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*APPLICATION NUMBER:*

**22-127**

**MEDICAL REVIEW(S)**

## CLINICAL AND STATISTICAL REVIEW

Application Type NDA  
Submission Number 22,127  
Submission Code

Letter Date December 20, 2006  
Stamp Date December 20, 2006  
PDUFA Goal Date October 19, 2007

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Review Completion Date August 24, 2007

Established Name sevelamer carbonate  
Proposed Trade Name Renvela<sup>TM</sup>  
Therapeutic Class Phosphate binder  
Applicant Genzyme

Priority Designation S

Formulation 800 mg tablets  
Dosing Regimen Three times a day  
Indication Hyperphosphatemia  
Intended Population Patients on hemodialysis

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## 1 EXECUTIVE SUMMARY

Sevelamer carbonate was developed as a pharmaceutical alternative to sevelamer hydrochloride (Renagel®). Sevelamer carbonate is an anion exchange resin with the same polymeric structure as sevelamer hydrochloride in which carbonate replaces chloride as the counterion. Since the active moiety is the same and the counterion does not play a role in the binding of phosphate, equivalent phosphate binding activity is expected with both salt forms of sevelamer.

The clinical study submitted with this NDA demonstrates that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus in chronic kidney disease patients on hemodialysis. Overall, the adverse event profiles for sevelamer carbonate and sevelamer hydrochloride are similar. Deaths occurring in patients during this study were rare (one death during each treatment) and were assessed by the Investigator as not related to the study drug. The most common adverse event leading to early discontinuation was renal transplant, which is not unexpected in this chronic kidney disease population.

In patients with chronic kidney disease on hemodialysis, the results of this study demonstrate that sevelamer carbonate and sevelamer hydrochloride were equivalent in controlling serum phosphorus. Sevelamer carbonate and sevelamer hydrochloride have a similar safety and tolerability profile.

### 1.1 Recommendation on Regulatory Action

Approve

### 1.2 Recommendation on Postmarketing Actions

None

#### 1.2.1 Risk Management Activity

NA

#### 1.2.2 Required Phase 4 Commitments

NA

#### 1.2.3 Other Phase 4 Requests

NA

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

The Sponsor has submitted one small, double-blind, cross-over clinical study demonstrating that the change in ion from sevelamer hydrochloride to sevelamer carbonate results in similar efficacy and safety.

#### 1.3.2 Efficacy

Based on this one, small, bioequivalent study, sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus in patients with chronic kidney disease on hemodialysis.

#### 1.3.3 Safety

The adverse event profiles for sevelamer carbonate and sevelamer hydrochloride were similar. Deaths occurring in patients during this study were rare (one death during each treatment) and were assessed by the Investigator as not related to study drug. Serious adverse events were consistent with the patients' underlying renal disease and assessed by the investigator as not related to the study treatment. The most common adverse event leading to early discontinuation was renal transplant, which is not unexpected in this chronic kidney disease population.

#### 1.3.4 Dosing Regimen and Administration

Both sevelamer hydrochloride and sevelamer carbonate were given orally three times a day.

#### 1.3.5 Drug-Drug Interactions

NA

#### 1.3.6 Special Populations

NA

## **2 INTRODUCTION AND BACKGROUND**

### **2.1 Product Information**

Sevelamer hydrochloride (Renagel®) has been on the market since 1998 to treat hyperphosphatemia in patients with chronic renal disease (CKD) on hemodialysis. In this new NDA the Sponsor has changed the ion for hydrochloride to carbonate in order to decrease the frequency of monitoring serum chloride and bicarbonate.

### **2.2 Currently Available Treatment for Indications**

There are three FDA approved phosphate binders: Renagel® (sevelamer hydrochloride), PhosLo (calcium acetate), and Fosrenol (lanthanum carbonate).

### **2.3 Availability of Proposed Active Ingredient in the United States**

NA

### **2.4 Important Issues With Pharmacologically Related Products**

NA

### **2.5 Presubmission Regulatory Activity**

NA

### **2.6 Other Relevant Background Information**

NA

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

This review is not currently available and will be submitted separately.

### **3.2 Animal Pharmacology/Toxicology**

This review is not currently available and will be submitted separately.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The Sponsor submitted one clinical trial for this NDA submission.

### 4.2 Tables of Clinical Studies

The Sponsor submitted one clinical trial for this submission.

### 4.3 Review Strategy

There was one clinical trial submitted for this NDA which was reviewed and discussed here.

### 4.4 Data Quality and Integrity

It was determined by the review team that a DSI inspection was not required.

### 4.5 Compliance with Good Clinical Practices

The submitted clinical trial was conducted in accordance with good ethical standards.

### 4.6 Financial Disclosures

There are no questions raised as to the integrity of the data.

## 5 CLINICAL PHARMACOLOGY

The following comments are from Dr. Robert Kumi's Review:

“The sevelamer carbonate clinical development program consists of in vitro phosphate binding studies and an in vivo study, GD3-163-201. The in vivo study was conducted to bridge the existing clinical data for the hydrochloride salt of sevelamer to the carbonate salt in the target population. Sevelamer carbonate was studied in approximately 70 adult CKD patients on hemodialysis. This clinical pharmacology review is focused on the in vitro phosphate binding studies.

The Office of Clinical Pharmacology finds the clinical pharmacology and biopharmaceutics information submitted to NDA 22-127 acceptable. However, the following additional information is needed to provide supportive in vitro evidence of the comparability of sevelamer carbonate to sevelamer hydrochloride:

- Study equilibrium phosphate binding under physiologically relevant conditions, such as over the entire pH range likely to be encountered in gut

- Study kinetics of phosphate binding under physiologically relevant conditions, such as over the entire pH range likely to be encountered in gut
- Definitively determine which critical factors influence phosphate binding, such as varying ionic strength and disintegration time

The outlined studies may be conducted post-marketing assuming the product is approved based on the information provided in the current NDA submission. It should be noted that the proposed commercial formulation's phosphate binding characteristics (k1 and k2 values) differed from that of the formulations used in the pivotal clinical study. Thus assessment of the outlined studies prior to approval or shortly thereafter is strongly recommended."

