



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sevelamer carbonate Zentiva	sevelamer
Renvela	sevelamer carbonate

Procedure No. EMEA/H/C/xxxx/WS/0965

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BSA	Body surface area
CKD	Chronic kidney disease
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures-Human
DTP	Dose Titration Period
EMA	European Medicines Agency
FAS-DTP	full analysis set - dose titration period
FAS-FDP	full analysis set - fixed dose period
FDP	Fixed Dose Period
ERA	Environmental Risk Assessment
HDL	high density lipoprotein
ICF	informed consent form
IMP	investigational medicinal product
INR	international normalized ratio, international normalized ratio
iPTH	intact parathyroid hormone
LDL	low density lipoprotein
LLN	Lower Limit of Normal

MedDRA	Medical Dictionary for Regulatory Activities
PTAE	pre-treatment adverse event
SAP	Statistical Analysis Plan
SI	International system of units
TEAE	treatment emergent adverse event
TID	three times a day
ULN	Upper Limit of Normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Genzyme Europe BV submitted to the European Medicines Agency on 1 June 2016 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Renvela and Sevelamer carbonate Zentiva to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a Body Surface Area (BSA) of >0.75 m²) with chronic kidney disease. As a consequence, section 4.2 of the SmPC is updated to detail posology in the paediatric patients.

The Package Leaflet is updated in accordance.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteurs for the WS procedure: Bart Van der Schueren

Timetable	Actual dates
Submission date	1 June 2016
Start of procedure:	18 June 2016
CHMP Rapporteur Assessment Report	12 August 2016
PRAC Rapporteur Assessment Report	17 August 2016
PRAC members comments	24 August 2016
PRAC Outcome	2 September 2016
CHMP members comments	8 September 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 September 2016
Request for supplementary information (RSI)	15 September 2016
CHMP Rapporteur Assessment Report	23 December 2016
PRAC Rapporteur Assessment Report	3 January 2017
PRAC members comments	4 January 2017
Updated PRAC Rapporteur Assessment Report	5 January 2017
PRAC Outcome	12 January 2017
CHMP members comments	16 January 2017
Updated CHMP Rapporteur Assessment Report	19 January 2017
Request for supplementary information (RSI)	26 January 2017
CHMP-PRAC Joint Rapporteur Assessment Report	4 May 2017
PRAC Outcome	5 May 2017
CHMP members comments	11 May 2017
Updated CHMP Rapporteur Assessment Report	11 May 2017
Opinion	18 May 2017

2. Scientific discussion

2.1. Introduction

In Chronic Kidney Disease (CKD) the homeostatic system for maintaining physiological phosphorus balance is altered by the progressive loss of functioning nephrons. In early CKD, serum phosphorus levels are at near normal levels in children.

Hyperphosphatemia is almost always observed in children on dialysis. Failure to control hyperphosphatemia may be associated with debilitating sequelae and increased mortality. Studies in children with CKD have also demonstrated an association between hyperphosphatemia and CKD-associated vasculopathy. Additionally, children with CKD often have impairment of linear growth. Careful management of phosphate and other interrelated mineral and bone defects may improve CKD-related defects in bone mineralization.

The control of hyperphosphatemia is particularly challenging in paediatric CKD patients. Restricting phosphate intake by dietary means is the first line of treatment in CKD patients; however, this is difficult because of the need for adequate intake of proteins and calories to support skeletal growth. A major component of hyperphosphatemia management is the use of phosphate binders to decrease the intestinal absorption of dietary phosphorus.

No phosphate binders have been approved for use in children; however organizations including the National Kidney Foundation endorse their use in paediatric CKD patients whose serum phosphorus levels cannot be controlled despite dietary restriction.

In practice, aluminium containing phosphate binders are not used in children because of the risk for osteomalacia, encephalopathy and other neurological complications due to aluminium accumulation. Calcium-containing phosphate binders are widely used in children, but have been associated with hypercalcemia and may play a role in the development of a-dynamic renal osteodystrophy, as well as vascular calcification.

Lanthanum carbonate is approved for use in end-stage renal disease patients, but is not recommended in paediatric CKD patients due to concerns about lanthanum deposition in developing bone including the growth plate.

Sevelamer hydrochloride is also approved for adult patients on dialysis. Although an effective and well tolerated phosphate binder, studies in paediatric CKD patients suggest that sevelamer hydrochloride may not be optimal for use in paediatric patients who are vulnerable to acid-base imbalance.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

This application for already licensed products containing sevelamer carbonate will increase the environmental exposure to these medicinal products in case this new indication for paediatric patients is granted.

However, the Environmental Risk Assessment (ERA) performed for the already licenced products applies to the new indication and indicates no significant environmental risk and therefore no additional ERA study is indicted.

As such, no precautionary and safety measures need to be imposed regarding the environmental release from use in patients or from disposal of unused products or waste materials derived from the medicinal products.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of study	- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers	- Objective(s) of study - Study design and type of control	Test product(s): - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	Number of subjects - Total ^{a, b, c} - Gender ^b (M/F) - Race ^b (C/B/O) - Age ^b mean \pm SD (range) - Treatment group ^b	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
Efficacy	SVCARB07609 or DRI12793	Efficacy and safety of sevelamer carbonate versus placebo on the control of serum phosphate Double-blind, parallel group, placebo-controlled 2 week fixed dose period followed by an open label 26 week dose titration period study	- 800 mg tablets and 0.8 g powder for oral suspension - Three time per day - Oral	- Placebo tablets and powder for oral suspension - Three times per day - Oral	- 101/100/66 - 63/37 - 54/35/11 - 14.1 \pm 2.93 (6-18) - Sevelamer carbonate group: 49 / Placebo group: 51	Hyperphosphate mic pediatric patients with chronic kidney disease	28 weeks (2 week double blind placebo controlled period; 26 week open label period)	Complete Full

^a Randomized, ^b Treated, ^c Completed study drug according to Investigator (end-of-treatment form).
M: male, F: female, C: Caucasian, B: black, O: other, SD: standard deviation.

2.4. Clinical efficacy

2.4.1. Dose response studies

Not applicable

2.4.2. Main study

Title of Study

A 2-week, randomized, placebo-controlled, fixed dose period followed by a 6-month, single-arm, open-label, dose titration period study to investigate the efficacy and safety of sevelamer carbonate in hyperphosphatemic paediatric patients with chronic kidney disease

Methods

Study participants

The inclusion criteria are summarised below:

1. The patient and/or their parent/legal guardian were willing and able to provide signed informed consent.
2. The patient was 0 to <19 years old at Visit 1.
3. The patient had CKD requiring dialysis or CKD not on dialysis with an estimated GFR <60 mL/min/1.73 m² based on central laboratory results.
 - Patients taking phosphate binder(s) at screening: At Visit 1a
 - Patients not taking phosphate binder(s) at screening: At Visit 1
4. The patient had a serum phosphorus level greater than the age-appropriate upper limit of normal based on central laboratory results (Table 1).
 - Patients taking phosphate binder(s) at screening: At or between Visit 1a and Visit 1b
 - Patients not taking phosphate binder(s) at screening: At Visit 1
5. The patient, if female with reproductive capacity, had a negative pregnancy test based on central laboratory results.
 - Patients taking phosphate binder(s) at screening: At Visit 1a
 - Patients not taking phosphate binder(s) at screening: At Visit 1

The main exclusion criteria were:

