EU RISK MANAGEMENT PLAN FOR SEVELAMER CARBONATE/SEVELAMER HYDROCHLORIDE

COVER PAGE

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Pharmaco-therapeutic group (ATC Code)	**V03A E02**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Medicinal product(s) to which this RMP refers	**3**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Data lock point (DLP) for current Risk Management Plan (RMP)	**30-OCT-2019**
Version number of the current RMP	**Version 10.0**
Date of final sign-off	**02-DEC-2019**

Table 1 - RMP version to be assessed as part of this application

RMP Version number	Version 10.0
Data lock point for this RMP	30-OCT-2019
Date of final sign off	02-DEC-2019
Rationale for submitting an updated RMP	During the procedure for the renewal of the marketing authorization for SEVELAMER CARBONATE WINTHROP (EMEA/H/C/003971/R/0022), the CHMP requested: following SmPC update at the end of the last PSUSA procedure for sevelamer-containing products (PSUSA/00002697/201810), the important potential risk "sevelamer crystals associated with serious gastrointestinal disorders" should be removed from the list of safety concerns in the RMP of sevelamer hydrochloride/carbonate products. He requested that MAH should adapt the Summary of safety concerns of the RMP in line with the requirements outlined in the Rev. 2 of the GVP module V. This RMP version 10.0 is transferred to new EU-RMP template (GVP Module V Revision 2: effective on 31-Mar-2017).
Summary of significant changes in this RMP	The significant RMP changes are in the simplified list of safety concerns, in compliance with GVP Module V Revision 2.

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; EU: European Union; GVP: Good Pharmacovigilance Practices; MAH: Marketing Authorization Holder; PSUSA: Periodic Safety Update Report Single Assessment; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	Not applicable	Not applicable

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	9.1
Approved with procedure	Centralized procedure (RMP reviewed within the frame of line extension procedures, EMEA/H/C/000993/X/0039 for RENVELA and EMEA/H/C/3971/X/11 for SEVELAMER CARBONATE WINTHROP, concerning the addition of a new strength).
Date of approval (opinion date)	20 to 21-Sep-2018

EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	[redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Eric Teo, QPPV for Sanofi.

QPPV: Qualified Person for Pharmacovigilance.

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ABBREVIATIONS

ATC:	Anatomical Therapeutic Chemical
CHMP:	Committee for Medicinal Products for Human Use
DLP:	Data Lock Point
EMEA:	European Medicines Agency
EU:	European Union
GVP:	Good Pharmacovigilance Practices
INN:	International Nonproprietary Name
MAH:	Marketing Authorization Holder
PIL:	Product Information Leaflet
PSUSA:	Periodic Safety Update Report Single Assessment
QPPV:	Qualified Person for Pharmacovigilance
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

Table 5 - Overview of the RMP Parts and Modules in the current RMP

PART	MODULE or ANNEX	Module version number	Date of approval (opinion date)	Rationale for update
Part I – Product(s) overview		10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
Part II - Safety specification	**SI** - Epidemiology of the indication(s) and target population(s)	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
	SII - Non-clinical part of the safety specification	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
	SIII - Clinical trial exposure	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
	SIV - Populations not studied in clinical trials	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
	SV - Post-authorization experience	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
	SVI - Additional EU requirements for the safety specification	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
	SVII - Identified and potential risks	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2. Revision of list of safety concerns.
	SVIII - Summary of the safety concerns	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2. Revision of list of safety concerns.
Part III - Pharmacovigilance plan (including post-authorization safety studies)		10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
Part IV - Plans for post-authorization efficacy studies		10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.

Part V - Risk minimization measures (including evaluation of effectiveness of risk minimization activities)		10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
Part VI - Summary of the risk management plan		10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
Part VII - Annexes	**Annex 1** – Eudravigilance Interface	Not applicable	Not applicable	Not applicable
	Annex 2 – Tabulated summary of planned, on-going and completed studies in the pharmacovigilance plan	Not applicable	Not applicable	Not applicable
	Annex 3 – Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan	Not applicable	Not applicable	Not applicable
	Annex 4 – Specific adverse event follow-up forms	Not applicable	Not applicable	Not applicable
	Annex 5 – Protocols for proposed and on-going studies in Part IV	Not applicable	Not applicable	Not applicable
	Annex 6 – Details of proposed additional risk minimization activities	Not applicable	Not applicable	Not applicable
	Annex 7 – Other supporting data (including referenced material)	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.
	Annex 8 - Summary of changes to the risk management plan over time	10.0	-	Transfer to new EU-RMP template of GVP Module V Revision 2.

Signature Page for VV-PV-0371019 v1.0
RMP Sevelamer Carbonate + Hydrochloride Part 0 v10.0 Prelimin

Approve & eSign	[redacted]

RISK MANAGEMENT PLAN - PART I

PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
PRODUCT(S) CONCERNED (BRAND NAME(S))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 10.0**

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ABBREVIATIONS

ATC:	Anatomical Therapeutic Chemical
BSA:	Body Surface Area
DLP:	Data Lock Point
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMEA:	European Medicines Agency
EU:	European Union
INN:	International Nonproprietary Name
RMP:	Risk Management Plan

Table 1 - Product Overview

Active substance(s) (INN or common name)	Sevelamer carbonate/sevelamer hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	V03A E02
Marketing Authorization Holder	Genzyme Europe B.V. Paasheuvelweg 25 1105 BP Amsterdam, The Netherlands
Medicinal products to which this RMP refers	3
Invented name(s) in the EEA	RENVELA, SEVELAMER CARBONATE WINTHROP, RENAGEL
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class Sevelamer carbonate and sevelamer hydrochloride contains sevelamer, a non-absorbed phosphate binding cross-linked polymer, free of metal and calcium.
	Summary of mode action Sevelamer contains multiple amines separated by one carbon from the polymer backbone which become protonated in the stomach. These protonated amines bind negatively charged ions such as dietary phosphate in the intestine. Regular monitoring of serum phosphorus levels is always necessary during phosphate binder administration.
	Important information about its composition Not applicable
Hyperlink to the product information	RENAGEL - emea-h-c-000254: 0059 RENVELA - emea-h-c-000993: 0121 SEVELAMER CARBONATE WINTHROP - emea-h-c-003971: 0060
Indication(s) in the EEA	Current Renvela/Sevelamer carbonate Winthrop and Renagel are indicated for the control of hyperphosphatemia in adult patients receiving hemodialysis or peritoneal dialysis. Renvela/Sevelamer carbonate Winthrop are also indicated for the control of hyperphosphatemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus $\geq$1.78 mmol/L. Renvela/Sevelamer carbonate Winthrop are indicated for the control of hyperphosphatemia in pediatric patients (>6 years of age and a BSA of >0.75 m^2) with chronic kidney disease. Renvela/Sevelamer carbonate Winthrop and Renagel should be used within the context of a multiple therapeutic approach, which could include calcium

	supplements, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.
	Proposed Not applicable
Dosage in the EEA	Current **Renagel (sevelamer hydrochloride) 400 and 800 mg film-coated tablets-** *Posology in adult patients:* • *Starting dose:* The recommended starting dose is 2.4 g, 3.6 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renagel must be taken 3 times per day with meals. • *Titration and Maintenance:* The dose should be adapted until a stable serum phosphate level is reached (level ≤1.76 mmol/L (5.5 mg/dL) or less). The dose range may vary between 1 and 10 tablets per meal. The average actual daily dose used in the chronic phase of a one year clinical study was 7 grams of sevelamer. **Renvela/Sevelamer carbonate Winthrop (sevelamer carbonate) 800 mg film-coated tablets/Renvela (sevelamer carbonate) 0.8, 1.6 and 2.4 g powder for oral suspension/Sevelamer carbonate Winthrop 0.8 and 2.4 g powder for oral suspension –** *Posology in adult patients:* • *Starting dose:* The recommended starting dose is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renvela/Sevelamer carbonate Winthrop tablets must be taken 3 times per day with meals. • *Titration and Maintenance:* The dose should be adapted until a stable serum phosphate level is reached. The daily dose is expected to be an average of approximately 6 g per day. **Renvela (sevelamer carbonate) 0.8, 1.6 and 2.4 g powder for oral suspension/Sevelamer carbonate Winthrop 0.8 and 2.4 g powder for oral suspension –** *Posology in pediatric patients (>6 years of age and a BSA of >0.75 m^2):* • *Starting dose:* The recommended starting dose is between 2.4 g and 4.8 g per day based on the patient's BSA category. Renvela/Sevelamer carbonate Winthrop must be taken three times per day with meals and/or snacks. • *Titration and Maintenance:* The dose of sevelamer carbonate must be titrated in increments based on patient's BSA, three times per day every 2-4 weeks until an acceptable serum phosphorus level is reached.
	Proposed Not applicable
Pharmaceutical form(s) and strength(s)	Current Renagel 400 mg film coated tablets. Renagel, Renvela and Sevelamer carbonate Winthrop 800 mg film coated tablets. Renvela 0.8 g, 1.6 g and 2.4 g powder for oral suspension and Sevelamer carbonate Winthrop 0.8 g, 2.4 g powder for oral suspension.

	Proposed Not applicable
Is the product subject to additional monitoring in the EU?	No

ATC: Anatomical Therapeutic Chemical; BSA: Body Surface Area; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EMEA: European Medicines Agency; EU: European Union; INN: International Nonproprietary Name; RMP: Risk Management Plan.