### 5.1 Pharmacokinetics

NA

### 5.2 Pharmacodynamics

NA

### 5.3 Exposure-Response Relationships

NA

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

Sevelamer hydrochloride, a phosphate binder which has been on the market since 1998, is approved of in at least 50 countries. Over 750, 000 patients worldwide have been exposed to this binder. In this NDA the Sponsor has replaced the hydrochloride ion with a carbonate ion in order to prevent the need for the frequent monitoring of serum chloride and bicarbonate. The polymeric structure has remained identical. Since the counterion hydrochloride or carbonate does not play a role in the binding of phosphate, equivalent phosphate binding activity is expected with both salt forms of sevelamer. One clinical study was submitted to demonstrate that the two salts are bioequivalent in patients.

#### 6.1.1 Methods

One clinical study was submitted for review utilizing sevelamer carbonate and sevelamer hydrochloride in a double-blind, cross-over manner in patients on hemodialysis. In order to demonstrate efficacy of phosphate control in patients on dialysis, we generally expect that at least some of the patients have a high phosphate level. Instead, this submitted study is a bioequivalence study. In this study, a wash-out period was added to the end of the study after a number of the patients had already begun the study. Not all of the patients participated in this

wash-out period; the given reason that most patients did not proceed to the washout period was because they withdrew their consent forms. Only fifty percent of the patients completed the study; therefore, this clinical submission has distinct limitations. However, in the provided cross-over design, both forms of sevelamer appear to be effective for phosphate reduction in patients on hemodialysis and both forms appear to be equally safe.

### 6.1.3 Study Design

Title: A Double-Blind, Cross-Over Design Study of Sevelamer Hydrochloride (Renagel®) and Sevelamer Carbonate in Chronic Kidney Disease Patients on Hemodialysis

Study Centers: 13 sites within the U.S.

Study Dates: March 30, 2005 to March 16, 2006

Objectives:

Primary:

1. Compare the effects of sevelamer carbonate and sevelamer hydrochloride on the control of serum phosphorus in CKD patients on hemodialysis.
2. Compare the safety and tolerability of sevelamer carbonate and sevelamer hydrochloride in CKD patients on hemodialysis.

Secondary:

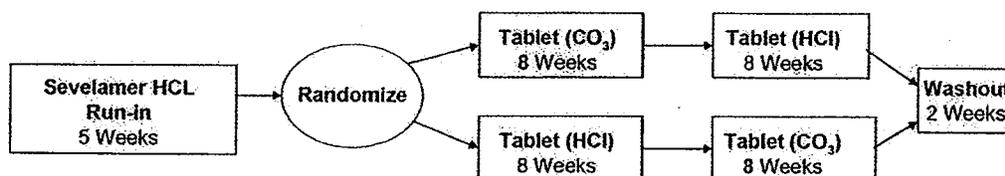
1. Compare the effects of sevelamer carbonate and sevelamer hydrochloride on serum lipid profiles in CKD patients on hemodialysis.

Study Design:

This was a double-blind, randomized, cross-over study conducted at 13 centers in the United States. A total of 79 hemodialysis patients were assigned randomly (1:1) to one of two treatment sequences: sevelamer carbonate for eight weeks followed by sevelamer hydrochloride for eight weeks, or sevelamer hydrochloride for eight weeks followed by sevelamer carbonate for eight weeks.

The study consisted of five periods: a two-week Screening Period, a five-week Run-In Period, two eight-week study Treatment Periods and a two-week Washout Period as shown in the figure below.

Figure 1: Study Design



Eligible patients entered a five-week Run-In Period during which sevelamer hydrochloride was prescribed for all patients. The Investigator had one opportunity during this Run-In Period to titrate the sevelamer hydrochloride dose, the Sensipar dose, vitamin D therapy and the hemodialysis prescription (dialysate calcium level, dialysate bicarbonate level, and treatment time). On three randomly selected days during this period, a 24-hour dietary recall was done. On the last day of the Run-In Period, the eligibility criteria were reviewed along with any adverse experiences, changes in concomitant medications, and drug accountability.

Patients were then randomized in a 1:1 fashion to one of the two treatment sequences: sevelamer carbonate for eight weeks followed by sevelamer hydrochloride for eight weeks, or sevelamer hydrochloride for eight weeks followed by sevelamer carbonate for eight weeks. The starting dose was individualized for each patient based on the most recently prescribed daily dose during the previous Run-In Period. Patients were instructed to maintain a fixed daily dose throughout both treatment periods.

During Treatment Period 1, patients were required to return for a study visit on Weeks 2, 4, 6, and 8. At these visits blood samples were drawn, adverse events and changes in medications were addressed. Between Weeks 6 and 8, a 24-hour dietary recall was collected on three randomly selected days. At the Week 8 visit, a physical exam was performed, the study drug was collected, Treatment Period 1 drug accountability was performed, and the study drug for Treatment Period 2 was dispensed. Patients were instructed to continue to maintain a stable dose based on the prescribed Run-In Period dose at randomization.

During Treatment Period 2, patients were required to return for a study visit on Weeks 10, 12, 14, and 16. At these visits blood samples were drawn and adverse events and changes in medications were assessed. Between Weeks 14 and 16, a 24-hour dietary recall was collected on three randomly selected days. At the Week 16 visit, a physical exam was performed, study drug was collected, Treatment Period 2 drug accountability was calculated, and the patient was instructed to discontinue all phosphate binders for the next two weeks.

At the end of the Study during the Washout Period, patients were required to return for a study visit on Week 18. Blood samples were drawn and adverse events and changes in medications were assessed at this visit. Patients were then instructed to resume their previously prescribed phosphate binders. The schedule for these procedures is shown on the following table.