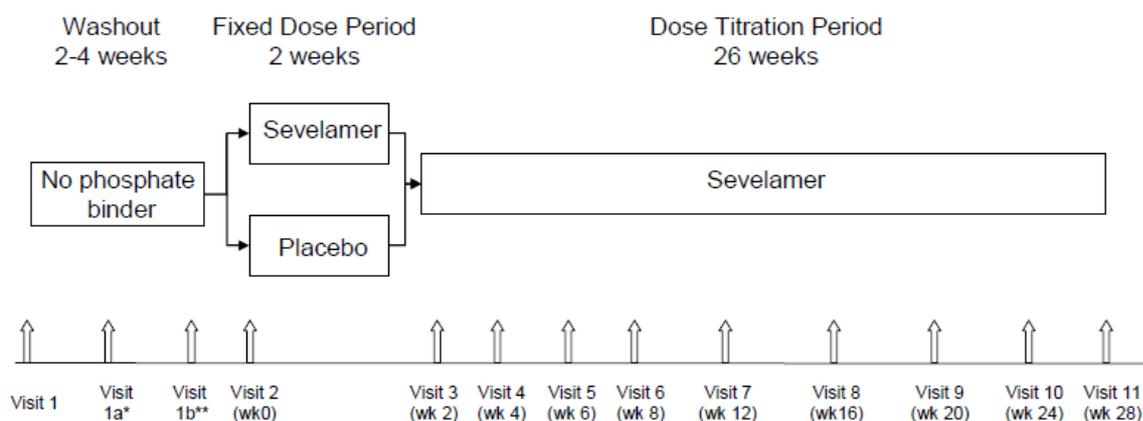
1. The patient had active dysphagia, swallowing disorders or a predisposition to or current bowel obstruction, ileus or severe gastrointestinal motility disorder(s) including severe constipation, or major GI tract surgery.
2. The patient had a non-renal cause of hyperphosphatemia.

3. The patient had participated in a study of an investigational drug during the 30 days preceding the start of the screening period.
4. The patient had a history of, or active, ethanol or drug dependence or abuse, excluding tobacco use.
5. The patient required continuous tube feeds. Patients requiring bolus tube feeds were not excluded.
6. The patient had any evidence of active malignancy except for basal cell carcinoma of the skin. A history of malignancy was not an exclusion criterion.
7. The patient was receiving immunosuppressive medication for a functioning organ transplant.
8. The patient used anti-arrhythmic medications for treatment of arrhythmias. Antiarrhythmic medications used for other indications were not excluded by this criterion.
9. The patient used anti-seizure medications for treatment of seizures. Anti-seizure medications used for other indications were not excluded by this criterion.
10. The patient had a known allergy to sevelamer or any of its constituents.

Treatments

The study design is presented in **Figure 1**.

Figure 1. Schematic design of study SVCARB07609



The study consisted of 3 periods with a total duration of 32 weeks for each patient:

- 2 to 4-week phosphate binder Washout Period
- 2-week randomized, double-blind, placebo-controlled, Fixed Dose Period (FDP) and
- 26-week open-label, sevelamer carbonate Dose Titration Period (DTP).

Eligible patients taking a phosphate binder at Screening were to enter the Washout Period, in which the phosphate binder was to be discontinued for 2 to 4 weeks depending on the serum phosphorus levels.

Once the patient's blood serum phosphorus level was greater than the age appropriate upper limit of normal (ULN) (**Table 1**), patients who met all other eligibility criteria proceeded to the FDP. Patients not taking phosphate binder at screening, with serum phosphorus greater than their age appropriate ULN and satisfying all eligibility criteria, were to directly proceed to the FDP.

Table 1. Serum phosphorus normal range by age (Source: National Kidney Foundation, 2009, Am J Kidney Dis)

Age	Normal Range
0 to <6 months	5.2 to 8.4 mg/dL (1.68 to 2.71 mmol/L)
≥6 to <12 months	5.0 to 7.8 mg/dL (1.61 to 2.52 mmol/L)
≥1 to <6 years	4.5 to 6.5 mg/dL (1.45 to 2.10 mmol/L)
≥6 to <13 years	3.6 to 5.8 mg/dL (1.16 to 1.87 mmol/L)
≥13 to <20 years	2.3 to 4.5 mg/dL (0.74 to 1.45 mmol/L)

The dose of blinded sevelamer carbonate or placebo during the FDP was based on the patient's Screening BSA category (<0.75, ≥0.75 to <1.2, ≥1.2 m²) as described in **Table 2**.

Table 2. Fixed Dose Period dosing of study SVCARB07609

Screening BSA (m ²)	Dose	# Tablets/Sachets
<0.75	0.4 g TID*	Half sachet TID
≥0.75 to <1.2	0.8 g TID*	1 sachet TID
≥1.2	1.6 g TID*	2 tablets or 2 sachets TID

*If a child eats less than 3 meals/snacks per day, sevelamer carbonate or placebo should only be given with meals/snacks and not on an empty stomach. For example, if the patient's Screening BSA is ≥0.75 to <1.2 m² and eats 2 meals/snacks per day that patient will take 0.8 g BID with meals.

Following the FDP, patients were to proceed to the open label DTP during which all patients were to receive sevelamer carbonate for additional 26 weeks. The starting dose of sevelamer carbonate for the DTP was the same as the dose prescribed during the FDP. However, if the patient's serum phosphorus at Visit 3/Week 2 was below the age-defined lower limit of normal (LLN), the sevelamer carbonate dose was to be decreased or temporarily interrupted.

In the DTP, the dose of sevelamer carbonate could be increased or decreased every 2 weeks for the first 6 weeks and every 4 weeks thereafter, as necessary, to achieve a serum phosphorus level within the age appropriate normal values, or until, in the Investigator's opinion, the administered dose was the maximum that the patient could practically take or tolerate with meals.

Dose titration increases or decreases were to be based on Screening BSA category. Dose titration increases or decreases smaller than indicated in **Table 3** were permitted based on the Investigator's judgment, but could not be lower than 0.2 g TID with meals/snacks.

Table 3. Sevelamer carbonate dosing during dose titration period of study SVCARB07609

Screening BSA (m ²)	Starting dose	Titration increases/decreases
<0.75	0.4 g TID*	Titrate up/down by 0.2g TID
≥0.75 to <1.2	0.8 g TID*	Titrate up/down by 0.4g TID
≥1.2	1.6 g TID*	Titrate up/down by 0.8g TID

*If a child eats less than 3 meals/snacks per day, sevelamer carbonate should only be given with meals/snacks and not on an empty stomach. For example, if the patient's Screening BSA is ≥0.75 to <1.2 m² and eats 2 meals/snacks per day that patient will take 0.8 g BID with meals.

Objectives

The objectives of the study were to:

- Evaluate the safety and tolerability of sevelamer carbonate
- Evaluate the efficacy of sevelamer carbonate on the control of serum phosphorus, in hyperphosphatemic paediatric patients with CKD.
- **Outcomes/endpoints**

The primary efficacy endpoint was - change from baseline to Visit 3 (Week 2) in serum phosphorus (in mg/dL).

The secondary efficacy endpoint was change from baseline to Visit 11/ET (Week 28/ET) in serum phosphorus (mg/dL).

Sample size

The following assumptions were used for the statistical power calculations:

- Detect a 0.75 mg/dL (0.24 mmol/L) difference in mean change from baseline to Week 2 between treatment groups.
- Standard deviation for the change from baseline of 1.32 mg/dL (0.43 mmol/L), using analysis of covariance (ANCOVA) modelling based on data from study GD3-199-301 (which has been evaluated during the initial authorisation application for Renvela).
- Two-group t-test with two-sided 5% type I error rate and 80% power.