REFERENCES

None

RISK MANAGEMENT PLAN - PART II MODULE SI

EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (brand name(s))	**RENVELA, RENAGEL, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 10.0**

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ABBREVIATIONS

BMI:	Body Mass Index
CAKUT:	Congenital Anomalies of the Kidney and the Urinary
CI:	Confidence Interval
DLP:	Data Lock Point
eGFR:	Estimated Glomerular Filtration Rate
ESRD:	End Stage Renal Disease
GFR:	Glomerular Filtration Rate
HD:	Hemodialysis
HR:	Hazard Ratio
INN:	International Nonproprietary Name
PD:	Peritoneal Dialysis
PMARP:	Per Million of the Age-Related Population
PMP:	Per Million Population
RMP:	Risk Management Plan
SD:	Standard Deviation
SEEK:	Study for the Evaluation of Early Kidney Disease
US:	United States
USRDS:	United States Renal Data System

Renvela/Sevelamer carbonate Winthrop and Renagel are indicated for the control of hyperphosphatemia in adult patients receiving hemodialysis or peritoneal dialysis.

Renvela/Sevelamer carbonate Winthrop are also indicated for the control of hyperphosphatemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus ≥1.78 mmol/L.

Renvela/Sevelamer carbonate Winthrop are indicated for the control of hyperphosphatemia in pediatric patients (>6 years of age and a BSA of >0.75 m2) with chronic kidney disease.

Renvela/Sevelamer carbonate Winthrop and Renagel should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

The epidemiology of the disease is summarized in the following tables.

Table 1 - Epidemiology of chronic kidney disease patients on hemodialysis

Indication	**Chronic kidney disease patients on hemodialysis**
Incidence	United States renal data system estimates that the incidence of CKD patients commencing dialysis in 2016 was 378 per million. (1) Approximately 87.3% of this number comprise the HD population (330 per million). In 2016, 71 661 individuals commenced HD for ESRD, which equated to an overall incidence of 121 PMP. (2) Hemodialysis rates vary from country to country within Europe and population demographics differ, with a higher incidence for Greece (251 PMP) and lowest for Ukraine (29 PMP). The median incidence of children on renal replacement therapy in 2016 was 9 PMARP; based on limited epidemiologic information. Incidence has remained constant. (3) One thousand three hundred seventy-three (1373) children in the US began an ESRD care in 2015. Data from 2015 demonstrate that 51.9% of children have initiated ESRD therapy with HD. This represents an incidence rate of 7.5 per million per year. (1)
Prevalence	United States renal data system estimates the point prevalence of ESRD patients undergoing hemodialysis in 2016 was 450 887. Employing the estimates above, this would equate to a prevalence in excess of 564 638 across Europe, corresponding to an overall unadjusted prevalence of 823 PMP. Again, there was considerable variation between countries, with the highest prevalence in Iberian peninsula (>1388 PMP). (2) Prevalence has increased more than incidence due to improved survival and treatment. The prevalence of ESRD in children was reported as 65 PMARP worldwide. (2) Moreover, high values have been reported in the US, data from 2015 demonstrate that 9672 children were being treated for ESRD. (1)
Demographics of the population in the authorized indication	**Demographics of the target population** ADULTS Mean age at institution of hemodialysis was 66.6 years in Europe, the BMI was lower in Europe. (4) **Europe** / **US Non-Black/African American** / **US Black/African American**

Indication	Chronic kidney disease patients on hemodialysis

Age (years)	66.6 ± 14.5	65.3 ± 14.7	60.2 ± 15.1
Female sex (%)	44%	43%	46%
BMI, mean (SD)	26.7 ± 5.5	28.6 ± 6.9	28.5 ± 7.4
Hemoglobin, mean (SD), g/dL	10.0 ± 1.4	10.2 ± 1.4	10.0 ± 1.5
Serum albumin, mean (SD), g/dL	3.4 ± 0.6	3.4 ± 0.5	3.4 ± 0.5

BMI: Body Mass Index; SD: Standard Deviation; US: United States.

CHILDREN

Gender: Most patients were male (56.1%) and 32.3% started dialysis due to CAKUT. (5)

Age: The incidence of renal replacement therapy is higher in adolescents. Also, younger patients are more likely to be treated with PD and adolescents are more likely to be treated with HD.

The percentage of children on HD versus PD varies by country and by age. For example, North America favors HD and Europe, Australia and New Zealand favor PD. (6) Initial therapy varies by age: PD is the preferred choice in children 0-14 in Europe and the US, but 3/4 of children aged 15-19 start with HD. (6)

Country: The incidence and prevalence range widely by country. For example, the incidence was 9.5 PMARP 11 countries in Western Europe versus 15.5 in the US.

Race: African American children are reported to have a 2-fold greater incidence of ESRD compared to Whites. In the United Kingdom, the incidence of those receiving renal replacement therapy was 1.5 times greater in the south Asian children than white children. (6)

Risk factors for the disease

Chronic Kidney Disease regardless of dialysis status is associated with a wide spectrum of causative and consequent co-morbidities. The preponderance of serious associated conditions includes diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease and heart failure. (7)

The etiology of CKD is very different in children than in adults. For children, congenital disorders and hereditary nephropathies are responsible for approximately 2/3 of the cases of CKD in developed countries. In developing countries major risk factors include chronic glomerulonephritis, perhaps due to bacterial, viral and parasitic infections. (6)

Main existing treatment options	The main treatment options of kidney failure are dialysis or kidney transplant.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Mortality rate among hemodialysis patients vary greatly across regions. The crude 1-year mortality rates were 15.6% in Europe and 21.7% in US. Against matched general population controls, the mortality HR was 12.6 (95% CI 10.8 to 14.6) for hemodialysis patients. (8) The mortality rate for pediatric ESRD is significantly lower than the adult population but is still between 30 and 150 times that of the general pediatric population. (6)(9) In 2013, the one-year adjusted all-cause mortality rate in incident ESRD patients (aged 0-21 years) with HD was 46 per 1000 patient year. And the one-year adjusted cardiovascular mortality rate in incident ESRD patients (aged 0-21 years) with HD was 16 per

Indication	Chronic kidney disease patients on hemodialysis
	1000 patient year. (1)
Important co-morbidities	Patients with CKD tend to have more co-morbidities such as cardiovascular disease, metabolic abnormalities, an increased propensity for infection, pulmonary disease and uremic syndrome. The co-morbidities associated with CKD are broadly similar, whether or not the patients are on dialysis. The major co-morbidities in the pediatric population include cardiovascular disease, hypertension, anemia, proteinuria, and dyslipidemia, metabolic bone disease, and growth failure. There are no co-medications required when administering sevelamer carbonate. Other medications commonly used in the target population are those commonly prescribed for patients with the co-morbidities found in the target population. Due to the non-absorbed nature of sevelamer carbonate, the primary risk is the potential for a drug-drug interaction in the gut.

BMI: Body Mass Index; CAKUT: Congenital Anomalies of the Kidney and the Urinary Tract; CI: Confidence Interval; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; eGFR: Estimated Glomerular Filtration Rate; GFR: Glomerular Filtration Rate; HD: Hemodialysis; HR: Hazard Ratio; PD: Peritoneal Dialysis; PMP: Per Million Population; PMARP: Per Million of the Age-Related Population; SD: Standard Deviation; US: United States.

Table 2 - Epidemiology of hyperphosphatemic chronic kidney disease patients on peritoneal dialysis

Indication	Hyperphosphatemic chronic kidney disease patients on peritoneal dialysis
Incidence	The incidence of CKD started with peritoneal dialysis was 14.5 PMP throughout Europe. (2) In 2016, 9.7% started with PD, this represents 36 PMP in US. In the US, data from 2016, demonstrate that 13.8 PMP children were being treated for ESRD. The ESRD incidence varies by age group; in 2016 there were 204 cases in those aged 0-4 years, 139 aged 5-9, 202 aged 10-13, 295 aged 14-17, and 532 aged 18-21 years, for a total of 1372 children with incident ESRD in 2016. Within these age-based cohorts, incidence rates in 2016 were 9.2 PMP per year for 0-4 year olds, 6.4 for 5-9 year olds, 11.0 for 10-13 year olds, 15.5 of those aged 14-17 years, and 29.0 PMP aged 18-21 years. (1)
Prevalence	The prevalence is approximately of 41 PMP PD patients. (2) Data from European countries suggests that the PD population is about 5% of the total population on dialysis. (2) The usage rates for PD among European countries vary considerably from a high of 35% in Estonia and 26% in Denmark (expressed as a percentage of the total dialysis population in each country) to a low of 5% in Germany. (2) In 2016, the highest utilization of PD occurred in Hong Kong (71%), the Jalisco region of Mexico (61%), Guatemala (57%), New Zealand (30%), Thailand (28%), and Qatar (27%); for the remaining countries, PD utilization was less than 22% of dialysis patients. The percentage of children with CKD on PD versus HD varies by country and age. Hyperphosphatemia is commonly observed in patients with pediatric CKD. One study found that 17% of children with CKD had metabolic bone disease and the prevalence varied by stage; stage 2: 15%; stage 3: 47%; stages 4 and 5: 100%. (10) Another study found that among the pediatric patients, only 51% of HD and 74% of PD patients achieve the age-related targets for phosphate. (11) PD was the most frequent initial treatment modality in children aged 9 years and younger and also for children weighing less than 20 kg. (1) In 2016, the prevalence of children and adolescents, 0 to 21 years of age, with ESRD was