Table 1: Assessment and Procedures performed at each study visit

	Screening Period	Run-In Period				Treatment Period 1		Treatment Period 2		Washout Period
	Visit 1 (Week -7)	Visit 2 (Week -5)	Visit 3 (Week -4)	Visit 4 (Week -1)	Visit 5 (Week 0) RANDOMIZATION	Visits 6,7,8 (Weeks 1, 4, 6)	Visit 9/ET (Week 8)	Visits 10,11,12 (Weeks 10, 12, 14)	Visit 13/ET (Week 16)	Visit 14 (Week 18)
Describe Study and Obtain Informed Consent	✓									
Review Inclusion & Exclusions	✓	✓	✓	✓	✓					
Assign Patient Number	✓									
Review Medical and Renal History	✓									
Review the two most recent consecutive total lab phosphorus values within 60 days of Screening	✓									
Review the most recent iPTH and serum calcium values within 90 days of Screening	✓									
Review Prior Medication	✓									
Weight and Height <sup>o</sup>		✓			✓		✓		✓	
Physical Exam (including Vial Signs) <sup>1</sup>					✓		✓		✓	
Serum ECG (Women of Child bearing Potential)		✓					✓		✓	
Serum Chemistry Profile		✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum iPTH				✓	✓		✓		✓	✓
Serum 25-OH D and 1,25-OH D			✓	✓	✓		✓		✓	✓
Serum Lipid Profile					✓		✓		✓	
Serum Hematology Profile					✓	✓	✓	✓	✓	
Clinical Assessment (Adverse Events, Concomitant Meds)					✓	✓	✓	✓	✓	
Serum Storage Sample		✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomize Patient					✓		✓		✓	✓
Dispense Study Drug		✓	✓	✓	✓	✓	✓	✓	✓	
Perform Study Drug Accountability					✓	✓	✓	✓	✓	
Discontinue Run-In/Treatment Period					✓					

	Screening Period	Run-In Period				Treatment Period 1		Treatment Period 2		Washout Period
	Visit 1 (Week -7)	Visit 2 (Week -5)	Visit 3 (Week -4)	Visit 4 (Week -1)	Visit 5 (Week 0) RANDOMIZATION	Visits 6,7,8 (Weeks 1, 4, 6)	Visit 9/ET (Week 8)	Visits 10,11,12 (Weeks 10, 12, 14)	Visit 13/ET (Week 16)	Visit 14 (Week 18)
Discontinue Treatment Period 1							✓			
Discontinue Treatment Period 2									✓	
Patient Dietary Summary Review									✓	
USC 24-hour dietary recall		✓		✓		✓		✓		

- <sup>o</sup>Weight only at Visit 5, Visit 9/ET and Visit 13/ET. Post-dialysis weight captured.
- <sup>1</sup>Chemistry profile at Visit 2-4: Serum phosphorus, calcium (adjusted for albumin), and albumin only.
- <sup>2</sup>Chemistry Profile at Visits 6-8 and 10-12 only: Serum phosphorus, calcium (adjusted for albumin), albumin, chloride and bicarbonate only.
- <sup>3</sup>Lipid Profile at Visits 7 and 11 only
- <sup>4</sup>Dispense 800 mg tablets for Run-In-Treatment Period
- <sup>5</sup>Dispense study drug for Treatment Period 1
- <sup>6</sup>Dispense study drug for Treatment Period 2
- <sup>7</sup>Review the patient dietary summary and fax patient information to USC.
- <sup>8</sup>On three randomly selected days during the last 2 weeks of each treatment period, dietary recalls were performed by USC.
- <sup>9</sup>Post-dialysis vital signs collected.

Patients who terminated early during Treatment Period 1 were asked to complete all of the assessments associated with Week 8. Patients who terminated early during Treatment Period 2 were asked to complete all of the assessments associated with Week 16.

One hundred one patients were enrolled in the study and 79 patients were randomized. Sixty-nine patients completed both treatment periods, 47 patients entered the final Washout Period, and 40 patients completed this Washout Period.

**Inclusion Criteria included:**

1. Patients on sevelamer hydrochloride alone (e.g. not using other types of phosphate binders concomitantly) or, patients on combination therapy (e.g. using sevelamer hydrochloride as the primary phosphate binder and calcium phosphate binders concomitantly) not exceeding a total daily binder dose of 13.6 g, for at least 60 days prior to screening.
2. Have the following measurements documented in both a local and central laboratory at randomization:
  - a) A serum phosphorus measurement  $\geq 3.0$  and  $\leq 6.5$  mg/dL
  - b) An iPTH measurement  $\leq 600$  pg/mL
3. Willing to discontinue use of antacids containing calcium, aluminum or magnesium at screening for the duration of the study unless prescribed by investigator as an evening calcium supplement

**Exclusion Criteria included:**

1. In the opinion of the investigator, the patient currently has poorly controlled diabetes mellitus, poorly controlled hypertension, active vasculitis, HIV infection, or any clinically significant, unstable medical condition
2. Active dysphagia, swallowing disorder, bowel obstruction, or severe gastrointestinal motility disorder

**Medications:**

During the Run-In Period, all patients received sevelamer hydrochloride. The dose was based on the most recently prescribed phosphate binder dose prior to Screening on a gram per gram basis. Both sevelamer hydrochloride and sevelamer carbonate were given in 800 mg tablets. During the Run-In Period, the patients were blinded to the study medication. For Treatment Periods 1 and 2, both the Investigator and the patients were blinded to the treatment sequence assignment. The Sponsor also remained blinded to treatment sequence assignments for the duration of the study. No patients were unblinded during the conduct of the study.

If a patient's serum calcium (adjusted for albumin) fell below normal (defined by the central laboratory range) during the study, the Investigator could at their discretion prescribe an evening calcium supplement on an empty stomach starting with 0.6 grams of elemental calcium (3 TUMS 500 mg tablets) and titrate the dose as necessary to return serum calcium to within the normal range.

The Investigator maintained the dose of Vitamin D, Sensipar, sodium bicarbonate and the hemodialysis regimen recorded at randomization, including the dialysate bicarbonate, calcium concentrations, and treatment time through the duration of the treatment periods, unless changes

were needed to be made for safety reasons. Also, if the patient was taking a lipid-lowering drug, this was maintained.

#### Efficacy:

The two treatment regimens were compared on the basis of serum phosphorus at the end of each treatment period using a time-weighted mean of the phosphorus values from the last three visits in each treatment period. A time-weighted mean of the measurements from the non-missing assessments from the last three visits in each treatment period (Weeks 4, 6, and 8 for Treatment Period 1 and Weeks 12, 14, and 16 for Treatment Period 2) were used for the purposes of analysis. According to the Sponsor, this gives a more accurate assessment of phosphorus control than would be attained by a single time point. No imputation or extrapolation was used to replace missing or invalid observations.