Given these assumptions, 100 evaluable patients (50 per group) were required. Enrolment required that at least 20% of the patients be less than 13 years of age and at least 70% be receiving dialysis.

Randomisation

At Visit 2 (Week 0), patients meeting all entry criteria, were randomized in a 1:1 ratio, stratified by screening body surface area (BSA) (≥ 1.2 versus < 1.2 m²) and qualifying serum phosphorus (≥ 7.0 versus < 7.0 mg/dL [≥ 2.26 versus < 2.26 mmol/L]), to receive either blinded sevelamer carbonate or placebo during the 2-week FDP.

Blinding (masking)

The randomised phase of this trial was double-blinded.

Statistical methods

All data collected in this study were documented using summary tables and patient data listings. Computations for all results were performed using the SAS statistical software package. Descriptive summary statistics for categorical variables included frequency counts and percentages (n [%]), with percentages reported to the first decimal place.

Continuous variables were summarized by the number of non-missing observations of patients, mean, standard deviation, median, minimum and maximum values. Formal statistical inference (i.e., p-values) was performed only for comparisons of the efficacy parameters between treatment groups with two-sided

5% significance level. All p-values (except the one for the primary efficacy analysis) were presented for descriptive purposes; therefore, no adjustment for multiplicity was needed.

Results

Participant flow

Patients were enrolled at 29 study centres (23 sites in USA and 6 in Europe).

A total of 128 patients were screened for this study, of which 27 patients (21.1%) were screen failures.

A total of 101 patients were randomized in the trial as indicated in **Table 4**. Of these, 50 patients were randomized to receive sevelamer carbonate and 51 patients to receive placebo. A total of 100 patients were treated (received at least one dose of study medication). One patient, randomized to sevelamer carbonate, did not take any dose of the study medication (patient not treated) and was discontinued from the study by the Investigator (physician's decision) due to noncompliance. This patient was considered as discontinued prior to being treated.

Table 4. Patient disposition in study SVCARB07609 following randomisation - All randomised patients

	Placebo (N = 51) n (%)	Sevelamer Carbonate (N = 50) n (%)	Total (N = 101) n (%)
Randomized	51 (100.0)	50 (100.0)	101 (100.0)
Treated	51 (100.0)	49 (98.0)	100 (99.0)
Discontinued Prior to Being Treated	0	1 (2.0)	1 (1.0)
Physician Decision**	0	1 (2.0)	1 (1.0)
Discontinued After Being Treated	16 (31.4)	18 (36.0)	34 (33.7)
Adverse Event	1 (2.0)	3 (6.0)	4 (4.0)
Lost to Follow-up	0	0	0
Pregnancy	0	0	0
Study Terminated by Sponsor	0	0	0
Death	0	0	0
Withdrawal by Subject	2 (3.9)	4 (8.0)	6 (5.9)
Physician Decision	5 (9.8)	3 (6.0)	8 (7.9)
Other*	8 (15.7)	8 (16.0)	16 (15.8)
<i>Kidney transplant</i>	8 (15.7)	8 (16.0)	16 (15.8)
Completed	35 (68.6)	31 (62.0)	66 (65.3)

Note: The denominator for percentages is the number of randomized patients in each treatment group.

Note: Treated refers to a patient taking at least one dose of study drug.

Note: *Mainly Kidney transplant.

Note: **Patient SVCARB07609/8017-0001 was randomized and dispensed treatment, was not dosed and was discontinued by Investigator due to non-compliance.

Recruitment

Study initiation date: 11 May 2012 Sep 2011 (first patient enrolled).

Study completion date: 16 June 2015 (last patient completed the last visit).

Conduct of the study

The study protocol was amended once, to add an exclusion criterion and provide some clarifications regarding the conduct of the study.

These amendments were considered minor.

There were no major changes in the planned analyses from the protocol to the statistical analysis plan and no changes from the statistical analysis plan to database lock and after database lock.

Baseline data

The demographic and baseline characteristics of the patients included in the safety set from Study SVCARB07609 are provided in **Table 5**.

Table 5. Demographic and baseline characteristics of patients in Study SVCARB07609

	Placebo (N = 51)	Sevelamer Carbonate (N = 49)	Total (N = 100)
Age (years)			
N	51	49	100
Mean (SD)	14.3 (3.11)	13.9 (2.75)	14.1 (2.93)
Median	15.0	14.0	15.0
Min, Max	6 , 18	6 , 18	6 , 18
Q1, Q3	12.0, 17.0	12.0, 16.0	12.0, 16.0
95% CI of the Mean	13.4, 15.1	13.1, 14.7	13.5, 14.7
Age Categories (years), n (%)			
N	51	49	100
0-12	13 (25.5)	13 (26.5)	26 (26.0)
13-18	38 (74.5)	36 (73.5)	74 (74.0)
Sex, n (%)			
N	51	49	100
Male	33 (64.7)	30 (61.2)	63 (63.0)
Female	18 (35.3)	19 (38.8)	37 (37.0)
Childbearing Potential for Females, n (%)			
N	18	19	37
Yes	12 (66.7)	15 (78.9)	27 (73.0)
No	6 (33.3)	4 (21.1)	10 (27.0)
Race, n (%)			
N	51	49	100
American Indian or Alaska Native	0	1 (2.0)	1 (1.0)
Asian	1 (2.0)	1 (2.0)	2 (2.0)
Black	19 (37.3)	16 (32.7)	35 (35.0)
Native Hawaiian or Other Pacific Islander	0	0	0
White	27 (52.9)	27 (55.1)	54 (54.0)
Multiple	0	0	0
Not Reported	0	2 (4.1)	2 (2.0)
Unknown	4 (7.8)	2 (4.1)	6 (6.0)
Ethnicity, n (%)			
N	51	49	100
Hispanic or Latino	9 (17.6)	11 (22.4)	20 (20.0)
Not Hispanic or Latino	41 (80.4)	38 (77.6)	79 (79.0)
Not Reported	0	0	0
Unknown	1 (2.0)	0	1 (1.0)