<table>
<tr><th>Indication</th><th>Hyperphosphatemic chronic kidney disease patients on peritoneal dialysis</th></tr>
<tr><td></td><td>9721, or 99.1 PMP. (1)</td></tr>
<tr><td>Demographics of the population in the authorized indication</td><td><u>Demographics of the target population</u>
<u>ADULTS:</u>
The PD patients with incident ESRD were younger, more likely to be white, and less likely to have other comorbidities than HD patients. (7)(8)
<table>
<tr><th>Age (years)</th><th>60 ± 15</th></tr>
<tr><td>Female sex (%)</td><td>36%</td></tr>
<tr><td>BMI, mean (SD)</td><td>27 ± 6</td></tr>
<tr><td>Hemoglobin, mean (SD), g/dL</td><td>10.3 ± 1.8</td></tr>
<tr><td>Serum albumin, mean (SD), g/dL</td><td>3.4 ± 0.6</td></tr>
</table>
BMI: Body Mass Index; SD: Standard Deviation.
<u>Risk factors for the disease</u>
Peritoneal dialysis and CKD are associated with a wide spectrum of causative and consequent co-morbidities. The preponderance of serious associated conditions includes diabetes mellitus, hypertension, glomerulonephritis. (7)</td></tr>
<tr><td>Main existing treatment options</td><td>The main treatment options of kidney failure are dialysis or kidney transplant. The main treatment options of hyperphosphatemia are dietary phosphate restriction, phosphate binders therapies such as calcium containing binders or calcium free binders (sevelamer, lanthanum, magnesium).</td></tr>
<tr><td>Natural history of the indicated condition in the untreated population including mortality and morbidity</td><td>No 1 year survival difference is present between HD and PD patients after correction for age, cardiovascular disease, (12) and diabetes 14% per 100 person years is the current best estimate of patient mortality for GFR <15 mL/min/1.73 m^2.
In 2016, the one-year adjusted all-cause mortality rate in incident ESRD patients (aged 0-21 years) with PD was 35 per 1000 patient-year. And the one-year adjusted cardiovascular mortality rate in incident ESRD patients (aged 0-21 years) with PD was 9 per 1000 patient-year. (1)</td></tr>
<tr><td>Important co-morbidities</td><td>Patients with CKD tend to have more co-morbidities such as cardiovascular disease, metabolic abnormalities, an increased propensity for infection, pulmonary disease and uremic syndrome. The co-morbidities associated with CKD are broadly similar, whether the patients are on dialysis.
The major co-morbidities in the pediatric population include cardiovascular disease, hypertension, anemia, proteinuria, and dyslipidemia, metabolic bone disease, and growth failure.
There are no co-medications required when administering sevelamer carbonate. Other medications commonly used in the target population are those commonly prescribed for patients with the co-morbidities found in the target population. Due to the non-absorbed nature of sevelamer carbonate, the primary risk is the potential for a drug-drug interaction in the gut.</td></tr>
</table>

a Data on file at Genzyme

CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; GFR: Glomerular Filtration Rate; HD: Hemodialysis; PD: Peritoneal Dialysis; PMP: Per Million Population; US: United States; USRDS: United States Renal Data System.

Table 3 - Epidemiology of hyperphosphatemic chronic kidney disease patients not on dialysis

Indication	Hyperphosphatemic chronic kidney disease patients not on dialysis
Incidence	The incidence of new CKD is reported to be between 2 and 3% (USRDS) (1) of the prevalence: extrapolating to Europe, this would suggest a figure of between 19 000 and 28 000.
Prevalence	The size of the identified upper range of the hyperphosphatemic CKD population not on dialysis can be estimated based on published literature. The SEEK (12) evaluated 1814 CKD patients not on dialysis with an eGFR <60 mL/min/1.73 m^2. Approximately 5% of these subjects had an eGFR <20 mL/min/1.73 m^2 and about 6% of the total CKD population not on dialysis had serum phosphorus >4.6 mg/dL. In the study of CKD patients by Kestenbaum, 194 535 veterans in primary care were examined and of 6730 patients identified to have CKD, 6.6% were found to have a serum phosphorus >4.5 mg/dL. (13) Therefore, these 2 published reports suggest that even using these significantly lower thresholds for hyperphosphatemia (defined as >4.5 mg/dL) than were employed in study SVCARB00105, the prevalence of hyperphosphatemic is not more than about 6% of the identified CKD patients not on dialysis. Therefore, taking into account the fact that a higher threshold of hyperphosphatemia of ≥1.78 mmol/L (≥5.5 mg/dL) was used and that other necessary exclusionary criteria were applied, it is understandable that the eligible population for SVCARB00105 was small, but still allowed study of a population sample representative of the continuum of hyperphosphatemic CKD. Hyperphosphatemia is commonly observed in patients with pediatric CKD. One study found that 17% of children with CKD had metabolic bone disease and the prevalence varied by stage; stage 2: 15%; stage 3: 47%; stages 4 and 5: 100%. (10) Another study found that among the pediatric patients, only 51% of HD and 74% of PD patients achieve the age-related targets for phosphate. (11) No published data in English on the hyperphosphatemic CKD children population not on dialysis was found.
Demographics of the population in the authorized indication	**Demographics of the target population** Chronic disease patients not on dialysis presented mean age of 58 years and most of them were men (55.2%). (14) **Age (years)** — **58 ± 11** Female sex (%) — 44.8% BMI, mean (SD) — 32 ± 8 Hemoglobin, mean (SD), g/dL — 10.3 ± 1.8 Serum albumin, mean (SD), g/dL — 3.9 ± 0.5 BMI: Body Mass Index; SD: Standard Deviation. Risk factors for the disease Chronic kidney disease is associated with a wide spectrum of causative and consequent co-morbidities. The preponderance of serious associated conditions includes diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, acid/base imbalances and heart failure. (12)
Main existing treatment options	The main treatment options of hyperphosphatemia are dietary phosphate restriction, phosphate binders' therapies such as calcium containing binders or calcium free binders (sevelamer, lanthanum, magnesium).

Indication	Hyperphosphatemic chronic kidney disease patients not on dialysis
Natural history of the indicated condition in the untreated population including mortality and morbidity	Fourteen (14) percent per 100 person years is the current best estimate of patient mortality for those with GFR <15 mL/min/1.73 m² (stage 5 CKD). This figure is within the estimate given by USRDS (10-22%). (1) Mortality in CKD is strongly related to age and stage of disease as measured by eGFR. (15)
Important co-morbidities	Patients with CKD tend to have more co-morbidities such as cardiovascular disease, metabolic abnormalities, an increased propensity for infection, pulmonary disease and uremic syndrome. The co-morbidities associated with CKD are broadly similar, whether or not the patients are on dialysis. The major co-morbidities in the pediatric population include cardiovascular disease, hypertension, anemia, proteinuria, and dyslipidemia, metabolic bone disease, and growth failure. There are no co-medications required when administering sevelamer carbonate. Other medications commonly used in the target population are those commonly prescribed for patients with the co-morbidities found in the target population. Due to the non-absorbed nature of sevelamer carbonate, the primary risk is the potential for a drug-drug interaction in the gut.

CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; GFR: Glomerular Filtration Rate; HD: Hemodialysis; PD: Peritoneal Dialysis; SEEK: Study for the Evaluation of Early Kidney disease; USRDS: United States Renal Data System.

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RISK MANAGEMENT PLAN - PART II MODULE SII

NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 10.0**

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ABBREVIATIONS

CKD:	Chronic Kidney Disease
Cmax:	Maximum Concentration
DLP:	Data Lock Point
EMA:	European Medicines Agency
GLP:	Good Laboratory Practice
GVP:	Good Pharmacovigilance Practices
INN:	International Nonproprietary Name
NOAEL:	No Observed Adverse Effect Level
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

The two sevelamer salts (hydrochloride and carbonate) are non-absorbed phosphate binding polymers developed to control hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Sevelamer carbonate, developed as an alternative to sevelamer hydrochloride, is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD) not on dialysis with serum phosphorus ≥1.78 mmol/L.

The two sevelamer salts have similar safety profiles with the important distinction that the carbonate salt has a reduced propensity for association with potentially adverse acid-base changes, which makes sevelamer carbonate more appropriate for use in hyperphosphataemic CKD patients including those patients not on dialysis. While the anions differ for the two salt forms, the polymer itself, the active moiety responsible for binding of phosphate, remains the same. An in-vitro equivalence study showed that sevelamer carbonate (either as powder or tablet) and sevelamer hydrochloride tablets are equivalent in their phosphate binding properties. Therefore, no additional non-clinical pharmacodynamic and safety pharmacology studies were conducted using sevelamer carbonate. All pharmacodynamic and safety pharmacology studies were conducted using sevelamer hydrochloride. A bridging pharmacokinetic study in the dog was conducted with sevelamer carbonate and the results from this study confirmed that sevelamer carbonate like sevelamer hydrochloride is non-absorbed. In addition to the toxicology studies carried out with sevelamer hydrochloride, two Good Laboratory Practice (GLP) studies were conducted with sevelamer carbonate to bridge from the existing toxicology data for the hydrochloride salt of sevelamer to the carbonate salt: 4-week oral toxicity study in rats and 4-week oral toxicity study in dogs.

Sevelamer hydrochloride was evaluated for its safety pharmacology profile including effects on general activity, and effects on the central nervous system, respiratory system, cardiovascular system, and gastrointestinal system, urinary system, blood coagulation and isolated smooth muscle. At doses up to 2000 mg/kg, sevelamer hydrochloride produced no changes in the behavioral, neurological or autonomic profiles in male mice. Treatment of animals with sevelamer hydrochloride at doses up to 2000 mg/kg had no effect on the hexobarbital-induced sleeping time, the incidence of tonic cramp due to electroshock or the acetic acid-induced writhing count. No significant differences in mean blood pressure, heart rate, left ventricular pressure, renal arterial blood flow, femoral arterial blood pressure, respiration rate, or electrocardiogram waveforms were found between the pre and post administration values with administration of sevelamer hydrochloride to dogs at a dose of 2000 mg/kg. No effects on spontaneous contraction in the isolated ileum and gastric fundus preparations were observed with sevelamer hydrochloride treatment.

Drug interaction studies were performed to evaluate the potential for sevelamer hydrochloride to alter the pharmacokinetic profiles of some drugs that are commonly used in patients with CKD. In these studies, beagle dogs were co-administered 100 mg/kg of sevelamer hydrochloride with clinically relevant doses of digoxin, oestrone, propranolol, thyroxin, tetracycline, verapamil, valproic acid, dihydroxyvitamin D_3 or warfarin. Sevelamer hydrochloride had no effect on the oral bioavailability when administered in combination with each drug, and there were no statistically significant differences in maximum concentration (C_{max}) or area under curve in sevelamer hydrochloride treated and non-treated groups. Since sevelamer is not absorbed, interactions other than through binding in the gastrointestinal tract are not anticipated.