The Sponsor also compared the total, LDL and HDL cholesterol, and triglycerides, using the mean of these values for each parameter from the two post-baseline assessments in each treatment period. This information was not included in this review.

#### Safety:

Safety was evaluated on the basis of adverse events (reported and/or observed), changes in laboratory parameters, and vital signs. Clinically significant changes in physical examination were recorded and evaluated as adverse events.

#### Statistical Methods:

The primary efficacy measure was based on a comparison of serum phosphorus control observed in each treatment regimen performed on the Per-Protocol Population (according to the Sponsor, this excludes patients with major protocol deviations and minimizes the degree of bias in equivalence testing). Analyses were also performed on the Full Analysis set (excludes patients not treated or with no post-baseline assessments of serum phosphorus) as confirmatory.

The effects of sevelamer carbonate and sevelamer hydrochloride on the control of serum phosphorus were determined by using equivalence testing. The time-weighted mean of the measurements from the last three visits in each treatment period (Weeks 4, 6 and 8 for Treatment Period 1 and Weeks 12, 14 and 16 for Treatment Period 2) were used for the purpose of analysis. Equivalence was assessed using natural-log transformed time-weighted mean serum phosphorus data. Least squares means for each treatment and the mean squared error from a 2x2 analysis of variance (ANOVA) with a random subject effect and fixed sequence, period, and treatment effects were used to derive the 90% confidence interval for the difference between sevelamer carbonate (test) and sevelamer hydrochloride (reference) data on the log scale. Back transformation to the original scale yielded an estimate of the ratio (test/reference) and corresponding 90% confidence interval which was the basis of a 5% Two One-Sided Test (TOST) equivalence test. This test required that the 90% confidence interval for the ratio be within the interval (0.80, 1.25) to conclude equivalence.

Serum phosphorus levels at the end of Treatment Period 2, at the end of Washout, and the change from the end of Treatment Period 2 to the end of Washout were summarized overall and

by treatment sequence for FAS patients with Washout visit data. This assessment provides a measure of the degree of underlying hyperphosphatemia in the study population. The changes were assessed using Wilcoxon signed rank tests.

**Amendment:**

The original study design did not include the two-week phosphate binder Washout Period. This period was added to the study to confirm that the patients included in the study were hyperphosphatemic. This and other changes from Protocol Amendment 1 (July 11, 2005) are outlined as following:

- To clarify study procedures and broaden the visit windows in order that a study visit could take place on the next dialysis visit day.
- The maximum dose of phosphate binder was increased from 12g/day to 13.6 g/day to allow for higher doses within the constraint of the patient kits containing six 180 count bottles of each study treatment.
- Historical iPTH values could now be within the last 90 days rather than 60 days since standard practice was to draw this lab every 90 days.
- Sensipar use was no longer excluded, although the dose had to be kept stable, given the increased use of this treatment.
- To confirm that patients included in this study were hyperphosphatemic, a two-week Washout Period was added after Treatment Period 2. Additional labs were drawn at the end of this period.

Because the Washout Period was implemented while the study was in progress, not all of the patients opted to participate in the Washout Period. Of the 12 sites with patients who completed Treatment Period 2, three sites had all patients complete the Washout Period, none of the patients completed the Washout Period at 5 sites, and 4 sites had some patients complete the Washout Period. Twenty-two patients did not enter the Washout Period after Treatment Period 2. All of these patients withdrew their consent forms. A total of 47 patients entered the Washout Period. Seven (8.9%) patients discontinued during the Washout Period: 1 patient was withdrawn for non-compliance with study procedures, 2 patients were withdrawn due to Investigator Decision, 1 patient discontinued due to "other" reasons and 3 patients were missing Week 18 data. Forty (50.6%) patients completed the study. The following table summarizes the patient disposition information.

Table 2: Patient Disposition according to Randomized Group

	Overall (N=101)	Carbonate/ Hydrochloride Sequence (N=40)	Hydrochloride/ Carbonate Sequence (N=39)
<b>Screened</b>	<b>101</b>		
<b>Patients Who Did Not Enter Run-In Period</b>	<b>4 (4.0)</b>		
Withdrawal of Consent	1 (1.0)		
Did Not Meet Inclusion/Exclusion Criteria	3 (3.0)		
<b>Patients Entered Run-In Period</b>	<b>97 (96)</b>		
<b>Non-Randomized Patients Among Run-In Patients</b>	<b>18 (17.8)</b>		
Adverse Event	2(2.0)		
Withdrawal of Consent	7 (6.9)		
Did Not Meet Inclusion/Exclusion Criteria	4 (4.0)		
Non-Compliance with Study Procedures	2 (2.0)		
Investigator Decision	3 (3.0)		
<b>Randomized Patients</b>	<b>79 (78.2)</b>	<b>40</b>	<b>39</b>
<b>Discontinued Drug During Treatment Period 1</b>	<b>5 (6.3)</b>	<b>1 (2.5)</b>	<b>4 (10.3)</b>
Adverse Event	4 (5.1)	0	4 (10.3)
Non-Compliance with Study Procedures	1 (1.3)	1 (2.5)	0
<b>Completed Treatment Period 1</b>	<b>74 (93.7)</b>	<b>39 (97.5)</b>	<b>35 (89.7)</b>
<b>Discontinued Between Treatment Periods 1 and 2</b>	<b>1 (1.3)</b>	<b>0</b>	<b>1 (2.6)</b>
Adverse Event*	1 (1.3)	0	1 (2.6)
<b>Entered Treatment Period 2</b>	<b>73 (92.4)</b>	<b>39 (97.5)</b>	<b>34 (87.2)</b>
<b>Discontinued During Treatment Period 2</b>	<b>4 (5.1)</b>	<b>2 (5.0)</b>	<b>2 (5.1)</b>
Adverse Event	1 (1.3)	1 (2.5)	0
Death	1 (1.3)	0	1 (2.6)
Lost to Follow-up	1 (1.3)	0	1 (2.6)
Other	1 (1.3)	1 (2.5)	0
<b>Completed Treatment Period 2</b>	<b>69 (87.3)</b>	<b>37 (92.5)</b>	<b>32 (82.1)</b>
<b>Discontinued Between Treatment Period 2 and Washout</b>	<b>22 (27.8)</b>	<b>12 (30.0)</b>	<b>10 (25.6)</b>
Withdrawal of Consent	22 (27.8)	12 (30.0)	10 (25.6)
<b>Entered Washout Period</b>	<b>47 (59.5)</b>	<b>25 (62.5)</b>	<b>22 (56.4)</b>
<b>Discontinued During Washout Period</b>	<b>7 (8.9)</b>	<b>6 (15.0)</b>	<b>1(2.6)</b>
Non-Compliance with Study Procedures	1 (1.3)	1 (2.5)	0
Investigator's Decision	2 (2.5)	2 (5.0)	0
Other	1 (1.3)	1 (2.5)	0
Missing	3 (3.8)	2 (5.0)	1 (2.6)
	Overall (N=101)	Carbonate/ Hydrochloride Sequence (N=40)	Hydrochloride/ Carbonate Sequence (N=39)
<b>Completed Washout Period</b>	<b>40 (50.6)</b>	<b>19 (47.5)</b>	<b>21 (53.8)</b>