	Placebo (N = 51)	Sevelamer Carbonate (N = 49)	Total (N = 100)
Weight (kg)			
N	51	49	100
Mean (SD)	56.43 (24.460)	49.82 (17.492)	53.19 (21.484)
Median	53.00	48.50	50.25
Min, Max	19.6 , 115.4	17.6 , 101.6	17.6 , 115.4
Q1, Q3	39.00, 65.00	40.40, 57.00	39.75, 58.50
95% CI of the Mean	49.55, 63.31	44.79, 54.84	48.93, 57.45
Height (cm)			
N	51	49	100
Mean (SD)	154.0 (17.49)	153.5 (15.30)	153.8 (16.37)
Median	160.0	156.0	157.0
Min, Max	113 , 187	113 , 181	113 , 187
Q1, Q3	141.0, 166.0	142.0, 166.0	141.5, 166.0
95% CI of the Mean	149.1, 158.9	149.1, 157.9	150.5, 157.0
Body Mass Index (kg/m²)			
N	51	49	100
Mean (SD)	23.05 (7.765)	20.81 (5.832)	21.95 (6.943)
Median	19.96	18.90	19.52
Min, Max	14.6 , 48.7	13.8 , 41.8	13.8 , 48.7
Q1, Q3	18.49, 25.59	17.13, 21.94	17.84, 23.39
95% CI of the Mean	20.86, 25.23	19.14, 22.49	20.57, 23.33
Screening BSA (m²)			
N	51	49	100
Mean (SD)	1.56 (0.394)	1.47 (0.299)	1.52 (0.352)
Median	1.50	1.50	1.50
Min, Max	0.8 , 2.4	0.8 , 2.2	0.8 , 2.4
Q1, Q3	1.30, 1.80	1.30, 1.60	1.30, 1.65
95% CI of the Mean	1.45, 1.68	1.38, 1.56	1.45, 1.59
Screening BSA Categories (m²), n (%)			
N	51	49	100
< 0.75	0	0	0
>=0.75 - <1.2	6 (11.8)	8 (16.3)	14 (14.0)
>=1.2	45 (88.2)	41 (83.7)	86 (86.0)
Qualifying Serum Phosphorus (mg/dL)			
N	51	49	100
Mean (SD)	7.15 (1.920)	7.22 (2.073)	7.19 (1.987)
Median	7.10	6.70	6.90
Min, Max	2.9 , 12.5	3.6 , 12.5	2.9 , 12.5
Q1, Q3	5.80, 8.30	5.80, 8.40	5.80, 8.35
95% CI of the Mean	6.61, 7.69	6.63, 7.82	6.79, 7.58
Qualifying Serum Phosphorus Level (mg/dL), n (%)			
N	51	49	100
< 7.0	24 (47.1)	26 (53.1)	50 (50.0)
>=7.0	27 (52.9)	23 (46.9)	50 (50.0)

Numbers analysed

Three datasets (the safety set, the full analysis set, and the per protocol set) were analysed and are presented in **Table 6**, as overall and by treatment group.

Table 6. Analysis sets in Study SVCARB07609

	Placebo (N = 51) n (%)	Sevelamer Carbonate (N = 50) n (%)	Total (N = 101) n (%)
Number of Patients Randomized	51 (100.0)	50 (100.0)	101 (100.0)
Number of Patients in Safety Set	51 (100.0)	49 (98.0)	100 (99.0)
Number of Patients Excluded	0	1 (2.0)	1 (1.0)
Never Treated	0	1 (2.0)	1 (1.0)
Number of Patients in Full Analysis Set for the Fixed Dose Period	49 (96.1)	48 (96.0)	97 (96.0)
Number of Patients Excluded	2 (3.9)	1 (2.0)	3 (3.0)
No Baseline Phosphorus Value or No Phosphorus Assessment Taken Post First Study Treatment Dose and on or Before Visit 3 (Week 2)	2 (3.9)	1 (2.0)	3 (3.0)
Number of Patients in Per Protocol Set for the Fixed Dose Period	23 (45.1)	24 (48.0)	47 (46.5)
Number of Patients Excluded	26 (51.0)	24 (48.0)	50 (49.5)
Investigational Product	2 (3.9)	0	2 (2.0)
Low Compliance With Study Treatment	24 (47.1)	24 (48.0)	48 (47.5)
Other	1 (2.0)	0	1 (1.0)
Study Conduct/Procedures	2 (3.9)	1 (2.0)	3 (3.0)

The Full Analysis Set for the Dose Titration Period (FAS–DTP) included 95 patients (94.1%), of whom, 46 patients (92.0%) were on sevelamer carbonate in the FDP (“sevelamer carbonate group”) and 49 patients (96.1%) were on placebo in the FDP (“placebo group”).

A total of 5 patients were excluded from the FAS-DTP (3 patients who were on sevelamer carbonate in the FDP and 2 patients who were on placebo in the FDP) due to no baseline phosphorus value or no phosphorus assessment taken post Visit 3 (Week 2).

Outcomes and estimation

The primary efficacy endpoint - change from baseline to Visit 3 (Week 2) in serum phosphorus (in mg/dL) using FAS-FDP is presented in **Table 7**.

Table 7. Serum phosphorus (mg/dL) change from baseline to Visit 3 (Week 2) in Study SVCARB07609- Full analysis set - Fixed dose period

Visit/ Statistics	Placebo (N = 49)	Sevelamer Carbonate (N = 48)
Change from Baseline to Visit 3 (Week 2)		
N	49	48
Mean (SD)	0.04 (1.478)	-0.87 (1.649)
Median	-0.20	-0.65
Min, Max	-3.5, 6.3	-5.2, 3.5
Q1, Q3	-0.70, 0.60	-1.60, 0.00
95% CI of the Mean	-0.38, 0.47	-1.35, -0.39
Treatment Comparison (Sevelamer Carbonate - Placebo)		
LS Mean Difference (SE) [a]		-0.90 (0.270)
95% CI [a]		-1.44, -0.37
p-value [a]		0.001

The secondary efficacy endpoint, which is change from baseline to Visit 11/ET (Week 28/ET) in serum phosphorus (mg/dL), is presented in **Table 8**.

Table 8. Serum phosphorus (mg/dL) change from baseline to Visit 11/ET (Week 28/ET) in Study SVCARB07609 - Full analysis set - Dose titration period

Visit/ Statistics	Placebo (N = 49)	Sevelamer Carbonate (N = 46)	Total (N = 95)
Change from Baseline to Visit 11/ET (Week 28/ET)			
N	49	46	95
Mean (SD)	-1.13 (2.061)	-1.23 (2.206)	-1.18 (2.122)
Median	-1.10	-1.30	-1.10
Min, Max	-7.6, 3.4	-5.9, 4.1	-7.6, 4.1
Q1, Q3	-2.20, -0.10	-2.80, 0.30	-2.60, 0.30
95% CI of the Mean	-1.72, -0.54	-1.89, -0.58	-1.61, -0.75
p-value (Wilcoxon Signed Rank)	0.0001	0.0010	<0.0001

Ancillary analyses

The confirmatory analysis for the primary efficacy endpoint was conducted using the PPS-FDP and showed that sevelamer carbonate significantly reduced serum phosphorus through Week 2 by an LS Mean difference of -1.15 (SD 0.407) mg/dL compared to placebo (p=0.007). Mean change from baseline to Week 2 was -0.90 (SD 1.714) mg/dL in sevelamer carbonate and 0.25 (SD 1.654) mg/dL in placebo.

Subgroup analysis

The results of the subgroup analysis in the FAS FDP (by Screening BSA < or \geq 1.2 m² and by mean

baseline serum phosphorus < or ≥ 7.0 mg/dL [< 2.26 versus ≥ 2.26 mmol/L]) were:

- Screening BSA (m²) < 1.2: mean change from baseline: -0.91 (SD 1.857) mg/dL in sevelamer carbonate and 0.27 (SD 1.615) mg/dL in placebo;
- Screening BSA (m²) ≥ 1.2 : mean change from baseline: -0.86 (SD 1.631) mg/dL in sevelamer carbonate and 0.01 (SD 1.476) mg/dL in placebo;
- Mean baseline serum phosphorus < 7.0 mg/dL: mean change from baseline: 0.05 (SD 1.097) mg/dL in sevelamer carbonate and 0.18 (SD 1.511) mg/dL in placebo;
- Mean baseline serum phosphorus ≥ 7.0 mg/dL: mean change from baseline: -1.95 (SD 1.541) mg/dL in sevelamer carbonate and -0.08 (SD 1.468) mg/dL in placebo.

