COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sevelameercarbonaat Sandoz 2,4 g, powder for oral suspension (sevelamer carbonate)

NL/H/5109/001/DC

Date: 13 December 2022

This module reflects the scientific discussion for the approval of Sevelameercarbonaat Sandoz 2,4 g, powder for oral suspension. The procedure was finalised on 15 September 2016 in Denmark (DK/H/2549/001/DC). After a transfer on 27 August 2020 the current RMS is the Netherlands. 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
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sevelameercarbonaat Sandoz 2,4 g, powder for oral suspension, from Sandoz B.V.

The product is indicated for:

- The control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
- The control of hyperphosphataemia in adult 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.

The application is approved with Renagel 403 mg capsules, Genzyme Europe BV authorised through the central procedure since 28 January 2000, as original product used for establishing the expiry date of the data protection period.

The product under consideration is a pharmaceutical equivalent to Sevelamer carbonate 2,4 g, powder for oral suspension from Genzyme Europe B.V (Genzyme). The originator's product, available under the name Renvela®, is present on the market as powder for oral suspension in the strengths 1.6 g and 2.4 g, as well as immediate release film-coated tablet in the strength of 800 mg. *In vitro* studies, in relation to the already approved sevelamer carbonate film-coated tablet formulation has been made and an adequate justification for extrapolation of the *in vivo* study with the tablet formulation to the present application for a powder for oral suspension is provided.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC as bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Each sachet contains 2.4 g sevelamer carbonate as active substance. The oral suspension is an off-white to yellow powder.

The oral suspension is packaged in a sachet of polyethylene terepthalate, low density polyethylene and aluminium foil laminate.

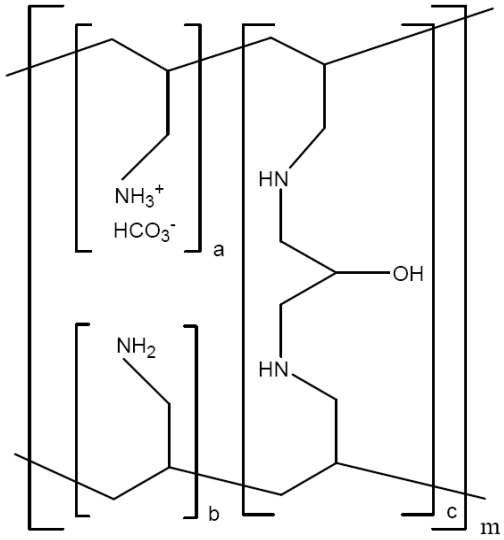
The excipients in the suspension are: microcrystalline cellulose, carmellose sodium, sucralose lemon flavour, orange flavour and Iron oxide yellow (E172)

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The drug product contains the active substance sevelamer carbonate. Sevelamer carbonate is a white to off-white powder.

International Non-proprietary Name (INN): sevelamer carbonate
Chemical Name(s): Poly (Allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate
Chemical Structure:



a,b = number of primary amine groups a + b = 9

c = number of crosslinking groups c = 1

m = large number to indicate extended polymer network groups

Molecular formula: $[(C_3H_7N)m\ (C_9H_{17}N_2O)n \times HCO_3]$ where m : n = 9:1
Molecular mass: As sevelamer carbonate is a cross-linked polymer the molecular weight is not applicable.

Sevelamer carbonate is a cross-linked poly (allylamine carbonate) polymer, which is insoluble in any solvent but swells in contact with water. The cross-linking agent is epichlorohydrin (1-chloro-2,3-epoxypropane). The cross-linking groups consist of two secondary amine groups derived from the starting material, poly (allylamine hydrochloride)

and one molecule of epichlorohydrin giving 2-hydroxypropyl linkers. A portion of the amine is present as the carbonate salt, at 15-26% by weight; this is similar to sevelamer hydrochloride where the chloride salt is present at 15-20%, by weight. There is no evidence for stereoregularity of the cross-linked polymer according to 1H and 13C NMR data. Similarly, there is no stereochemical preference for the cross-linking reaction, i.e., randomly distributed crosslinks are expected.

