference bound phosphate ratios were demonstrated to be comparable at the various times evaluated at both low and high phosphate concentration.

IV.1 Pharmacodynamics

Pharmacodynamic study
During the development of the sevelamer carbonate tablets, a pharmacodynamic (PD) study was performed. Sevelameercarbonaat Aurobindo 800 mg (Aurobindo Pharma B.V., the Netherlands) was compared to Renvela 800 mg film-coated tablets (Genzyme Europe B.V., the Netherlands).
The study was a multicentre, randomised, double-blind, multiple-dose cross-over study in chronic kidney disease (CKD) patients on hemodialysis. The primary objective of the study was the evaluation of safety and tolerability in patients with CKD on hemodialysis. A secondary objective was to prove the equivalence of Sevelameercarbonaat Aurobindo as compared to Renvela on the control of serum phosphorus in CKD patients on hemodialysis. The exploratory objective of the study was to provide further information on the tolerability of the test product based on the evaluation of vital signs and laboratory parameters (hematology and biochemistry).

The study showed that the test drug and the reference drug were comparable regarding the safety and efficacy endpoints evaluated in the study. Regarding safety, no differences in the rate of treatment emergent adverse events between the test and reference drug were discovered.
The secondary endpoint was to prove equivalence between the test drug and the reference drug regarding s-phosphorus levels. No relevant difference was seen and the test/reference drug ratio was 0.98 (90% CI 0.95-1.02).

The MAH argued that it is not necessary to perform an additional PD study to demonstrate the safety and phosphate binding of Sevelameercarbonaat Aurobindo powder for oral suspension, based on the following:

- The *in vitro* test is considered the most sensitive test for comparing the phosphate binding. The outcome of the *in vitro* study is more precise in comparing the pharmaceutical quality against the originator product with respect to therapeutic efficacy than an *in vivo* test.
- Formal equivalence with regard to phosphate binding of test and reference product has been demonstrated by *in vitro* (kinetic and equilibrium phosphate binding) studies.
- For the powder for oral suspension formulation, the same active substance as been used as in the tablet formulation.
- The powder for oral suspension formulation consists mainly of active substance (75% on anhydrous basis), which was tested in the PD study
- The excipients in the formulation are presented in relatively small amounts only (total< 25%) and the excipients are commonly used and have a known safety profile.
- The main excipients in the formulation are microcrystalline cellulose and in smaller amount carboxymethyl cellulose. These excipients are known to be inert, i.e. the excipients have no effect on phosphate binding.
- Similar excipients as in the sevelamer powder for oral suspension are already present in the GI tract (e.g. due to co-administration of other medicinal products or food) or they are also present in the formulation of Renvela (e.g. iron oxides, flavours).
- The excipients have no influence on disintegration, as is applicable for the tablet formulation.

IV.2 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 Sevelameercarbonaat Aurobindo 2.4 g, powder for oral suspension.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Intestinal perforation, obstruction and ileus
Important potential risks	- Serious gastrointestinal disorders associated with sevelamer crystals - Hypersensitivity reactions, including angioedema and anaphylactic reactions - Difficulty swallowing tablets - Vitamin deficiency - Drug interaction with levothyroxine, ciprofloxacin, immunosuppressants, antiarrythmics, anticonvulsants and antifungal drugs - Off label use in patients < 18 year-old
Missing information	- Use in pregnancy and lactation - Use in hepatic impairment and in immunocompromised patients

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

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Renvela 2.4 g powder for oral suspension. No new clinical studies were conducted.
Sevelamer is not absorbed from the gastro-intestinal tract and a standard bioequivalence study cannot be carried out. Instead, as applied to the tablet formulation, *in vitro* equivalence studies (kinetic and equilibrium phosphate binding) were carried out, in accordance with the FDA guidance. The MEB considers this acceptable. Comparable binding has been shown between Sevelameercarbonaat Aurobindo and Renvela. Adequate justification for extrapolation of the results of the PD study with the tablet formulation to the powder for oral suspension has been provided. The same active substance is used as in the tablet formulation and the excipients are commonly used. Risk management is adequately addressed.
Overall, equivalence between the test and reference product has been adequately demonstrated. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The MAH submitted a bridging report in which reference is made to the successfully user tested PL for Renagel 800 mg film-coated tablets. Few content-related differences between the two leaflets exist. These are in line with Renvela 2.4 g powder for oral suspension. Non content-related differences are present as well but are minor and mostly related to the company house-style. These differences are in line with a successful user tested PL for another product of the MAH, Eplerenone 25 mg and 50 mg. The bridging report submitted has been found acceptable. No additional user testing is considered necessary.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sevelameercarbonaat Aurobindo 2.4 g, powder for oral suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Renvela 2.4 g powder for oral suspension. Renvela is a well-known medicinal product with an established favourable efficacy and safety profile

As sevelamer is not absorbed from the gastro-intestinal tract, it is not possible to demonstrate equivalence by means of a bioequivalence study. Equivalence has been adequately demonstrated based on *in-vitro* equivalence studies. Furthermore, it has been sufficiently justified that the results of the *in-vivo* PD study with Sevelameercarbonaat Aurobindo 800 mg film-coated tablets can be extrapolated to the powder for oral suspension.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for this medicinal product with the reference product, and has therefore granted a marketing authorisation. Sevelameercarbonaat Aurobindo 2.4 g, powder for oral suspension was authorised in the Netherlands on 16 February 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse
Replacement or addition of a manufacturer responsible for importation and/or batch release.	IA	PL only	17-5-2017	Approval	N
Redefinition of a starting material into a reagent.	IB	--	27-11-2017	Approval	N