Results of subgroup analysis using the PPS FDP supported the results of subgroup analysis on FAS-FDP:

- Screening BSA (m²) < 1.2: mean change from baseline: -1.90 (SD 2.007) mg/dL in sevelamer carbonate and -0.33 (SD 0.306) mg/dL in placebo.
- Screening BSA (m²) ≥ 1.2 : mean change from baseline: -0.70 (SD 1.632) mg/dL in sevelamer carbonate and 0.34 (SD 1.759) mg/dL in placebo.
- Mean qualifying serum phosphorus < 7.0 mg/dL: mean change from baseline: 0.03 (SD 1.250) mg/dL in sevelamer carbonate and 0.59 (SD 2.094) mg/dL in placebo.
- Mean qualifying serum phosphorus ≥ 7.0 mg/dL: mean change from baseline: -2.19 (SD 1.434) mg/dL in sevelamer carbonate and -0.01 (SD 1.249) mg/dL in placebo.

Ad hoc analysis on patients with normal serum phosphorus

In the FAS-FDP, at Week 2, four patients in each group (8.3% in sevelamer carbonate and 8.2% in placebo) had a serum phosphorus level within their age appropriate normal ranges. A similar percentage (8.3% [2 patients]) in sevelamer carbonate and 8.7% [2 patients] in placebo) was observed in the PPS-FDP.

Analysis of serum phosphorus levels over time in in FAS-FDP showed a decrease in serum phosphorus level during treatment with sevelamer carbonate. The most pronounced decrease in mean phosphorus level from baseline was achieved at the end of the first two weeks of active treatment (the mean change from baseline was -0.87 [SD 1.649, n=48] mg/dL at Week 2 in patients on sevelamer carbonate in the FDP and -0.77 [SD 1.592, n=46] mg/dL at Week 4 in patients on placebo in the FDP).

At the end of treatment the mean change from baseline was -0.94 (SD 2.116, n=33) mg/dL at Week 28 (-1.17 [SD 2.184, n=48] mg/dL at Week 28/ET) in patients who were on sevelamer carbonate in the FDP and -1.12 [SD 1.840, n=33] mg/dL at Week 28 (-1.19 [SD 1.981, n=47] mg/dL at Week 28/ET) in patients who were on placebo in the FDP.

At the last study visit (Week 28/ET), overall 26 patients (27.4%) had a serum phosphorus level within their age-appropriate normal ranges.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9. Summary of Efficacy for trial SVCARB07609

Title: A 2-week, randomized, placebo-controlled, fixed dose period followed by a 6-month, single-arm, open-label, dose titration period study to investigate the efficacy and safety of sevelamer carbonate in hyperphosphatemic pediatric patients with chronic kidney disease			
Study identifier	SVCARB07609		
Design	Randomized, double-blind, placebo-controlled		
	Duration of main phase:	2 weeks	
	Duration of Extension phase:	26 weeks (dose titration period)	
Hypothesis	Superiority		
Treatments groups	Sevelamer carbonate	0.4-1.6 g TID depending on BSA at screening. Dose could be increased or decreased every 2 weeks for the first 6 weeks and every 4 weeks thereafter in the dose titration period of the study as necessary. 50 patients randomised.	
	Placebo	51 patients randomised.	
Endpoints and definitions	Primary endpoint	Change in serum phosphorus levels	Change from baseline [Visit 2 (Week 0)] to Visit 3 (Week 2) in serum phosphorus
	Secondary endpoint	Change in serum phosphorus levels	Change from baseline [Visit 2 (Week 0)] to Visit 11/ET (Week 28/ET) in serum phosphorus
Database lock	16 June 2015		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full analysis set, consisting all treated patients with a baseline phosphorus value and at least 1 phosphorus assessment taken after the first dose of study drug and on or before Visit 3 (Week 2).		
Descriptive statistics and estimate variability	Treatment group	Sevelamer carbonate	Placebo
	Number of subjects	48	49
	Change in serum phosphorus levels at week 2 Mean (SD)	-0.87 (1.649)	0.04 (1.478)
	Treatment group	Sevelamer carbonate	Placebo
	Number of subjects	46	49
	Change in serum phosphorus levels at week 28 Mean (SD)	-1.23 (2.206)	-1.13 (2.061)
Effect estimate per comparison	Primary endpoint	Comparison groups	Sevelamer carbonate vs. Placebo
		LS Mean Difference (SE)	-0.90 (0.270)
		95% CI	-1.44, -0.37
		P-value	0.001
Notes	The analysis used an ANCOVA model with treatment as fixed effect and screening BSA and baseline phosphorus as covariates.		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical study

This phase II study was a 2-week, randomized, placebo-controlled, fixed dose period (FDP) followed by a 6-month, single-arm, open-label, dose titration period (DTP) to study the efficacy and safety of sevelamer carbonate in hyperphosphatemic paediatric patients with chronic kidney disease.

The proposed indication was for the control of hyperphosphataemia in paediatric patients (≥ 6 years of age and a body surface area (BSA) of ≥ 0.75 m²) with chronic kidney disease, as no patients below those cut-off values were included in the study. Furthermore, Section 4.2 of the SmPC states that safety and efficacy of sevelamer carbonate have not been established in children below the age of 6 years or in children with a BSA below 0.75 m².

Eligible patients were randomized 1:1 to receive sevelamer carbonate or placebo for 2 weeks. As there are no approved medications to treat hyperphosphatemia in children with CKD a placebo-controlled FDP was considered appropriate. Furthermore, the 2-week duration was selected to minimize the time patients may be receiving placebo.

The DTP was a single-arm period during which all patients received sevelamer carbonate for a long-term period (6 months).

The dose of sevelamer carbonate required in paediatric patients was expected to be less than that required in adults because the dietary phosphorus intake in children is less than that in adults and thus the phosphate binder needs are lower. Hence, the dosing strategy was that the starting and titration dose in patients was to be adjusted based on a patient's screening BSA.

A BSA < 0.75 m² typically represents young children not yet of school age whereas a BSA of ≥ 1.2 m² represents larger/adolescent children. As their phosphate binder needs are thought to be similar to that of adults, their dose was consistent with adult dosing.

Therefore the recommended starting dose for paediatric patients is based on the patient's body surface area (BSA) category. Similar to the recommendation in adults, sevelamer carbonate must be taken three times per day with meals and /or snacks. If a child eats less than 3 meals/snacks per day, sevelamer carbonate should only be given with meals/snacks and not on an empty stomach. This proposal was considered appropriate.

Efficacy data and additional analyses

A total of 81 patients (81.0%) were taking a phosphate binder at screening visit, similar in both groups. 53 patients were taking sevelamer-based binder, again similarly divided in both groups. A calcium-based binder was taken by 36 patients.

In paediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus through Week 2 by an LS Mean difference of -0.90 (SE 0.270) mg/dL compared to placebo ($p=0.001$). When patients with a baseline serum phosphorus levels in the normal range or below were excluded, LS mean difference was -1.07 mg/dL compared to placebo ($p<0.001$). This result was further supported by the analysis conducted on the PPS-FDP (LS Mean difference of -1.15 [SD 0.407] mg/dL in sevelamer carbonate compared to placebo [$p=0.007$]).

Adult studies with various phosphate binders, e.g. lanthanum carbonate and colestilan, have determined that a clinically meaningful difference is at least 1.0 mg/d. Even though there are no such studies published for the paediatric population, there is no evidence to suggest that children should have a different criterion for what constitutes a clinically significant change in serum phosphorus.

The CHMP noted that the overall proportion of serum phosphorus responders in paediatric patients in the current study (27.4%) was lower than the proportion observed in adult patients with chronic kidney disease (around 50%).