The toxicology profiles observed in the comparative 4-week studies in rats and dogs were similar for both salts. The results were also similar to past studies performed during the development of the sevelamer hydrochloride salt. In conclusion, there are no new or different findings with sevelamer carbonate when compared to sevelamer hydrochloride. The only safety concerns that are found in non-clinical studies which are of unknown significance to humans refer to the results on reproductive toxicity and developmental toxicity found in rats with sevelamer hydrochloride. These toxicology results are described in Table 1 and have the recommendations in Sections 5.3 (Preclinical safety data) and 4.6 (pregnancy and lactation) of the sevelamer hydrochloride/carbonate summary of product characteristics (SmPC).

Non-clinical safety concerns regarding the use of sevelamer carbonate/sevelamer hydrochloride in the hyperphosphataemic CKD population are reflected in Table 1.

Table 1 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Key issues identified from acute or repeat-dose toxicity studies Single doses of sevelamer hydrochloride (2 g/kg by gavage to rats and 4 g/kg by capsule to dogs) were well tolerated. A single dose study with sevelamer carbonate at doses of 10, 15 and 20 g/kg by oral route (dietary admixture) was conducted in rats. It was considered that the NOAEL for sevelamer carbonate administered over a 24-hour period was 20 g/kg/day. Repeated administration at 10 or 12 g/kg of sevelamer hydrochloride was tolerated for several weeks before any deaths occurred. These treatment-related deaths are attributed to effects on clotting function, probably caused through insufficient absorption of vitamin K. No systemic toxicity related to the administration of sevelamer carbonate or sevelamer hydrochloride was observed in the 4-week comparator studies in rats and dogs other than reduced serum levels of fat soluble vitamins in rats. Apart from differences in serum and urinary chloride, identical results were obtained with both salt forms, sevelamer carbonate and sevelamer hydrochloride. In rats, both sevelamer carbonate and sevelamer hydrochloride were clinically well tolerated at all dose-levels (1000 and 4500 mg/kg/day) following dietary administration. At 1000 mg/kg/day of each test item, treatment resulted in changes in urinary excretions of electrolytes. At 4500 mg/kg/day, lower body weight gain was noted in treated males given sevelamer carbonate, whereas higher food consumption was noted in females given each of the test items. Changes in blood biochemical parameters and in vitamins D and E levels were noted in animals given sevelamer carbonate or sevelamer hydrochloride.	Based on non-clinical toxicology studies, the toxicity profile between sevelamer carbonate and sevelamer hydrochloride were similar. Reduced absorption of fat soluble vitamins D, E and K (coagulation factors), and folic acid were important potential risks in human in the initial RMP and further removed in order to be in line with the guideline on Good pharmacovigilance practices (GVP) Module V - Risk Management systems -EMA/838713/2011 (Rev.2). Sevelamer hydrochloride should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1, 25- dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease. Depending on diet intake and the nature of end stage renal failure, dialysis patients may develop low vitamin A, D, E and K levels. It cannot be excluded that sevelamer hydrochloride can bind fat-soluble vitamins contained in ingested food. Therefore, in patients not taking these vitamins, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of thromboplastin time should be considered and the vitamins should be supplemented if necessary. Additional monitoring of vitamins and folic acid is recommended in patients receiving peritoneal dialysis, since in the clinical study, vitamin A, D, E and K levels were not measured in these patients.

Key Safety Findings	Relevance to human usage
Higher urine pH value was noted in treated males and changes in urinary electrolyte excretion were seen in all treated animals. No relevant findings were noted in organ weights or macroscopic and histopathological examination. The NOAEL is 761 mg/kg/day in males and 793 mg/kg/day in females for sevelamer carbonate (nominal dose-level of 1000 mg/kg/day) and 775 mg/kg/day in males and 785 mg/kg/day in females for sevelamer hydrochloride (nominal dose-level of 1000 mg/kg/day). In conclusion, comparable findings were obtained with both test items. In dogs, both sevelamer carbonate and sevelamer hydrochloride were clinically well tolerated at all dose-levels (200 and 1000 mg/kg/day) following oral administration (capsule). The principle findings were emaciated appearance at 200 and 1000 mg/kg/day of sevelamer carbonate and 1000 mg/kg/day of sevelamer hydrochloride as well as yellow and soft feces in animals given sevelamer hydrochloride at 1000 mg/kg/day. No laboratory changes and no histopathological findings were noted at any dose-level, with either test item. Group mean body weight evolution did not differ from control group; nevertheless, the control group did not gain weight during the study period as normally expected. This effect was considered to be without relationship to treatment with the test items. Since the vehicle caused adverse effects on the body weight evolution, a NOAEL could not be established. However, the NOAEL for all other toxicological end points was 1000 mg/kg/day for both sevelamer carbonate and sevelamer hydrochloride. In conclusion, comparable findings were obtained with both test items.	
• <u>Reproductive/developmental toxicity studies</u> Deficits in skeletal ossification were observed in several locations in foetuses of female rats dosed with sevelamer hydrochloride at intermediate and high doses (human equivalent dose less than the maximum clinical trial dose of 14.4 g). The effects may be secondary to vitamin D depletion. In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose). In the pre- and postnatal study, there was no evidence of maternal toxicity at any dose level. There was also no effect on reproductive performance during gestation, parturition or lactation and no effect on the survival, physical development, behaviour or reproductive performance of the F1 generation or on the survival and development of the F2 generation pups at the doses evaluated (≤1.0 g/kg/day).	<u>Pregnancy</u> Studies in animals have shown some reproductive toxicity (deficit in skeletal ossification) when sevelamer hydrochloride was administered to rats. The potential risk to humans is unknown. Sevelamer carbonate/Sevelamer hydrochloride should only be given to pregnant women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the fetus. <u>Lactation</u> The safety of sevelamer hydrochloride has not been established in lactating women. Sevelamer hydrochloride should only be given to lactating women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the infant (see Section 5.3 Preclinical safety data). Pregnancy and lactation is considered missing information in the initial RMP and further removed in order to be in line with the guideline on GVP Module V - Risk Management

Key Safety Findings	Relevance to human usage
	systems - EMA/838713/2011 (Rev.2)

EMA: European Medicines Agency; GVP: Good Pharmacovigilance Practices; NOAEL: No Observed Adverse Effect Level; RMP: Risk Management Plan.

No additional non-clinical data have been collected on the use of sevelamer carbonate/sevelamer hydrochloride in any special populations.

REFERENCES

None

RISK MANAGEMENT PLAN - PART II MODULE SIII

CLINICAL TRIAL EXPOSURE

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 10.0**

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ABBREVIATIONS

CKD:	Chronic Kidney Disease
DLP:	Data Lock Point
INN:	International Nonproprietary Name
iPTH:	Intact Parathyroid hormone
PD:	Peritoneal dialysis
PREA:	Pediatric Research Equity Act
QD:	Once a day
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
TID:	Three times a day

Sevelamer was initially developed using the hydrochloride salt. Sevelamer carbonate was developed as a new salt.

Clinical studies in the hemodialysis population and in hyperphosphatemic chronic kidney disease (CKD) patients not on dialysis have been conducted with sevelamer carbonate and confirmed a clinically important reduction in serum phosphorus levels and have demonstrated a favorable benefit/risk ratio. Sevelamer carbonate has not been studied in CKD patients on peritoneal dialysis (PD) however, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in PD patients. The safety profile of sevelamer hydrochloride in PD CKD patients was shown to be consistent with the patient's underlying disease and with the known safety profile of sevelamer hydrochloride. Sevelamer carbonate and sevelamer hydrochloride have been shown to be therapeutically equivalent in terms of control of serum phosphorus, and have a similar safety profile with the important distinction that the carbonate salt has the potential for increase in serum bicarbonate levels and the resultant improvement in metabolic state in hyperphosphatemic CKD patients. Clinical trials with sevelamer carbonate did not identify any new risks with sevelamer.

The safety of sevelamer hydrochloride and sevelamer carbonate has been investigated in clinical studies in dialysis and non-dialysis patients.

As part of Pediatric Research Equity Act (PREA) requirements, a study was conducted to evaluate the effect of sevelamer carbonate, to lower serum phosphorus levels in pediatric CKD patients. The results were consistent with the known safety and efficacy profile of sevelamer carbonate. The study therefore supports a favorable risk/benefit profile of sevelamer carbonate in pediatric CKD patients.

Clinical trial exposure for sevelamer carbonate

A cumulative of total 1114 subjects were exposed to sevelamer carbonate in company sponsored clinical studies. Information on sevelamer carbonate exposure prior to marketing authorization is presented below:

Table 1 - Total Sevelamer carbonate exposure in clinical studies

Study number	Number of patients in safety set	Estimated number of patient years[a]
GD3-163-201	73	11.1
SVCARB00105	49	6.9
SVCARB00205	31	2.2
GD3-199-301	141	49.2
SVCARB07609	98	44
Total Exposure	**392**	**113.4**

a Calculated from the exposure in person-time in weeks from the tables below

Genzyme has conducted 5 clinical trials with sevelamer carbonate to support the marketing authorization.

GD3-163-201: A double-blind, cross-over design study of sevelamer hydrochloride (RENAGEL) and sevelamer carbonate (RENVELA) in chronic kidney disease on hemodialysis.

This was a double-blind, randomized, cross-over study comparing sevelamer carbonate tablets dosed three times a day (TID) with sevelamer hydrochloride tablets dosed TID in 79 hyperphosphatemic (serum phosphorus ≥1.78 mmol/L) CKD patients on hemodialysis. Patients were treated over two randomized 8 week treatment periods. The mean actual daily dose was 5.8 ± 2.8 g/day of sevelamer carbonate tablets. The mean treatment duration was 8.0 ± 0.4 weeks on sevelamer carbonate tablets.