Sevelamer carbonate is a highly cross-linked polymer of varying size, and each particle can be considered as one molecule. Since the molecular weight is equal to the weight of the particle itself, the molecular weight distribution of a cross-linked polymer is a function of the distribution of particle sizes.

Quality control of drug substance

The documentation on the active substance sevelamer carbonate is presented as an Active Substance Master File (ASMF). Both Applicant's and Restricted Part have been presented together with a suitable Letter of Access. Manufacture, characterisation and testing of the drug substance according to the specification is described.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described and the functions of the excipients explained.

Quality control of drug product

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.

Validations of the analytical methods have been presented and are found sufficient. Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product

The conditions used in the stability studies are according to the ICH stability guideline. The proposed shelf-life of 24 months with the storage condition "no special precautions for storage" is considered acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The active substance and the finished product have been adequately described.
From a quality point of view the benefit/risk ratio of the product is considered positive

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of sevelamer carbonate are well known. As sevelamer carbonate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

The Applicant has submitted an environmental risk assessment for this application, in line with the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00). The original ERA for Sevelamer carbonate 800 mg film-coated tablets was reformatted by Aloys L.A. Sesink to also reflect Sevelameercarbonaat Sandoz 2,4 g, powder for oral suspension and no changes in content were considered necessary. The highest daily dose of Sevelameercarbonaat applied in the original (and reformatted) ERA for calculation of PEC surfacewater was 14.4 grams in chronic kidney disease patients on dialysis. As this application concerns addition of a new pharmaceutical formulation, no increase in the total amount of drug used is expected and thus, the reformatted ERA for this application is acceptable. No further ERA studies are necessary.

III.2 Discussion on the non-clinical aspects

No new studies have been performed. Sevelamer carbonate is already used in existing marketed products and no significant increase in environmental exposure is anticipated as the current application is for a generic product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sevelameercarbonaat Sandoz 2,4 g is not systemically absorbed from the gastro-intestinal tract; therefore, it is not possible to carry out a conventional bioequivalence study. Instead, *in vitro* equivalence studies were conducted. The test and reference product was compared at pH 4.0 and pH 7.0 with and without acid pre-treatment. The studies consisted of equilibrium binding studies and kinetic studies. The *in vitro* equivalence studies are modelled after the interim guidance entitled, "Cholestyramine powder *In vitro* Bioequivalence" and after the work of Swearingen, et al., "Determination of the Binding Parameter Contents of Renvela® Capsules and Tablets Utilizing the Langmuir Approximation at various pH by Ion Chromatography". The design of the *in vitro* studies is based on the FDA recommendation in the "draft guidance on sevelamer carbonate". In addition to the *in vitro* studies, in relation to the already approved sevelamer carbonate filmcoated tablet formulation a pharmacodynamic (PD) study with safety (primary study outcome) and efficacy (secondary outcome) have been carried out. Adequate justification for extrapolation of the results of the PD study with the tablet formulation to the powder for oral suspension has been provided.

IV.2 Pharmacokinetics

In vitro equivalence studies

The test formulation Sevelameercarbonaat Sandoz 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 T/R ratio was within the acceptance range of 80.00-125.00%. Similar results were obtained with and without acid pre-treatment.

IV.3 Clinical efficacy and Clinical safety

Pharmacodynamic (PD) study

The Applicant has performed a PD study with the primary endpoint incidence of treatment emergent AEs and rate of withdrawal due to AEs. Secondary endpoint was level of phosphorus in the blood in hemodialysis patients.