However, in addition to responder rate, the proportion of patients achieving a serum phosphorus decrease even if not reaching normal range is also a relevant parameter to consider. In this respect serum phosphorus levels corresponding to the 75th percentile (Q3) provide relevant information. Q3 value in the placebo group evolved from 8.20 mg/dL to 8.30 mg/dL in the FDP. In the sevelamer carbonate group, Q3 value evolved from 8.45 mg/dL to 7.35 mg/dL, which highlights the substantial proportion of patients having their serum phosphorus levels decreased.

In light of the above, the CHMP considered that the clinical effects demonstrated in the current study are of clinical relevance in the paediatric population.

The treatment response during the 2-week FDP was not affected by BSA, and a slight increase in mean serum phosphorus was observed in patients with qualifying phosphorus levels <7.0 mg/dL.

Results of subgroup analysis in FAS-FDP and PPS-FDP were consistent with results of primary efficacy analysis except for the subgroup with mean qualifying serum phosphorus <7.0 mg/dL (mean change from baseline: 0.05 [SD 1.097] mg/dL in FAS-FDP and 0.03 [SD 1.250] mg/dL in PPS-FDP), and this is reflected in Section 5.1 of the SmPC.

A similar treatment response was observed in patients who received sevelamer carbonate during the 6-month open-label DTP. Sevelamer carbonate significantly reduced serum phosphorus through Week 28/ET: the mean change from baseline to Week 28/ET was -1.18 (SD 2.122) mg/dL [p<0.0001].

Analysis of serum phosphorus levels over time clearly showed a decrease in serum phosphorus level during treatment with sevelamer carbonate.

An ad hoc analysis showed that at Week 2, 8% of patients on sevelamer carbonate achieved a serum phosphorus level within their age appropriate normal ranges (a similar percentage was in patients on placebo). At the last study visit (Week 28/ET), overall 26 patients (27.4%) had a serum phosphorus level within their age-appropriate normal ranges. A similar percentage [28.4% (19 patients)] was observed at Week 28.

For paediatric patients, serum phosphorus levels must be monitored and the dose of sevelamer carbonate titrated in increments based on patient's BSA, three times per day every 2 to 4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

2.4.4. Conclusions on the clinical efficacy

In paediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus levels compared to placebo during a 2-week FDP. The effect size was comparable to what is accepted as a meaningful response in adult patients. The results of the primary analysis were also supported by sub-group analyses based on BSA and baseline phosphorus levels.

Serum phosphorus levels were within their age-appropriate normal ranges in approximately a quarter of the paediatric patients who received sevelamer carbonate during the 6-month open-label DTP.

Overall the CHMP concluded that the available clinical efficacy data were adequate to support this

application for use of sevelamer carbonate for the control of hyperphosphataemia in paediatric patients (>6 years of age and a body surface area (BSA) of >0.75 m²) with chronic kidney disease.

2.5. Clinical safety

Introduction

Sevelamer carbonate is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. The most frequently occurring adverse reactions are from the gastrointestinal disorders system organ class.

Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, and levothyroxine.

Patient exposure

A total of 100 patients received the study drug. Of these, 49 patients received sevelamer carbonate and 51 patients received placebo in the FDP of the study.

In the Safety Set, the extent of exposure was similar across the two groups with a median exposure of 15 days in each group in the FDP and a median exposure of 183.5 days and 183 days in the sevelamer carbonate group and the placebo group respectively in the DTP.

The median prescribed daily dose in the FDP was 4.8 g in the sevelamer carbonate and placebo groups. The median prescribed daily dose in the DTP was higher in the sevelamer carbonate group (7.01 g) compared with the placebo group (6.42 g).

The mean study treatment compliance in the FDP was slightly higher in patients on sevelamer carbonate (71%) compared with patients on placebo (68%). Mean study treatment compliance in the DTP was higher in the placebo group (77%) compared with the sevelamer carbonate group (71%).

The demographics and baseline characteristics of the Safety Set are detailed in **Table 10**.

Table 10. Demographics and baseline characteristics in study SVCARB07609 – Safety set

	Placebo (N = 51)	Sevelamer Carbonate (N = 49)	Total (N = 100)
Age (years)			
N	51	49	100
Mean (SD)	14.3 (3.11)	13.9 (2.75)	14.1 (2.93)
Median	15.0	14.0	15.0
Min, Max	6, 18	6, 18	6, 18
Q1, Q3	12.0, 17.0	12.0, 16.0	12.0, 16.0
95% CI of the Mean	13.4, 15.1	13.1, 14.7	13.5, 14.7
Age Categories (years), n (%)			
N	51	49	100
0-12	13 (25.5)	13 (26.5)	26 (26.0)
13-18	38 (74.5)	36 (73.5)	74 (74.0)
Sex, n (%)			
N	51	49	100
Male	33 (64.7)	30 (61.2)	63 (63.0)
Female	18 (35.3)	19 (38.8)	37 (37.0)
Childbearing Potential for Females, n (%)			
N	18	19	37
Yes	12 (66.7)	15 (78.9)	27 (73.0)
No	6 (33.3)	4 (21.1)	10 (27.0)

Note: Denominators for percentages are based on the number of patients with non-missing data in each treatment group the relevant variable. Childbearing potential percentages are based on the number of females only.

Note: Age is calculated as (informed consent date - date of birth + 1)/365.25 and reported as whole years without rounding

Note: Body Mass Index (kg/m²) = Weight (kg) / (Height (m))².

Note: Qualifying Serum Phosphorus from CRF data.

Adverse events

Fixed dose period:

A total of 70 treatment emergent adverse events (TEAEs) occurred in 39 patients (39.0%) in the FDP: 34 TEAEs in 19 patients (38.8%) on sevelamer carbonate and 36 TEAEs in 20 patients (39.2%) on placebo.

There were 2 TEAEs leading to study drug discontinuation in the FDP: 1 event in 1 patient (2%) on sevelamer carbonate (hyperphosphatemia) and 1 event in 1 patient (2%) on placebo (blood phosphorus increased)..

Most TEAEs were mild in severity (47 events in 30 patients [30.0%]: 24 in 15 patients [30.6%] on sevelamer carbonate and 23 in 15 patients [29.4%] on placebo). 4 TEAEs in 2 patients (2.0%) were reported with severe severity (1 event in 1 patient [2.0%] on sevelamer carbonate and 3 events in 1 patient [2.0%] on placebo).

Seven TEAEs in 5 patients (5.0%) were reported as being related or possibly related to study drug: 4 events in 2 patients (4.1%) on sevelamer carbonate and 3 events in 3 patients (5.9%) on placebo. Four TEAEs in sevelamer carbonate reported as related or possibly related to study drug included: hyperphosphataemia, abdominal pain, ocular hyperaemia, and muscle spasms.

The most frequent TEAE in sevelamer carbonate was hypertension (3 events in 2 patients [4.1%] versus 0 in placebo). The most frequent TEAE in placebo was vomiting (4 events in 3 patients [5.9%] versus 0 in sevelamer carbonate).

Dose titration period:

Overall 525 TEAEs occurred in 77 patients (77.0%) in the DTP: 253 TEAEs in 35 patients (71.4%) in the sevelamer carbonate group and 272 TEAEs in 42 patients (82.4%) in the placebo group.

There were 3 TEAEs in 3 patients (3.0%) leading to study drug discontinuation in the DTP (2 of these events were reported as SAE): septic shock, varicella zoster virus infection, and chronic kidney disease*.

Out of 525 TEAEs that occurred in 77 patients (77.0%) in the DTP, 313 TEAEs reported in 69 patients (69.0%), were mild in severity and 43 TEAEs in 20 patients [20.0%] were severe.