SVCARB00205: A randomized, cross-over study to demonstrate equivalence of sevelamer carbonate powder and sevelamer hydrochloride tablets dosed three times per day in hemodialysis patients

This was an open-label, randomized, cross-over study, of sevelamer carbonate powder dosed TID with meals versus sevelamer hydrochloride tablets dosed TID with meals in hyperphosphatemic CKD patients on hemodialysis. A total of 31 patients were randomized. At baseline eligible patients were randomly assigned to one of two treatment sequences:

- Sevelamer carbonate powder dosed TID with meals for 4 weeks followed by sevelamer hydrochloride tablets dosed TID with meals for 4 weeks; or
- Sevelamer hydrochloride tablets dosed TID with meals for 4 weeks followed by sevelamer carbonate powder dosed TID with meals for 4 weeks. The mean actual daily dose was 5.9 ± 2.7 g/day of sevelamer carbonate powder. The mean treatment duration was 3.7 ± 1.3 weeks on sevelamer carbonate powder.

GD3-199-301: A randomized, parallel, open-label study to compare once per day sevelamer carbonate powder dosing with three times per day sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis

This was a randomized, parallel, open-label study in CKD patients on hemodialysis. The study consisted of a 24 week randomized treatment period. Patients were randomized (stratified by screening intact parathyroid hormone (iPTH) ≤400 or >400 pg/mL and cinacalcet treatment at baseline) to one of 2 treatment groups in a 2:1 fashion:

- Sevelamer carbonate powder dosed once a day (QD) with the largest meal or;
- Sevelamer hydrochloride tablets dosed TID with meals. A total of 217 patients were randomized: 144 to sevelamer carbonate powder QD and 73 to sevelamer hydrochloride tablets TID. The mean actual daily dose was 6.2 ± 2.6 g/day of sevelamer carbonate powder QD. The mean treatment duration was 18.4 ± 7.9 weeks on sevelamer carbonate powder.

SVCARB00105: An open label, dose titration study of sevelamer carbonate tablets dosed 3 times per day in hyperphosphatemic CKD patients not on dialysis

This was an open label, single-arm, and dose titration study of sevelamer carbonate tablets in hyperphosphatemic CKD patients not on dialysis. Patients acted as their own controls by utilizing pre and post-treatment washout periods. Patients with a serum phosphorus level ≥1.78 mmol/L (≥5.5 mg/dL) were enrolled. Study treatment was administered for 8 weeks. A total of 49 patients were randomized. The mean actual daily dose was 5.4 ± 1.7 g/day of sevelamer carbonate tablets. The mean treatment duration was 7.4 ± 2.4 weeks on sevelamer carbonate tablets.

SVCARB07609: 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 CKD

The safety and effectiveness of sevelamer carbonate in hyperphosphatemic pediatric patients with CKD was evaluated in a multicenter study with a 2 week, randomized, placebo-controlled, fixed dose period followed by a 6 month, single-arm, open-label, dose titration period. A total of 101 patients (6 to 18 years old) with a body surface area range of 0.8 m^2 to 2.4 m^2 were randomized in the study. Forty-nine (49) patients received sevelamer carbonate and 51 patients received placebo during the 2 week fixed dose period; thereafter all patients received sevelamer carbonate for the 26 week dose titration period. The study met its primary and secondary efficacy endpoints. In pediatric patients with hyperphosphatemia secondary to CKD, sevelamer carbonate significantly reduced serum phosphorus levels compared to placebo during a 2 week fixed dose period. The treatment response was maintained in the pediatric patients who received sevelamer carbonate during the 6 month open-label dose titration period. No new risks or safety signals were identified with the use of sevelamer carbonate during the study.

Exposure in adult patients (GD3-163-201, SVCARB00205, GD3-199-301 and SVCARB00105)

Study GD3-163-201

Table 2 - Exposure by maximum duration (GD3-163-201)

Maximum Duration of Exposure	Persons	Person-time (weeks)
Cumulative up to 4 weeks	0	0
Cumulative up to 8 weeks	36	281.1
Cumulative up to 12 weeks	72	575.3
Cumulative up to 16 weeks	72	575.3

Table 3 - Exposure by average actual daily dose (GD3-163-201)

Dose (grams)	Persons	Person-time (weeks)
Unknown*	1	5.1
≤4.8	30	240.7
>4.8-<9.6	34	273.6
≥9.6	7	55.9

Table 4 - Exposure by age group and gender (GD3-163-201)

Gender	Age Group (years)	Persons	Person-time (weeks)
	18-<45	5	40.3
Female	45-<65	19	151.4
	≥65	9	69.1
	18-<45	3	23.9
Male	45-<65	26	209.6
	≥65	10	81.0

Table 5 - Exposure by ethnic origin (GD3-163-201)

Ethnicity	Persons	Person-time (weeks)
Caucasian	19	152.7
Asian	0	0
Black	48	382.3
Other	5	40.3

Seventy three (73) patients were included in the Safety Set for sevelamer carbonate. Duration could not be determined for one patient.

Study SVCARB00205

Table 6 - Exposure by maximum duration (SVCARB00205)

Maximum Duration of Exposure	Persons	Person-time (weeks)
Cumulative up to 4 weeks	11	25.7
Cumulative up to 8 weeks	31	114.1
Cumulative up to 12 weeks	31	114.1
Cumulative up to 16 weeks	31	114.1

Table 7 - Exposure by average actual daily dose (SVCARB00205)

Dose (grams)	Persons	Person-time (weeks)
Unknown*	5	13.4
≤4.8	12	46.4
>4.8-<9.6	12	46.0
≥9.6	2	8.3

Table 8 - Exposure by age group and gender (SVCARB00205)

Gender	Age Group (years)	Persons	Person-time (weeks)
Female	18-<45	3	10.7
	45-<65	5	18.0
	≥65	2	8.6
Male	18-<45	7	29.7
	45-<65	10	32.9
	≥65	4	14.3

Table 9 - Exposure by ethnic origin (SVCARB00205)

Ethnicity	Persons	Person-time (weeks)
Caucasian	22	83.1
Asian	6	19.0
Black	3	12.0
Other	0	0

Study GD3-199-301

Table 10 - Exposure by maximum duration (GD3-199-301)

Maximum Duration of Exposure	Persons	Person-time (weeks)
Cumulative up to 4 weeks	13	23.3
Cumulative up to 8 weeks	26	97.5
Cumulative up to 12 weeks	32	151.9
Cumulative up to 16 weeks	38	234.5
Cumulative up to 24 weeks	139	2557

Table 11 - Exposure by average actual daily dose (GD3-199-301)

Dose (grams)	Persons	Person-time (weeks)
≤4.8	49	757.4
>4.8-<9.6	72	1392.7
≥9.6	18	406.9

Table 12 - Exposure by age group and gender (GD3-199-301)

Gender	Age Group (years)	Persons	Person-time (weeks)
Female	18-<45	12	204.6
	45-<65	23	440.1
	≥65	17	285.9
Male	18-<45	18	349.3
	45-<65	40	737.1
	≥65	29	540.0

Table 13 - Exposure by ethnic origin (GD3-199-301)

Ethnicity	Persons	Person-time (weeks)
Caucasian	59	1102.7
Asian	0	0
Black	74	1376.2
Other	6	78.1

One hundred and forty-one (141) patients were included in the Safety Set for sevelamer carbonate. Duration could not be determined for two patients.

Study SVCARB00105

Table 14 - Exposure by maximum duration (SVCARB00105)

Maximum Duration of Exposure	Persons	Person-time (weeks)
Cumulative up to 4 weeks	6	8.0
Cumulative up to 8 weeks	23	137.4
Cumulative up to 12 weeks	49	361.0
Cumulative up to 16 weeks	49	361.0

Table 15 - Exposure by average actual daily dose (SVCARB00105)

Dose (grams)	Persons	Person-time (weeks)
Unknown*	1	9.1
≤4.8	20	119.1
>4.8-<9.6	27	225.1

Dose (grams)	Persons	Person-time (weeks)
≥9.6	1	7.6

Table 16 - Exposure by age group and gender (SVCARB00105)

Gender	Age Group (years)	Persons	Person-time (weeks)
Female	18-<45	2	16.0
	45-<65	7	50.7
	≥65	8	53.3
Male	18-<45	2	16.6
	45-<65	15	115.6
	≥65	15	108.9

Table 17 - Exposure by ethnic origin (SVCARB00105)

Ethnicity	Persons	Person-time (weeks)
Caucasian	45	336
Asian	2	15.7
Black	1	8.3
Other	1	1.0

Exposure in pediatric patients (SVCARB07609)

Study SVCARB07609:

Table 18 - Exposure by maximum duration (SVCARB07609)

Maximum Duration of Exposure	Persons	Person-time (weeks)
Cumulative up to 4 weeks	6	10.6
Cumulative up to 8 weeks	8	23.0
Cumulative up to 12 weeks	15	92.4
Cumulative up to 16 weeks	20	162.3
Cumulative up to 20 weeks	22	199.3
Cumulative up to 24 weeks	32	416.4
Cumulative up to 28 weeks	63	1240.0
Cumulative up to 32 weeks	96	2222.6
Cumulative up to 36 weeks	98	2287.9

Table 19 - Exposure by average actual daily dose (SVCARB07609)

Dose (grams)	Persons	Person-time (weeks)
≤4.8	98	2287.9

Table 20 - Exposure by age group and gender (SVCARB07609)

Gender	Age Group (years)	Persons	Person-time (weeks)
Female	0 - 12	8	153.3
	13 - 18	28	658.1
Male	0 - 12	17	406.9
	13 - 18	45	1069.6

Table 21 - Exposure by ethnic origin (SVCARB070609)

Ethnicity	Persons	Person-time (weeks)
Caucasian	52	1212.7
Asian	2	54.6
Black	35	773.6
American Indian or Alaska Native	1	32.9
Unknown	6	153.6
Not Reported	2	60.6

Ninety-eight (98) patients were included in the pediatric Safety Set for sevelamer carbonate.