Data source: Table 14.1.1.1, Table 14.1.1.2.1 and Listing 16.2.1.1

#### 6.1.4 Efficacy Findings

The Full Analysis Set (FAS) included all randomized patients with at least one post-baseline assessment of serum phosphorus. The Per Protocol (PP) Set included all FAS evaluable patients who completed both Treatment Period 1 and Treatment Period 2 with no significant protocol

deviations. There were 22 patients with one or more protocol deviation for which they were excluded from the Per Protocol Set. The PP Set therefore includes 56 patients. This is shown on the following table.

Table 3: Patient Evaluability

	Overall	Carbonate/ Hydrochloride Sequence	Hydrochloride/ Carbonate Sequence
<b>Randomized</b>	<b>79</b>	<b>40</b>	<b>39</b>
Never Received Study Medication	1	1	0
<b>Included in Safety Set<sup>1</sup></b>	<b>78</b>	<b>39 (38)</b>	<b>39 (40)</b>
No post-baseline efficacy data	0	0	0
<b>Included in Full Analysis Set<sup>2</sup></b>	<b>78</b>	<b>39</b>	<b>39</b>
>15% difference in compliance between treatment periods	9	5	4
Significant study medication interruption	1	1	0
Proscribed medication usage	1	1	0
< 6 weeks on study treatment in either treatment period	9	2	7
Vitamin D/analogues changed significantly	7	3	4
<b>Included in Per-Protocol Set<sup>1</sup></b>	<b>56</b>	<b>32 (31)</b>	<b>24 (25)</b>

Data source: Table 14.1.2 and Listing 16.2.3.

<sup>2</sup>A patient may meet more than one exclusion reason.

#### Demographics:

In all three patient sets 40 (51%) patients were male and 38 (49%) patients were female, with a mean age of 58 years. Most patients were Black or African-American (67%), with Whites (27%), Others (5%) and American Indian or Alaskan Natives (1%) comprising the rest of the population. The mean weight was 84 kg, the mean height was 170 cm, and the mean body mass index was 29 kg/m<sup>2</sup>. There were no statistically significant differences between the treatment sequences in demographic characteristics. This is shown on the following table.

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Table 4: Patient Demographics

Parameter	Safety Set (N=78)
<b>Age (years)</b>	
Mean ± SD	58.1 ± 12.3
Range	29 – 88
<b>Gender [N (%)]</b>	
Male	40 (51)
Female	38 (49)
<b>Race [N (%)]</b>	
American Indian or Alaska Native	1 (1)
Black or African American	52 (67)
White	21 (27)
Other	4 (5)
<b>Weight (kg)</b>	
Mean ± SD	84.2 ± 25.2
Range	47.8-170.3
<b>Height (cm)</b>	
Mean ± SD	169.9 ± 10.1
Range	142.2-196.4
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	
Mean ± SD	29.0 ± 7.9
Range	18.0-57.1

Data source: Table 14.1.3.3; Listing 16.2.4.1.1

**Renal History:**

The three most common primary causes of chronic kidney disease were hypertension (23%), diabetes (42%) and other causes (21%). Ninety-two percent of the patients had used sevelamer hydrochloride alone as their pre-study phosphate binder. Patients had been on dialysis for a mean of 4.4 years and the mean dialysate bath calcium concentration was 2.4 mEq/L. The mean Urea Retention Ratio (URR) was 74.1%. The majority of patients (86%) were currently receiving vitamin D. Four patients had a partial parathyroidectomy.

There was a statistically significant difference between the treatment sequences for Time on Dialysis in the FAS. Patients in the carbonate/hydrochloride sequence had been on dialysis longer than patients in the hydrochloride/carbonate sequence (5.12 years versus 3.73 years, respectively, p=0.037). There were no other statistically significant differences between the treatment sequences.

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Table 5: Renal History

Parameter	Safety Set (N=78)
<b>Primary Cause of Chronic Renal Failure [N (%)]</b>	
Hypertension	18 (23)
Glomerulonephritis	7 (9)
Diabetes	33 (42)
Polycystic Kidneys	2 (3)
Hydronephrosis	1 (1)
Interstitial Nephritis	1 (1)
Other	16 (21)
<b>Previous Parathyroidectomy [N (%)]</b>	
No	74 (95)
Yes	4 (5)
<b>Currently on Vitamin D [N (%)]</b>	
No	11 (14)
Yes	67 (86)
<b>Time on Dialysis (years)</b>	
Mean ± SD	4.4 ± 4.9
Range	0.3-23.4
<b>Pre-Study Phosphate Binder [N (%)]</b>	
Sevelamer Hydrochloride	72 (92)
Sevelamer Hydrochloride and Calcium	6 (8)
Other	0 (0)
<b>Dialysate Bath Calcium Concentration (meq/L)</b>	
Mean ± SD	2.4 ± 0.3
Range	2.0-3.5
<b>URR (%)</b>	
Mean ± SD	74.1 ± 5.9
Range	62-96

Data source: Table 14.1.4.3; Listing 16.2.4.2

#### Medical History:

More than half of the patients, which is reflective of the extent of chronic illness in the patient population, reported prior or current disorders or abnormalities in the following body systems: cardiovascular (100%), surgical (99%), genitourinary/reproductive (94%), endocrine (92%), musculoskeletal (92%), hematologic (90%), gastrointestinal (89%), neurological (80%), respiratory (77%), HEENT (74%), other (62%), allergies (55%), and dermatologic (51%). In general, the prior and current disorders were similar between the two treatment sequences.