22 TEAEs in 13 patients (13.0%) were reported as related or possibly related to study drug. Most of these TEAEs occurred in the MedDRA SOC of Gastrointestinal disorders (15 events in 8 patients [8.0%]) with nausea (5 events), constipation (3 events), vomiting and abdominal pain upper (2 events for each term) reported most frequently.

TEAEs were most frequently reported for the MedDRA SOC of Gastrointestinal disorders.

The most frequently occurring TEAEs were: vomiting (29 events in 20 patients [20.0%], abdominal pain and nausea (21 events in 15 patients [15.0%] for each term), pyrexia (25 events in 19 patients [19.0%]), headache (19 events in 17 patients [17.0%]), hypotension (14 events in 9 patients [9.0%]), abdominal pain upper (13 events in 9 patients [9.0%]), upper respiratory tract infection (12 events in 12 patients [12.0%]), and diarrhea and hypertension (11 events in 7 patients [7.0%] for each term).

Serious adverse event/deaths/other significant events

Fixed dose period:

A total of 6 treatment emergent serious adverse events (SAEs) occurred in 5 patients (5.0%) in the FDP: a higher number of SAEs was reported in sevelamer carbonate (5 SAEs in 4 patients [8.2%] compared with placebo (1 SAE in 1 patient [2.0%])).

Among the SAEs in sevelamer carbonate, 1 was reported with severe severity, 2 SAEs were reported as moderate and 2 SAEs as mild. One SAE in placebo was reported with mild severity.

No SAE was reported as related to the study drug.

Five SAEs occurring in sevelamer carbonate were reported with the following PT: hypertension (2 events), device occlusion, peritonitis, and hyperkalaemia. One SAE in placebo was reported with the PT: gastroenteritis viral.

Dose titration period:

Overall, 79 SAEs occurred in 31 patients (31.0%) in the DTP.

38 SAEs in 18 patients (18.0%) were reported with severe severity, 24 SAEs in 15 patients (15.0%) with moderate severity and the remaining 17 SAEs in 8 patients (8.0%) had mild severity.

Four SAEs were reported as related or possibly related to study drug: constipation [2 events], post procedural constipation and gastritis.

The most frequent (3 and 4 events) SAEs included: abdominal pain, device malfunction, renal impairment and pyrexia.

Laboratory findings

Serum calcium and calcium (adjusted for albumin)

Changes in serum calcium over time from baseline to the last study visit showed clinically insignificant changes.

Serum calcium x phosphorus product

In patients on sevelamer carbonate, the mean calcium x phosphorus product level decreased from 70.81 (± 21.305 , n=49) mg²/dL² at baseline to 61.92 (± 13.461 , n=48) mg²/dL² at Week 2 (mean change from baseline of -8.63 [± 16.752 , n=48] mg²/dL²).

In patients on placebo, the mean calcium x phosphorus product level increased from 69.49 (± 19.429 , n=51) mg²/dL² at baseline to 70.39 (± 20.427 , n=49) mg²/dL² at Week 2 (mean change from baseline of 0.42 [± 16.616 , n=49] mg²/dL²). For the overall safety set, the mean calcium x phosphorus product level decreased from 70.14 (± 20.277 , n=100) mg²/dL² at baseline to 59.04 (± 18.233 , n=67) mg²/dL² at Week 28 (mean change from baseline of -9.60 [± 20.285 , n=67] mg²/dL²) and 58.81 (± 18.688 , n=98) mg²/dL² at the last study visit (Week 28/ET) (mean change from baseline of -10.94 [± 22.123 , n=98] mg²/dL²).

No particular safety issues or signals were identified in the review of the other clinical laboratory data (data not shown).

2.5.1. Discussion on clinical safety

Sevelamer carbonate was well tolerated in this group of paediatric patients with chronic kidney disease. There were 5 TEAE (2 reported as SAE) leading to withdrawal (4 in patients treated with sevelamer carbonate and 1 in patient on placebo).

There were no deaths reported during the study.

In the blinded fixed dose period (FDP), 19 patients (38.8%) on sevelamer carbonate experienced 34 TEAEs and 20 patients (39.2%) on placebo experienced 36 TEAEs. Of these, 1 patient on sevelamer carbonate and 1 patient on placebo had AEs of severe severity. One patient on sevelamer carbonate and 1 patient on placebo discontinued due to an AE (hyperphosphatemia and high phosphorus level, respectively).

TEAEs were most frequently reported for the MedDRA SOC of Gastrointestinal disorders which is expected given the available safety information from the adult population. To minimise such adverse events a warning has also been included in Section 4.2 sevelamer carbonate that should be taken with food and not on an empty stomach.

During the DTP, majority of the AEs were mild or moderate and assessed as not related to sevelamer carbonate.

There were no clinically meaningful changes in any of the laboratory parameters including serum chemistry, haematology, coagulation, and vitamins. Overall, there were no clinically meaningful changes in serum lipids measured (cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) over time from baseline to Week 28 of the study.

The CHMP noted that the submitted study in support of this application had been conducted with a 0.8 g sachet, instead of the proposed 1.6 and 2.4 gr sachets or with 800 mg tablets in some patients with screening BSA $\geq 1.2 \text{ m}^2$. The 0.8 g sachet would appear to be more suitable for use in the intended paediatric population, as the recommend dosage depending on the BSA of the patient ranges between 0.8-1.6 g three times daily and up/down titrations of 0.4-0.8 g three times daily. Furthermore, it was deemed that multiple daily tablets required to achieve the recommended doses would not be suitable for the paediatric population, and therefore the CHMP considered that the new paediatric indication should be granted only for the sachets but not for the tablet formulation.

To ensure correct dose administration in the paediatric population, section 4.2 of the SmPC states that the content of the sachet can be divided, and that sevelamer carbonate powder may be measured by volume (mL) using a measuring scoop or measuring spoon. In addition, medication errors in children have been included in the RMP as an important potential risk. The CHMP also recommended that the MAH further develops a pharmaceutical formulation, which would be more suitable for use in the intended paediatric population for sevelamer, e.g. a 0.8 g sachet and a suitable device which would allow the accurate administration of the minimum 0.4 g increments of sevelamer in accordance with the product's SPC.

2.5.2. Conclusions on clinical safety

Most of the AEs reported as related or possibly related to sevelamer carbonate were gastrointestinal in nature. No new risks or safety signals were identified with the use of sevelamer carbonate in the paediatric population and the safety profile of sevelamer appears to be acceptable and in line with the risks described in the SmPC for adults.