Clinical trial exposure for sevelamer hydrochloride

Clinical studies in the dialysis population have established the efficacy and safety of sevelamer hydrochloride and confirm a clinically important reduction in serum phosphorus levels. Clinical studies with sevelamer hydrochloride have demonstrated a favorable benefit/risk profile in the dialysis population.

The current sevelamer hydrochloride summary of product characteristics (SmPC) includes data from parallel design studies involving hemodialysis patients with treatment duration of up to 54 weeks and PD patients with treatment duration of 12 weeks, as well as safety data from uncontrolled clinical studies involving hemodialysis patients as described below:

- **GTC-49-301**: A randomized, open-label, parallel design study of sevelamer hydrochloride (RENAGEL) and calcium-based phosphate binders in hemodialysis patients.
  N = 202 hemodialysis patients (RENAGEL = 100; calcium = 102); treatment duration: upto 52 weeks.

- **GTC-68-402**: A randomized, open-label, parallel design study on the effects of sevelamer hydrochloride (RENAGEL) and calcium carbonate on bone turnover and mineralization in hemodialysis patients. N = 91 hemodialysis patients (RENAGEL = 44; calcium carbonate = 47); treatment duration: up to 54 weeks.
- **REN-003-04**: An open-label, randomized, parallel design study to investigate the efficacy and of safety sevelamer hydrochloride (RENAGEL) compared to calcium acetate in peritoneal patients. N = 143 PD patients (RENAGEL = 97; calcium acetate = 46); treatment duration: up to 12 weeks.
- Sevelamer hydrochloride Pooled Safety Analysis: An integration of RENAGEL safety data from 5 open-label, uncontrolled clinical studies (GTC-10-202, GTC-36-203, GTC-36-301, GTC-36-302 and GTC-45-901). Total N = 384 hemodialysis patients; treatment duration: 8 to 44 weeks.

A summary of exposure to sevelamer hydrochloride in these studies is provided in below tables.

Study GTC-49-301

Table 22 - Exposure by maximum duration (GTC-49-301)

Number of patients exposed	Mean duration (weeks)	Duration range (weeks)
99	48	2.9-60.9

Table 23 - Daily RENAGEL Dose (Mean and Range) Per Study (GTC-49-301)

Number of patients exposed	Mean actual dose (g/day)	Dose actual range (g/day)
99	6.5	0.8–13.1

Table 24 - Summary of demographic characteristics of patients (GTC-49-301)

Variable	Protocol GTC-49-301 (N = 99)
Mean age (years)	57
Gender [N (%)]	
Male	63 (64)
Female	36 (36)
Race [N (%)]	
Caucasian	70 (71)
Black	17 (17)
Hispanic	1 (1)
Asian	8 (8)
Other	3 (3)

Primary cause of CKD [N (%)]	
Hypertension	16 (16)
Diabetes	23 (23)
All other causes	60 (61)
Mean duration of dialysis (months)	61

CKD: Chronic Kidney Disease.

Study GTC-68-402

Table 25 - Exposure by maximum duration (GTC-68-402)

Number of patients exposed	Mean duration (weeks)	Duration range (weeks)
42	50	2.3-66.9

Table 26 - Daily RENAGEL dose (mean and range) (GTC-68-402)[a]

Number of patients exposed	Mean actual dose (g/day)	Dose actual range (g/day)
42	4.8	0.8-11.2

a Prescribed dose at the end of the study; actual dose was not calculated in this study.

Table 27 - Summary of demographic characteristics of patients (GTC-68-402)

Variable	Protocol GTC-68-402 (N = 42)
Mean age (years)	55
Gender [N (%)]	
Male	28 (67)
Female	14 (33)
Race [N (%)]	
Caucasian	39 (93)
Black	3 (7)
Hispanic	0 (0)
Asian	0 (0)
Other	0 (0)
Primary cause of CKD [N (%)]	
Hypertension	6 (14)
Diabetes	3 (7)
All other causes	33 (79)
Mean duration of dialysis (months)	52

CKD: Chronic Kidney Disease.

Study REN-003-04

Table 28 - Exposure by maximum duration (REN-003-04)

Number of patients exposed	Mean duration (weeks)	Duration range (weeks)
97	10	0.1-15.3

Table 29 - Daily RENAGEL Dose (Mean and Range) (REN-003-04)

Number of patients exposed	Mean actual dose (g/day)	Dose actual range (g/day)
97	5.8	0.8-14.3

Table 30 - Summary of demographic characteristics of patients (REN-003-04)

Variable	Protocol REN-003-04 (N = 97)
Mean age (years)	55
Gender [N (%)]	
Male	65 (67)
Female	32 (33)
Race [N (%)]	
Caucasian	87 (90)
Black	2 (2)
Hispanic	0 (0)
Asian	6 (6)
Other	2 (2)
Primary cause of CKD [N (%)]	
Hypertension	7 (7)
Diabetes	17 (18)
All other causes	73 (75)
Mean duration of dialysis (months)	28

CKD: Chronic Kidney Disease.

Study sevelamer hydrochloride pooled safety analysis

Table 31 - Exposure by maximum duration of Pooled Safety Analysis

Study Number	Number of patients exposed	Mean duration (weeks)	Duration range (weeks)
Sevelamer Hydrochloride Pooled Safety Analysis overall	384[a]	26	0.1-58.0

Study Number	Number of patients exposed	Mean duration (weeks)	Duration range (weeks)
GTC-10-202	48	7	2.1-10.3
GTC-36-203	75	10	0.3-14.0
GTC-36-301	82	8	0.1-10.1
GTC-36-302	172	8	0.1-10.0
GTC-45-901	192	36	0.7-45.9
Total	**622**		

a For the Sevelamer Hydrochloride Pooled Safety Analysis, patients from studies GTC-36-203, GTC-36-301, and GTC-36-302 were able to enrol and continue sevelamer hydrochloride in study GTC-45-901. Seven (7) unique patients also enrolled only in study GTC-45-901. Those patients enrolled in GTC-45-901 are only counted once for the overall number of patients.

Table 32 - Daily RENAGEL Dose (Mean and Range)

Study Number	Number of patients exposed	Mean actual dose (g/day)	Dose actual range (g/day)
Sevelamer Hydrochloride Pooled Safety Analysis	137	< 5.0	< 5.0
	132	5.0-6.75	5.0-6.75
	115	> 6.75	> 6.75
Total	**622**		

Table 33 - Summary of demographic characteristics of patients

Variable	Pooled analysis (N = 384)
Mean age (years)	54
Gender [N (%)]	
Male	238 (62)
Female	146 (38)
Race [N (%)]	
Caucasian	150 (39)
Black	189 (49)
Hispanic	37 (10)
Asian	5 (1)
Other	3 (1)
Primary cause of CKD [N (%)]	
Hypertension	119 (31)
Diabetes	110 (29)
All other causes	155 (40)
Mean duration of dialysis (months)	44

CKD: Chronic Kidney Disease.

REFERENCES

None

RISK MANAGEMENT PLAN - PART II MODULES SIV

POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 10.0**

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ABBREVIATIONS

ADR:	Adverse Drug Reaction
CKD:	Chronic Kidney Disease
DLP:	Data Lock Point
EU:	European Union
FDA:	Food and Drug Administraiton
IBD:	International Birth Date
ICSR:	Individual Case Summary Report
INN:	International Nonproprietary Name
PLLR:	Pregnancy, Lactation and Labelling Rule
PV:	Pharmacovigilance
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
US:	United States

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 1 – Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with history of bowel obstruction	Sevelamer is known to induce constipation. Patients with history of bowel obstruction are at higher risk of developing new bowel obstruction. Bowel obstruction is a known significant risk for medical and potentially surgical intervention.	No	"Bowel obstruction" is a contraindication for patients treated with sevelamer carbonate/sevelamer hydrochloride (SmPC section 4.3).
Patients with a history of dysphagia, swallowing disorders or gastrointestinal motility disorders, including severe constipation	These exclusion criteria were prospectively chosen early in development based on theoretical considerations, specifically the size of the tablets and the hydrophilic nature of the product; they were not added later based on observed events in clinical trials.	No	Sevelamer carbonate/sevelamer hydrochloride SmPC provides warnings and precautions for use regarding these conditions (Section 4.4). Caution should be exercised when sevelamer carbonate/sevelamer hydrochloride is used in patients with these disorders. For example, sevelamer carbonate powder for oral suspension may be considered in patients with a history of difficulty swallowing.
Patients under age of 18 years	The safety and efficacy of sevelamer hydrochloride has not been established in children below the age of 18 years.	No	Sevelamer hydrochloride is not recommended in children below the age of 18 years; children were excluded from the adult clinical trials. The safety and tolerability of sevelamer carbonate in hyperphosphatemic pediatric patients with CKD was evaluated in a multicenter study.
Pregnant or breast-feeding women:	Pregnant women and breast-feeding women were not included in pivotal studies for	No	No safety risk is expected. Limited information is available in post marketing

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	sevelamer carbonate/sevelamer hydrochloride. No data is available.		setting however a cumulative review of ICSRs from the global PV database and a review of the literature were performed in 2018 upon FDA request in the context of PLLR new legislation did not identified a safety issue in this population.
Patients with poorly controlled concomitant or clinically significant unstable medical conditions or cancer	Typically, these patients are excluded from clinical trials due to their difficulty to follow visit schedules and other necessary protocol requirements.	No	This is a practical study design element that is not reflective of the use of sevelamer carbonate/sevelamer hydrochloride.
Patients taking antiarrhythmic or anti-seizure medications for control of these disorders	These medications generally have a narrow therapeutic index and require continual monitoring and precise adjustments to their dose. Due to the altered serum concentrations of these drugs in the face of changes in homeostasis due to phosphate binder washout, subsequent phosphate binder titration, and potential effect on the bioavailability of concomitantly administered medications, patients taking these medications were excluded.	No	The sevelamer carbonate/sevelamer hydrochloride SmPC includes a specific warning in section 4.4 regarding antiarrhythmic and anti-seizure medicinal products as well as a specific warning in section 4.5 regarding a potential interaction with ciprofloxacin, ciclosporin, mycophenolate mofetil and tacrolimus.