#### Physical Examination:

The most frequent abnormalities at screening were found in the extremities (42%), other (20%), skin (18%), HEENT (18%), and cardiovascular (18%). In general, the physical examination abnormalities were similar between the two sequences.

#### Prior Medications:

All 78 patients (100%) had taken at least one medication within 30 days prior to Screening and during Screening. The most common classes of medication (> 25% of patients) were ace inhibitors, plain (29.5%), anilides such as doxyphene and paracetamol (55.1%), selective beta

blocking agents such as atenolol and metoprolol (46.2%), dihydropyridine derivatives such as amlodipine, felodipine, and nifedipine (38.5%), electrolyte solutions (64.1%), heparin (94.9%), HMG CoA reductase inhibitors (46.2%), iron bivalent, oral preparations (33.3%), other antianemic preparations such as erythropoietin and epoetin alpha (92.3%), platelet aggregation inhibitors excluding heparin such as acetylsalicylic acid and clopidogrel (47.4%), proton pump inhibitors (32.1%), vitamin D and analogues (88.5%). Prior medications for the two sequence groups were similar with the exception of the following: more patients in the carbonate/hydrochloride sequence had taken anilides (65.8% vs. 45.0%) than patients in the hydrochloride/carbonate sequence; more patients in the hydrochloride/carbonate sequence had taken oral iron (45.0% vs. 21.1%) and proton pump inhibitors (45.0% vs. 18.4%) than patients in the carbonate/hydrochloride sequence.

Concomitant Medications during treatment period:

During the randomized treatment periods, all (100%) patients took a concomitant medication. The drug categories with the most frequent (> 25%) concomitant medications are presented in the following table. The concomitant medications were similar between treatment regimens.

Table 6: Most Frequent Concomitant Medications

Therapeutic Class	Sevelamer Carbonate (N=73) (%)	Sevelamer Hydrochloride (N=78) (%)
Ace inhibitors, plain	32.9%	35.9%
Anilides	65.8%	60.3%
Beta blocking agents, selective	45.2%	43.6%
Dihydropyridine derivatives	39.7%	37.2%

Therapeutic Class	Sevelamer Carbonate (N=73) (%)	Sevelamer Hydrochloride (N=78) (%)
Electrolyte solutions	68.5%	66.7%
H2-receptor antagonists	28.8%	29.5%
Heparin group	94.5%	94.9%
HMG-CoA reductase inhibitors	45.2%	47.4%
Iron bivalent, oral preparations	30.1%	30.8%
Iron trivalent, oral preparations	35.6%	29.5%
Other antianemic preparations	91.8%	92.3%
Platelet aggregation inhibitors excluding heparin	49.3%	48.7%
Proton pump inhibitors	35.6%	38.5%
Vitamin D and analogues	91.8%	91.0%
Vitamins, other combinations	30.1%	29.5%

Data source: Table 14.1.9.1.2 and Listing 16.2.4.7.

A total of 71 (97.3%) patients treated with sevelamer carbonate and 72 (92.3%) of patients treated with sevelamer hydrochloride began new medications or had changes in existing medications during the randomized treatment periods. The drug categories with the most frequent concomitant medication changes (>10%) are presented in following table. The concomitant medications changes were similar between treatment regimens and similar to the medication changes were made during the Run-In Period.

Table 7: Medication Changes During the Randomized Treatment Periods

Therapeutic Class	Sevelamer Carbonate (N=73) (%)	Sevelamer Hydrochloride (N=78) (%)
Ace inhibitors, plain	5.5%	11.5%
Anilides	9.6%	10.3%
Cephalosporins and related substances	4.1%	10.3%
Glycopeptide antibacterials	6.8%	10.3%

Therapeutic Class	Sevelamer Carbonate (N=73) (%)	Sevelamer Hydrochloride (N=78) (%)
Heparin group	5.5%	11.5%
Influenza vaccines	19.2%	17.9%
Iron bivalent, oral preparations	11.0%	10.3%
Iron trivalent, oral preparations	19.2%	15.4%
Natural opium alkaloids	9.6%	10.3%
Other antianemic preparations	56.2%	43.6%
Proton pump inhibitors	8.2%	10.3%
Vitamin D and analogues	31.5%	17.9%

Data source: Table 14.1.9.2.2 and Listing 16.2.4.7.

#### Bicarbonate Concentration of Dialysate Bath:

There was no change for bicarbonate concentration of dialysate bath for either treatment and no statistically significant difference in the change in this parameter between the treatment groups.

#### Dietary Intake:

During the randomized treatment periods, there were no significant differences in dietary intake between treatments.

**Treatment Compliance:**

Percent compliance was calculated as the number of tablets taken in the period divided by the total number of tablets prescribed in the period, and multiplied by 100. The total number of tablets prescribed in the period was the number of tablets prescribed per day, multiplied by the number of medication days, where the number of medication days was the number of days between the end date and the start date (i.e., =End Date – Start Date + 1). Prescribed daily sevelamer dose for each treatment period was calculated by multiplying the number of tablets/day prescribed by 0.8 g (dose per tablet). The percent compliance is sometimes calculated as higher than 100% because unused tablets were not returned in all cases.

**Primary Efficacy Parameter-Serum Phosphorus:**

The analysis of the primary efficacy endpoint, equivalence in serum phosphorus, is presented using the PP Set and FAS was used for confirmation. In the Per Protocol Set, the mean serum phosphorus was  $4.6 \pm 0.9$  mg/dL during sevelamer carbonate treatment and  $4.7 \pm 0.9$  mg/dL during sevelamer hydrochloride treatment. The geometric least square mean ratio (sevelamer carbonate/sevelamer hydrochloride) was 0.99 with a corresponding 90% confidence interval of 0.95-1.03. The confidence interval is within the interval of 0.80-1.25, indicating that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus. The results of a confirmatory analysis conducted with the Full Analysis Set are similar. The following table shows the results of the equivalence tests for both the Per Protocol Set and Full Analysis Set.