Design

Patients were to be on stable hemodialysis (> 3 months) and have hyperphosphatemia (S-phosphorus ≥ 1.78 mmol/l) at screening for patients not treated with phosphate binders or for patients receiving phosphate binders after 2 weeks washout. The PD study was a 2x8 week double-blinded, randomized, cross-over study with a fixed daily dose of sevelamer carbonate (Renvela® and test product SVL). The daily dose to be used in the double-blind phase was determined in the run-in phase using over encapsulated Renvela®.

The primary objective of the study was to evaluate comparability of SVL and Renvela® regarding safety and tolerability, based on adverse events and compliance. Measurement of serum phosphorus was a secondary objective along with some exploratory objectives as calciumxphosphorus product and other laboratory parameters and vital signs. The primary endpoint was incidence of treatment-emergent adverse events and percentage of subjects withdrawing due to AEs. Secondary endpoint was comparison of the time-weighted mean serum phosphorus (determined from 4 measurements during the last 2 weeks of each 8-week treatment period) after treatment with Renvela® and SVL. Also clinically relevant changes in vital signs and laboratory parameters were assessed.

A sample size calculation for the secondary efficacy endpoint time-weighted mean of the serum phosphorus concentration (determined from 4 measurements during the last 2 weeks of each 8-week double-blind treatment period) estimated that 150 subjects had to be screened in order to achieve 80 subjects to be randomized. No sample size calculation was performed for the primary endpoint which was to compare the safety to the reference product Renvela®.

Subjects could be randomized if their sevelamer dose had been stable for at least 1 week and serum phosphorus ≥1 mmol/l and ≤2.1 mmol/l, Intact parathyroid hormone (iPTH) ≤87 pmol/l and stable dose of concomitant Vit. D. calcium, or cinacalcet. The non-blinding in the run-in phase, where all patients received Renvela® is acceptable since this period was only to find the appropriate dose of Sevelameercarbonaat Sandoz 2,4 g. The randomized treatment

period of 2x8 weeks was double-blind. The randomization was performed using a validated system.

The statistical safety analysis was based on the safety population and the secondary efficacy endpoint (mean serum phosphorus) was analysed using the per protocol population.

Results
93 subjects were randomized to the double-blind phase out of 124 subjects screened. For the evaluation of safety 93 subjects in the safety set were analysed. For the efficacy evaluation, 90 subjects in the per protocol set were evaluated. The study showed that the test drug (SVL) and the reference drug (Renvela®) was 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 was 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 mean s-phosphorus concentration was 1.69 ±0.37 for the test drug and 1.71 ±0.35 for the reference drug.

IV.4 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 Sandoz 2,4 g.

Table 1. 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, anticonvulsivants 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.

There are no additional pharmacovigilance or risk minimisation measures.

IV.5 Discussion on the clinical aspects

The two *in vitro* equivalence study and the *in vivo* PD study submitted with this application to establish similarity with the reference product are considered acceptable.
From a clinically point of view the benefit/risk ratio of the product is considered positive.

V. USER CONSULTATION

As this is a generic product of a reference medicinal product authorised by the Community the SmPC must according to Regulation (EC) no. 726/2004 of the European Parliament and of the Council be in all relevant respect consistent with that of the Brand leader. The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product.

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the User consultation for Renagel 800 mg film-coated tablets and Renvela powder for oral suspension 2.4 g. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sevelameercarbonaat Sandoz 2,4 g, powder for oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Renvela. Renvela is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with that of the brand leader product, except for any product specific information.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sevelameercarbonaat Sandoz 2,4 g with the reference product, and have therefore granted a marketing authorisation.

The decentralised procedure was finalised on September 15th 2016.

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5109/001/IB/006	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product: - Implementation of change(s) for which no new additional data is required to be submitted by the MAH.	Yes	10-2-2021	Approved	N/A
NL/H/5109/001/R/001	Renewal	Yes	26-2-2021	Approved	N/A
NL/H/5109/001/IB/007	Changes in the manufacturing process of the active substance: - Minor change to the restricted part of an Active Substance Master File.	No	2-4-2022	Approved	N/A