CKD: Chronic Kidney Disease; FDA: Food and Drug Administration; ICSR: Individual Case Summary Report; PV: Pharmacovigilance; PLLR: Pregnancy, Lactation and Labelling Rule; SmPC: Summary of Product Characteristics.

SIV.2. LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Given the long standing postmarketing experience, the limitations relative to adverse drug reaction (ADR) detection in clinical trials are no longer relevant.

SIV.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Due to the vast postmarketing experience with Sevelamer carbonate/Sevelamer hydrochloride since International Birth Date (IBD), 30 October 1998, the data from post-marketing exposure

compensate any limitations with respect to populations that may have been under represented in clinical trial development programs and are reflected in the current European Union (EU) SmPC.

Table 2 – Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breast-feeding women	Pregnant or lactating women were excluded from the main clinical trials. The safety of sevelamer carbonate/sevelamer hydrochloride has not been established in pregnant or lactating women. There have been no adequate well controlled studies in women undergoing labor and delivery. Studies in animals have shown some reproductive toxicity (deficit in skeletal ossification) when sevelamer hydrochloride was administered to rats. However, through the cumulative safety analysis including literature, and postmarketing experience, no safety signal has emerged. There have not been studies of the excretion of sevelamer in human milk, but since sevelamer is not absorbed, excretion in breast milk is not expected and consequently, safety issue is not expected.
Patients with relevant co-morbidities ○ Patients with hepatic impairment or immunocompromised patients	The safety of sevelamer carbonate/sevelamer hydrochloride has not been established in patients with hepatic impairment or patients who are immunocompromised. However, taken into account that the product is not absorbed, safety issue is not expected in patients with hepatic impairment or immunocompromised.
○ Patients with renal impairment	Not relevant as sevelamer carbonate/sevelamer hydrochloride is indicated for patients with renal impairment.
○ Patients with a disease severity different from the inclusion criteria in the clinical trial population	The study populations in the sevelamer carbonate/sevelamer hydrochloride clinical trials were large enough and representative of the majority of the important co-morbidities seen in hyperphosphatemic CKD patients. In addition, the many sevelamer hydrochloride clinical trials enrolled patients with the complex co-morbidities frequently seen in hyperphosphatemic CKD patients.
○ Patients with other relevant co-morbidity	Patients participating in sevelamer carbonate/sevelamer hydrochloride studies reported prior or current disorders or abnormalities that are expected in a population with CKD. These included findings in the following body systems: cardiovascular (97%), metabolic/endocrine/nutritional (92%), hematopoietic (88%), gastrointestinal/hepatic (80%), and musculoskeletal (78%).
Patients of different racial and/or ethnic origins	RENAGEL and RENVELA studies were conducted at US and European sites and included Caucasians, Asians, Blacks, and other races. Although no ethnic groups were excluded from the studies, most patients were Caucasian (49% for sevelamer carbonate and range: 39 to 93% for sevelamer hydrochloride), or Black (range: 2 to 49% for sevelamer hydrochloride).
Subpopulations carrying known and relevant genetic polymorphisms	No subpopulations with genetic polymorphisms were excluded from clinical trials with sevelamer carbonate/sevelamer hydrochloride.

Other o Children	The safety and tolerability of sevelamer carbonate in hyperphosphatemic pediatric patients with CKD was evaluated in a multicenter study. This study established the safety and tolerability of sevelamer carbonate in the control of serum phosphorus in pediatric patients (>6 years of age and a range of body surface area of [<0.75, ≥0.75 to <1.2, ≥1.2 m^2]) with CKD. Children were excluded from the adult clinical trials.
o Elderly	Elderly have been included in the clinical trials with sevelamer carbonate/sevelamer hydrochloride.

CKD: Chronic Kidney Disease; US: United States.

Pregnant or breast-feeding women:

There are no data for the use of sevelamer in pregnant women and it is unknown whether sevelamer is excreted in human breast milk. This is addressed in SmPC section 4.6.

Pregnancy: there are no data from the use of sevelamer in pregnant women. Studies in animals have shown some reproductive toxicity when sevelamer was administered to rats at high doses (see section 5.3). Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid (see sections 4.4 and 5.3). The potential risk to humans is unknown. Sevelamer carbonate should only be given to pregnant women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the fetus.

Breast-feeding: It is unknown whether sevelamer is excreted in human breast milk. The non-absorbable nature of sevelamer indicates that excretion of sevelamer in breast milk is unlikely. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with sevelamer carbonate should be made taking into account the benefit of breast-feeding to the child and the benefit of sevelamer carbonate therapy to the woman."

A cumulative review of ICSRs from the global PV database and a review of the literature performed in 2018 upon FDA request in the context of PLLR new legislation did not identify any safety issue in this population. Use of sevelamer carbonate/sevelamer hydrochloride in pregnant or lactating women is no more considered as missing information.

Patients with relevant co-morbidities:

- *Patients with hepatic impairment or immunocompromised patients:*

The safety of sevelamer carbonate/sevelamer hydrochloride has not been established in patients with hepatic impairment or patients who are immunocompromised. However, taken into account that the product is not absorbed, safety issue is not expected in patients with hepatic impairment or immunocompromised.

Use of sevelamer carbonate/sevelamer hydrochloride in hepatic impairment or immunocompromised patients are no more considered as missing information.

- *Patients with renal impairment:*

Use of sevelamer carbonate/sevelamer hydrochloride in patients with renal impairment are not considered as missing information.

- *Patients with a disease severity different from the inclusion criteria in the clinical trial population:*

The complex comorbidities seen in hyperphosphatemic CKD patients are well documented. (1)

- *Patients with other relevant co-morbidity:*

Patients with CKD are likely to have major co-morbidities including cardiovascular disease, metabolic abnormalities, pulmonary disease and an increased propensity for infection. The co-morbidities associated with CKD are broadly similar, whether or not they are on dialysis.

Patients of different racial and/or ethnic origins:

Use of sevelamer carbonate/sevelamer hydrochloride in patients of different racial and/or ethnic origins are not considered as missing information.

Subpopulations carrying known and relevant genetic polymorphisms:

Use of sevelamer carbonate/sevelamer hydrochloride in subpopulations carrying known and relevant genetic polymorphisms are not considered as missing information.

Other:

- *Children*:

The safety and efficacy of sevelamer hydrochloride has not been established in children below the age of 18 years. Sevelamer hydrochloride is not recommended in children below the age of 18 years

- *Elderly*:

In the general, the length of inpatient hospital stay is longer and mortality is increased in elderly patients with underlying oropharyngeal dysphagia. Reduced compliance with oral medicines due to dysphagia is observed in the elderly population.

REFERENCES

1. National Kidney Foundation. Clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease, executive summary. Am J Kidney Dis. 2004;43(5 Suppl 1):S16-41.

RISK MANAGEMENT PLAN - PART II MODULE SV

POST-AUTHORIZATION EXPERIENCE

Active substance(s) (INN or common name)	**Sevelamer carbonate/Sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-Oct-2019**
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ABBREVIATIONS

DDD:	Defined Daily Dose
DLP:	Data Lock Point
INN:	International Nonproprietary Name
MIDAS:	Modular Interactive Data Acquisition System
PARC:	Performance Analysis Reporting Center
RMP:	Risk Management Plan
WHO:	World Health Organization

SV.1. POST-AUTHORIZATION EXPOSURE

SV.1.1. Method used to calculate exposure

The performance analysis reporting center (PARC) application includes sales data from major countries are collected and maintained with the goal of capturing 85% to 90% of total world sales. For this reason, the extracted figures remain an approximation of the total quantity sold because PARC does not have access to the total amount distributed in all countries. Data may also vary from one reporting interval to another due to changes in subscription agreements and the number of data channels available within a given country (examples when applicable to product distribution channels include direct to consumer sales, hospital sales, home care sales). The PARC application collects data quarterly, which introduces a possible 3 month gap from closure of the previous quarter.

Methodology

- Calculating total sales in mg by multiplying counting units for oral formulation with the strength in mg.
- Total sales in mg was divided by World Health Organization (WHO) Defined Daily Dose (DDD) of 6 g for sevelamer to estimate patient-days.
- Total patient-days were divided by 365 to calculate total patient-years.

SV.1.2. Exposure

The cumulative sales utilizing the data obtained from PARC and Modular Interactive Data Acquisition System (MIDAS) from 01 October 2001 through 30 June 2019. A total of 4151.4 million tablets and 119.2 million capsules of sevelamer hydrochloride, 3242.6 million tablets and 193.5 million oral powder of sevelamer carbonate were sold worldwide cumulatively. The exposure was estimated to be 2.7 million patient-years (1.4 million patient-years for sevelamer hydrochloride and 1.3 million patient-years for sevelamer carbonate).

Non-study post-authorization exposure for sevelamer carbonate

A total of 3242.6 million tablets and 193.5 million oral powder of sevelamer carbonate were sold worldwide cumulatively up to 30 June 2019. The exposure was estimated to be 1.3 million patient-years for sevelamer carbonate).

Non-study post-authorization exposure for sevelamer hydrochloride

Exposure

A total of 4151.4 million tablets and 119.2 million capsules of sevelamer hydrochloride were sold worldwide cumulatively up to 30 June 2019. The exposure was estimated to be 1.4 million patient-years for sevelamer hydrochloride.

REFERENCES

None

RISK MANAGEMENT PLAN - PART II MODULE SVI

ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
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DLP:	Data Lock Point
INN:	International Nonproprietary Name
RMP:	Risk Management Plan

SVI.1. POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

There have been no reports of patient abuse or dependence on sevelamer hydrochloride or sevelamer carbonate. Sevelamer hydrochloride and sevelamer carbonate are not absorbed and are not metabolized. There is no reasonable mechanism by which sevelamer use is likely to be associated with addictive properties and therefore the potential for drug abuse is exceedingly low.