Table 8: Serum Phosphorus Equivalence Tests

Analysis Set	Sevelamer Carbonate [mean ± SD]	Sevelamer Hydrochloride [mean ± SD]	Geometric LS Mean Ratio	90% CI of Ratio
Per Protocol Set	N=56 $4.6 \pm 0.9$	N=56 $4.7 \pm 0.9$	0.99	0.95-1.03
Full Analysis Set	N=73 $4.8 \pm 0.9$	N=78 $4.8 \pm 1.0$	0.99	0.96-1.02

Data source: Table 14.2.1.1, Table 14.2.1.2, and Listing 16.2.7.1.2.

In the sponsor’s analysis, the time-weighted mean of the measurements from the non-missing assessments from the last three visits in each treatment period (visits 7, 8, and 9 from treatment period 1 and visits 11, 12, and 13 from treatment period 2) was used for the analysis. This time-weighted mean was calculated as the sum of the values from the following two intervals divided by the sum of the interval lengths for period 1:

1<sup>st</sup> interval (*visit8* → *visit7*): (days from visit 8 to visit 7) \* (*visit7* value + *visit8* value)/2

2<sup>nd</sup> interval (*visit9* → *visit8*): (days from visit 9 to visit 8) \* (*visit8* value + *visit9* value)/2

Same calculation was conducted for period 2.

*Reviewer’s comment:*

*The FDA statistician verified the sponsor’s analysis by using a simple mean calculated as the sum of the values of three visits divided by 3. The results were similar to that of the Sponsor’s.*

Post-hoc analyses were performed to understand the results across dose level as a marker for degree of underlying hyperphosphatemia. A regression analysis of the equivalence ratio (sevelamer carbonate/sevelamer hydrochloride) on prescribed dose was conducted. The flat regression line and non-significant p-value ( $y=0.95 + 0.01*x$ ;  $p=0.2745$ ) indicate that the equivalence ratio is invariant to prescribed dose.

As an alternative way to illustrate this relationship, an analysis of the geometric least squares mean ratio (sevelamer carbonate/sevelamer hydrochloride) was conducted by dose group and is presented in the following table. The confidence intervals for each of the dose groups are within the interval of 0.80-1.25 indicating that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus regardless of dose group.

Table 9: Serum Phosphorus by Dose Group

Prescribed Daily Dose (grams)	N	Ratio	Confidence Interval
≤4.8	22	0.97	0.91-1.04*
>4.8 to <9.6	14	0.95	0.85-1.05*
≥9.6	20	1.04	0.98-1.10*

\*90 % CI for the ratio is within the interval (0.8, 1.25)  
 Data Source: Post-hoc Table 3.

Serum Phosphorus during the Washout Period:

A two-week Washout Period was included following the active treatment period to confirm that the patients enrolled in this trial were hyperphosphatemic. At the end of the treatment period the serum phosphorus was  $5.0 \pm 1.3$  mg/dL in all FAS patients participating in the Washout Period. Following the two-week Washout Period, the serum phosphorus level increased significantly ( $1.5 \pm 1.9$  mg/dL;  $p<0.001$ ). This increase in serum phosphorus during the Washout Period was seen regardless of the salt form of sevelamer prescribed immediately preceding the Washout Period. In patients treated with sevelamer carbonate prior to washout, serum phosphorus increased  $1.3 \pm 2.2$  mg/dL (from  $5.3 \pm 1.4$ ,  $p=0.022$ ) and in patients treated with sevelamer hydrochloride immediately preceding the washout, serum phosphorus increased  $1.7 \pm 1.5$  mg/dL (from  $4.6 \pm 1.2$ ,  $p<0.001$ ). The results for serum phosphorus before and after the end of washout are presented in the following table overall and by treatment sequence.

Table 10: Serum Phosphorus (mg/dL) Before and After End of Washout-Full Analysis Set Patients

	Overall (N=40) [mean ± SD]	Sequence 1 (Carbonate/Hydrochloride) (N=19) [mean ± SD]	Sequence 2 (Hydrochloride/Carbonate) (N=21) [mean ± SD]
Week 16	$5.0 \pm 1.3$	$4.6 \pm 1.2$	$5.3 \pm 1.4$
Week 18	$6.5 \pm 1.9$	$6.3 \pm 1.8$	$6.6 \pm 2.0$
Change	$1.5 \pm 1.9$	$1.7 \pm 1.5$	$1.3 \pm 2.2$
P-Value	< 0.001	< 0.001	0.022

Data source: Table 14.2.1.3 and Listing 16.2.7.1.2.

A post-hoc analysis was performed to understand the association between dose and serum phosphorus changes during the Washout Period. A regression analysis of the change in serum phosphorus during the Washout Period on prescribed dose was conducted. The regression line and significant p-value ( $y=0.10+0.20*x$ ;  $p=0.0296$ ) indicate that patients with a higher prescribed dose experienced greater increases in serum phosphorus during the Washout Period thereby confirming that dose level is a reasonable marker of hyperphosphatemia.

#### Handling of Dropouts or Missing Data:

The primary efficacy measure was based on a comparison of serum phosphorus control observed with each treatment. The effect of sevelamer carbonate and sevelamer hydrochloride on the control of serum phosphorus was determined using equivalence testing. The primary efficacy measure was the time-weighted average of the serum phosphorus assessments for the non-missing assessments from the last three visits in each treatment regimen because this methodology can accommodate the varying number of assessments that could arise during the four week period and the varying intervals between assessments. Measurements were not carried forward.

#### Interim Analyses and Data Monitoring:

No interim analyses were planned or conducted.

#### 6.1.5 Clinical Microbiology

NA

#### 6.1.6 Efficacy Conclusions

Based on this one, small, bioequivalent study, sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus in patients with chronic kidney disease on hemodialysis.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The one clinical study in this submission that was evaluated for both safety and efficacy has only a small number of patients, and only half of them remained in the study during the added on final wash-out period. Therefore, limited safety information is provided in this submission. However, sevelamer hydrochloride has been approved and marketed since 1998 and its record post approval must also be considered. It has proved to be safe through the years with the most frequent adverse events occurring in the gastrointestinal tract, this is related to the fact that it is a

bulk agent. This singular study demonstrates that with the change in ion from hydrochloride to carbonate the safety profile remains similar.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 8.1. From the time of informed consent through study completion or termination adverse events were collected. All adverse events were summarized by system organ class (SOC) and the preferred term.