The potential for medication errors is addressed through appropriate wording in the product information and inclusion in the RMP. The MAH has also provided commitment to further develop a formulation more suitable in the paediatric population.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 30 October 2017.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.1 is acceptable. In addition, CHMP considered that the potential for medication errors should be considered as an important potential risk.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

Safety concerns

Table 11. Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Intestinal perforation, obstruction and ileus Diverticulitis (sevelamer hydrochloride formulation only) Acidosis, increased serum chloride levels (sevelamer hydrochloride formulation only)
Important potential risks	Serious gastrointestinal disorders associated with sevelamer crystals Hypersensitivity reactions, including angioedema and anaphylactic reactions Difficulty swallowing tablets Medication errors Medication error in children due to: <ul style="list-style-type: none"> • unavailability of dedicated paediatric presentation • and absence of dosing device Vitamin deficiency Drug interactions with levothyroxine, ciprofloxacin, immunosuppressants, antiarrhythmics, anticonvulsants and antifungal drugs Off-label use in patients <18 year-old (sevelamer hydrochloride formulation only)
Missing information	Use in pregnancy and lactation Use in hepatic impairment and in immunocompromised patients

Pharmacovigilance plan

None

Risk minimisation measures

Table 12. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities

Safety concern	Routine risk minimisation activities	Additional risk minimisation activities
Important identified risks		
Intestinal perforation, obstruction and ileus	SmPC, PIL, packaging	None
Diverticulitis (sevelamer hydrochloride formulation only)	SmPC, PIL, packaging	None
Acidosis, increased serum chloride levels (sevelamer hydrochloride formulation only)	SmPC, PIL, packaging	None
Important potential risks		
Serious gastrointestinal disorders associated with sevelamer crystals	SmPC, PIL, packaging	None
Hypersensitivity reactions, including angioedema and anaphylactic reactions	SmPC, PIL, packaging	None
Difficulty swallowing tablets	SmPC, PIL, packaging	None
Medication errors due to: <ul style="list-style-type: none"> • unavailability of dedicated paediatric presentation • and absence of dosing device 	SmPC, PIL, packaging	None
Vitamin deficiency	SmPC, PIL, packaging	None
Drug interactions with levothyroxine, ciprofloxacin, immunosuppressants, antiarrhythmics, anticonvulsants and antifungal drugs	SmPC, PIL, packaging	None
Off-label use in patients <18 year-old (sevelamer hydrochloride formulation only)	SmPC, PIL, packaging	None
Missing information		
Use in pregnancy and lactation	SmPC, PIL, packaging	None
Use in hepatic impairment and in immunocompromised patients	None	None

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: only minor changes to the leaflet have been made to reflect the extension of indication of sevelamer carbonate to the paediatric patients.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In CKD the homeostatic system for maintaining physiological phosphorus balance is altered by the progressive loss of functioning kidneys. In early CKD, serum phosphorus levels are at near normal levels in children.

Hyperphosphatemia is almost always observed in children on dialysis. Failure to control hyperphosphatemia may be associated with debilitating sequelae and increased mortality.

3.1.2. Available therapies and unmet medical need

The control of hyperphosphatemia is particularly challenging in paediatric CKD patients. Restricting phosphate intake by dietary means is the first line of treatment in paediatric CKD patients; however, this is difficult because of the need for adequate intake of proteins and calories to support skeletal growth. Dialysis removes some phosphorus in paediatric CKD patients, but it does not usually fully offset dietary absorption of phosphate.

In adults, a major component of hyperphosphatemia management is the use of phosphate binders to decrease the intestinal absorption of dietary phosphorus. However, no phosphate binders have been approved for use in children.

3.1.3. Main clinical studies

A phase 2, two-week, randomized, placebo-controlled, fixed dose period followed by a 6-month, single-arm, open-label, dose titration period study, (SVCARB07609 / DRI12793) was submitted to evaluate the safety and efficacy of sevelamer carbonate in paediatric CKD patients.

3.2. Favourable effects

The primary efficacy endpoint -change from baseline to Visit 3 (Week 2) in serum phosphorus (in mg/dL)- and the efficacy secondary endpoint -change from baseline to Visit 11/ET (Week 28/ET) in serum phosphorus (mg/dL)-were both reached . Even if the effect size appears to be small, it is of similar magnitude to what is considered as clinically meaningful in adults.

3.3. Uncertainties and limitations about favourable effects

Benefit in patients with baseline phosphorus levels <7.0 mg/dL was not demonstrated in this study. However it is difficult to draw conclusions about this sub-group of patients due to the small number of these patients.

The proportion of serum phosphorus responders in paediatric patients in the current study (27.4%) was lower than the proportion observed in adult patients with chronic kidney disease (around 50%). Nevertheless, even if not reaching completely normal serum phosphorus levels, a substantial proportion of patients had their serum phosphorus levels decreased.

3.4. Unfavourable effects

The safety and tolerability of sevelamer carbonate were similar to placebo during the FDP of the study. During the DTP, the majority of the AEs were mild or moderate and assessed as not related to sevelamer carbonate. The AEs were most frequently reported for the MedDRA SOC of Gastrointestinal disorders.

The data reviewed and summarized were consistent with the known safety profile of sevelamer carbonate. No new risks or safety signals were identified with the use of sevelamer carbonate.

3.5. Uncertainties and limitations about unfavourable effects

The study was conducted with a formulation which is not currently available. Even though, there no clear safety concern was identified in the case of incorrect dosage, the potential for medication errors has been included in the RMP and the MAH has committed to further develop a formulation and a device which could more easily facilitate correct dosing in children.

3.6. Effects Table

Table 13. Effects Table for control of hyperphosphatemia in paediatric patients (>6 years of age and a Body Surface Area (BSA) of >0.75 m²) with chronic kidney disease data cut-off: 16 June 2015.

Effect	Short description	Unit	Sevelamer	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Serum Phosphorus	Change from baseline to Visit 3 (Week 2) in serum phosphorus	mg/dL	-0.87 (N=48) Statistical significant compared to placebo (p=0.001)	+0.04	Subgroup analysis shows no effect when baseline serum phosphorus <7.0mg/dL Results from DTP also supportive of positive effect	SVCARB076 09

Effect	Short description	Unit	Sevelamer	Placebo	Uncertainties / Strength of evidence	References
Unfavourable Effects						
SAEs	Number of patients experiencing event	N (%)	4 (8.2)- FDP 31-DTP	1 (2%)	Isolated adverse events, the ones reported as related or possibly related to study drug from the GI disorders SOC	

Abbreviations: DTP: Dose titration period; FDP=Fixed dose period; SAE: serious adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The decrease seen in the paediatric population with this phosphate binder is expected to have an important role in serum phosphorus levels control in the paediatric population.

The safety profile of sevelamer carbonate is well characterised through the adult population and is limited primarily to gastrointestinal disorders which rarely have serious consequences.

As no new safety signals were identified, compared to the adult population, the current warnings in the product information are expected to be adequate to manage the known risks associated with sevelamer carbonate use.

3.7.2. Balance of benefits and risks

Phosphorus control in CKD patients is a combination of several measures, i.e. dietary measures, dialysis protocol and/or phosphate binders. Especially in view of the fact that no such products are currently authorised in the paediatric population, the observed decreases in serum phosphorus levels are considered of clinical relevance.

As no new safety signals were identified, compared to the adult population, the current warnings in the product information are expected to be adequate to manage the known risks associated with sevelamer carbonate use.

3.8. Conclusions

The overall B/R of Renvela/ Sevelamer carbonate Zentiva of product is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		
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Extension of indication for Renvela 1.6 g and 2.4 g powder for oral suspension and Sevelamer carbonate Zentiva 2.4 g powder for oral suspension to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a Body Surface Area (BSA) of >0.75 m²) with chronic kidney disease. As a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated in order to add information on posology and safety in paediatric patients and to reflect the results of the paediatric study. The Package Leaflet is updated in accordance.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication for Renvela 1.6 g and 2.4 g powder for oral suspension and Sevelamer carbonate Zentiva 2.4 g powder for oral suspension to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a Body Surface Area (BSA) of >0.75 m²) with chronic kidney disease. As a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated in order to add information on posology and safety in paediatric patients and to reflect the results of the paediatric study. The Package Leaflet is updated in accordance.

Summary

Please refer to the Scientific Discussion of Renvela and Sevelamer carbonate Zentiva EMEA/H/C/WS0965.