Moreover, sevelamer carbonate/sevelamer hydrochloride is not listed among drugs with addictive potential by the European Monitoring Centre for Drugs and Drug Addiction.

REFERENCES

None

RISK MANAGEMENT PLAN - PART II MODULE SVII

IDENTIFIED AND POTENTIAL RISKS

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
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ABBREVIATIONS

DLP:	Data Lock Point
EMA:	European Medicines Agency
EU:	European Union
GI:	Gastrointestinal
GVP:	Good Pharmacovigilance Practices
IBD:	International Birth Date
INN:	International Nonproprietary Name
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable since first RMP approved was version 1.0.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

As per the guideline on Good Pharmacovigilance Practices (GVP) Module V-Risk Management systems - European Medicines Agency (EMA)/838713/2011 (Rev.2), the following identified or potential risks have been removed from the list of safety concerns as these risks are fully characterized and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and their risk minimization activities recommending specific clinical measures to address the risk have become fully integrated into standard clinical practices.

- Intestinal perforation, obstruction and ileus
- Diverticulitis (sevelamer hydrochloride formulation only)
- Acidosis, increased serum chloride levels (sevelamer hydrochloride formulation only)
- Serious gastrointestinal (GI) disorders associated with sevelamer crystals
- Hypersensitivity reactions, including angioedema and anaphylactic reactions
- Difficulty swallowing tablets
- Vitamin deficiency
- Drug interactions with levothyroxine, ciprofloxacin, immunosuppressants, antiarrhythmics, anticonvulsants and antifungal drugs
- Off-label use in patients <18 years old (sevelamer hydrochloride formulation only)

The risk "Medication error in children due to absence of dosing device (sevelamer carbonate powder for oral suspension)" has been removed following the new presentation of 0.8 g sachet with spoon for oral suspension sachet adapted to children.

The below listed "missing information" have been removed:

- Pregnant or breast-feeding women: the cumulative safety data from post-marketing exposure (global PV database and literature review) since the International Birth Date (IBD) (October 1998) did not identify any safety issue in this population In addition, since sevelamer is not absorbed, excretion in breast milk is not expected and consequently, safety issue is not expected in lactating population. These populations are correctly reflected in the current European Union (EU)-Summary of Product Characteristics (SmPC).
- Patients with hepatic impairment or immunocompromised patients: taken into account that the product is not absorbed, safety issue is not expected in this population.

SVII.3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Not applicable.

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable.

SVII.3.2. Presentation of the missing information

Not applicable.

REFERENCES

None

RISK MANAGEMENT PLAN - PART II MODULE SVIII

SUMMARY OF THE SAFETY CONCERNS

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product's) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
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Summary of the safety concerns

Important identified risk	None
Important potential risk	None
Missing information	None

RISK MANAGEMENT PLAN - PART III

PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V.** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
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ABBREVIATIONS

DLP:	Data Lock Point
INN:	International Nonproprietary Name
PTC:	Product Technical Complaint
RMP:	Risk Management Plan

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of sevelamer carbonate/sevelamer hydrochloride.

The safety profile of sevelamer carbonate/sevelamer hydrochloride will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints (PTCs) relating to adverse events and signal detection.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities planned for this product.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities ongoing or planned for sevelamer carbonate/sevelamer hydrochloride.

No effectiveness evaluation is set up since there are no risk minimization activities beyond routine in place.

REFERENCES

None

RISK MANAGEMENT PLAN - PART IV

PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V. Paasheuvelweg 25 1105 BP Amsterdam, The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
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DLP:	Data Lock Point
INN:	International Nonproprietary Name
RMP:	Risk Management Plan

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for sevelamer carbonate/sevelamer hydrochloride.

REFERENCES

None

RISK MANAGEMENT PLAN - PART V

RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product(s) concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe B.V. Paasheuvelweg 25 1105 BP Amsterdam, The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
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ABBREVIATIONS

DLP:	Data Lock Point
INN:	International Nonproprietary Name
RMP:	Risk Management Plan

V.1. ROUTINE RISK MINIMIZATION MEASURES

Not applicable.

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Not applicable.

V.3. SUMMARY OF RISK MINIMIZATION MEASURES

Not applicable.

REFERENCES

None

RISK MANAGEMENT PLAN - PART VI

SUMMARY OF THE RISK MANAGEMENT PLAN

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product's concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
Name of Marketing Authorization Holder or Applicant	**Genzyme Europe BV** **Paasheuvelweg 25** **1105 BP Amsterdam,** **The Netherlands**
Data lock point (DLP) for this module	**30-OCT-2019**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 10.0**

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ABBREVIATIONS

BSA:	Body Surface Area
DLP:	Data Lock Point
EMA:	European Medical Agency
EPAR:	European Public Assessment Report
INN:	International Nonproprietary Name
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

This part VI is divided into two different summaries:

- The first applies to Sevelamer Carbonate: RENVELA and SEVELAMER CARBONATE WINTHROP.
- The second applies to Sevelamer Hydrochloride: RENEGEL.

Since the indications are different and they refer to different safety databases.

Summary of risk management plan for RENVELA and SEVELAMER CARBONATE WINTHROP (Sevelamer carbonate)

This is a summary of the RMP for RENVELA and SEVELAMER CARBONATE WINTHROP. The RMP details important risks of RENVELA and SEVELAMER CARBONATE WINTHROP how these risks can be minimized, and how more information will be obtained about RENVELA and SEVELAMER CARBONATE WINTHROP'S risks and uncertainties (missing information).

RENVELA and SEVELAMER CARBONATE WINTHROP's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how RENVELA and SEVELAMER CARBONATE WINTHROP should be used.

This summary of the RMP for RENVELA and SEVELAMER CARBONATE WINTHROP should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of RENVELA and SEVELAMER CARBONATE WINTHROP's RMP.

VI.1. THE MEDICINE AND WHAT IT IS USED FOR

RENVELA and SEVELAMER CARBONATE WINTHROP is authorized for following indications:

- The control of hyperphosphatemia in adult patients receiving hemodialysis or peritoneal dialysis.
- The control of hyperphosphatemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus ≥1.78 mmol/L.
- The control of hyperphosphatemia in pediatric patients (>6 years of age and a body surface area (BSA) of >0.75 m^2) with chronic kidney disease.

RENVELA/SEVELAMER CARBONATE WINTHROP should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25 dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease. (see SmPC for the full indication). It contains Sevelamer carbonate as the active substance and it is given by oral route.

Further information about the evaluation of RENVELA and SEVELAMER CARBONATE WINTHROP benefits can be found in RENVELA and SEVELAMER CARBONATE WINTHROP EPAR, including in its plain-language summary, available on the EMA (European Medical Agency) website, under the medicine's webpage:

RENVELA (last updated on 03 September 2019):
https://www.ema.europa.eu/en/medicines/human/EPAR/renvela

SEVELAMER CARBONATE WINTHROP (last updated on 06 September 2019): https://www.ema.europa.eu/en/medicines/human/EPAR/sevelamer-carbonate-winthrop-previously-sevelamer-carbonate-zentiva

VI.2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of RENVELA and SEVELAMER CARBONATE WINTHROP, together with measures to minimize such risks and the proposed studies for learning more about RENVELA and SEVELAMER CARBONATE WINTHROP's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

VI.2.1. List of important risks and missing information

Important risks of RENVELA and SEVELAMER CARBONATE WINTHROP are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of RENVELA and SEVELAMER CARBONATE WINTHROP. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1 - List of important risks and missing information

Important identified risk	None
Important potential risk	None
Missing information	None

VI.2.2. Summary of important risks

There is no important identified risk, no important potential risk, and no missing information.

VI.2.3. Post-authorization development plan

VI.2.3.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of RENVELA and SEVELAMER CARBONATE WINTHROP.

VI.2.3.2. Other studies in post-authorization development plan

There are no studies required for RENVELA and SEVELAMER CARBONATE WINTHROP.

Summary of risk management plan for RENAGEL (Sevelamer hydrochloride)

This is a summary of the RMP for RENAGEL. The RMP details important risks of RENAGEL, how these risks can be minimized, and how more information will be obtained about RENAGEL risks and uncertainties (missing information).

RENAGEL summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how RENAGEL should be used.

This summary of the RMP for RENAGEL should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of RENAGEL RMP.

VI.3. THE MEDICINE AND WHAT IT IS USED FOR

RENAGEL is authorized for following indications:

- The control of hyperphosphatemia in adult patients receiving hemodialysis or peritoneal dialysis.

RENAGEL should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25 dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease. (see SmPC for the full indication). It contains Sevelamer hydrochloride as the active substance and it is given by oral route.

Further information about the evaluation of RENAGEL benefits can be found in RENAGEL EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

- RENAGEL (last updated on 03 September 2019): https://www.ema.europa.eu/en/medicines/human/EPAR/renagel

VI.4. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of RENAGEL, together with measures to minimize such risks and the proposed studies for learning more about RENAGEL risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

VI.4.1. List of important risks and missing information

Important risks of RENAGEL are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of RENAGEL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 2 - List of important risks and missing information

Important identified risk	None
Important potential risk	None
Missing information	None

VI.4.2. Summary of important risks

There is no important identified risk, no important potential risk and no missing information.

VI.4.3. Post-authorization development plan

VI.4.3.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of RENAGEL.

VI.4.3.2. Other studies in post-authorization development plan

There are no studies required for RENAGEL.

REFERENCES

None

RISK MANAGEMENT PLAN - PART VII

ANNEXES

Active substance(s) (INN or common name)	**Sevelamer carbonate/sevelamer hydrochloride**
Product's concerned (Brand name(s))	**RENVELA®, RENAGEL®, SEVELAMER CARBONATE WINTHROP®**
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NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

NOT APPLICABLE