#### 7.1.1 Deaths

Two patients died during the study, one patient in each treatment regimen. Both patients' deaths were considered not to be related to the study drug by the Investigator. The first patient, a 73 year old female with a medical history significant for type II diabetes, myocardial infarction, angina, peripheral vascular disease, stroke, hypertensive and arteriosclerotic cardiovascular disease, and left ventricular hypertrophy, died of complications of worsening coronary artery disease approximately one month after starting sevelamer carbonate. The patient's death was assessed by the Investigator as not related to sevelamer carbonate.

The second patient, a 40 year old female with a medical history significant for diabetes, hypertension, hyperlipidemia, and kidney transplant discontinued the study approximately one month after starting the sevelamer hydrochloride treatment period due to a renal transplant. Three weeks after undergoing the transplant, the patient died due to complications of diabetes mellitus. The patient's death was assessed by the Investigator as not related to sevelamer hydrochloride.

#### 7.1.2 Other Serious Adverse Events

During the randomized treatment periods, 17 serious adverse events occurred in 8 (11.0%) of the patients during the sevelamer carbonate treatment and 17 serious adverse events occurred in 11 (14.1%) of the patients during the sevelamer hydrochloride treatment. Overall, SAEs occurred as single events in individual patients with no apparent patterns. The most frequently reported SAE was coronary artery disease. All SAEs during the randomized treatment periods were assessed by the Investigator as not to be related to the treatment.

Throughout the study, the majority of adverse events were mild or moderate in intensity. Five (6.8%) patients during the sevelamer carbonate and 6 (7.7%) patients during the sevelamer hydrochloride regimen experienced a severe adverse event. A majority of severe events occurred in a single patient each during the randomized treatment periods. Severe adverse events occurring in more than one patient during sevelamer carbonate treatment included: coronary artery disease in 2 patients. Severe adverse events occurring in more than one patient during sevelamer hydrochloride treatment included: renal transplant in 2 patients. All severe events were assessed by the Investigator as not related or unlikely related to study treatment.

*Reviewer's comment:*

*Although the Sponsor considers renal transplant as a serious adverse event, this Medical Reviewer does not concur with this designation.*

### 7.1.3 Dropouts and Other Significant Adverse Events

A total of 6 patients discontinued due to adverse events during sevelamer hydrochloride treatment. The most common adverse event that led to discontinuation was renal transplant (2 patients). Adverse events among the remaining patients that led to discontinuation included: dermatitis allergic, asthenia and muscular weakness, each occurring in unique patients during sevelamer hydrochloride treatment, and events of cardiac tamponade, arteriovenous fistula thrombosis, and hepatic ischemia occurring in one patient during sevelamer hydrochloride treatment.

### 7.1.4 Other Search Strategies

NA

### 7.1.5 Common Adverse Events

The study is divided into the Run-in Period, the two randomized treatment periods, and the Wash-out at the end. During the Run-In Period when all patients received sevelamer hydrochloride, a total of 12 events in 9 (11.5%) patients were considered by the Investigator as treatment related. The highest frequency of treatment related adverse events occurring during the Run-In Period were gastrointestinal disorders with 6 events in 5 (6.4%) patients. One serious adverse event, a faecoloma, assessed as mild in intensity, was considered by the Investigator as possibly related to sevelamer hydrochloride.

The overall frequency of adverse events was similar between treatment regimens: 195 events in 60 (82.2%) patients during sevelamer carbonate treatment and 226 events in 65 (83.3%) patients during sevelamer hydrochloride treatment. The most frequently occurring AEs ( $\geq 10\%$  of randomized patients in either treatment regimen, all causality) are shown in the following table.

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Table 11: Summary of all Causality AEs

System Organ Class	Sevelamer Carbonate (N = 73)		Sevelamer Hydrochloride (N = 78)	
	Patients n (%)	Events N	Patients n (%)	Events N
Gastrointestinal disorders	15 (20.5)	25	28 (35.9)	45
Infections and infestations	19 (26.0)	24	18 (23.1)	21
Injury, poisoning and procedural complications	16 (21.9)	26	16 (20.5)	20
Musculoskeletal and connective tissue disorders	12 (16.4)	18	16 (20.5)	24
Investigations	14 (19.2)	19	13 (16.7)	17
Metabolism and nutrition disorders	12 (16.4)	13	14 (17.9)	20
Nervous system disorders	12 (16.4)	12	13 (16.7)	15
Respiratory, thoracic and mediastinal disorders	12 (16.4)	16	13 (16.7)	20
General disorders and administration site conditions	10 (13.7)	14	13 (16.7)	17

Data source: Table 14.3.1.3, Listing 16.2.6.1

During the randomized Treatment Periods, the frequency of patients experiencing treatment related adverse events was similar between both treatment regimens: 20 events in 12 (16.4%) patients during sevelamer carbonate treatment and 33 events in 15 (19.2%) patients during sevelamer hydrochloride treatment. All treatment-related AEs were mild or moderate in severity. A summary of the treatment-related adverse events occurring in > 2% patients is shown in the following table.

Table 12: Treatment Emergent Adverse Events Occurring in >2% of Randomized Patients

System Organ Class Preferred Term	Sevelamer Carbonate (N=73)		Sevelamer Hydrochloride (N=78)	
	Patients N (%)	Events n	Patients N (%)	Events n
Gastrointestinal disorders	6 (8.2)	9	8 (10.3)	14
Nausea	2 (2.7)	2	2 (2.6)	5
Gastroesophageal reflux disease	1 (1.4)	1	3 (3.8)	4
Vomiting	2 (2.7)	2	1 (1.3)	1
Metabolism and nutrition disorders	2 (2.7)	2	4 (5.1)	4
Decreased appetite	0 (0.0)	0	2 (2.6)	2

Data source: Table 14.3.1.4, Listing 16.2.6.1

Treatment-related adverse events occurring in the gastrointestinal tract included: nausea (2 events in 2 patients during sevelamer carbonate treatment and 5 events in 2 patients during sevelamer hydrochloride treatment); gastroesophageal reflux disease (1 event in 1 patient during sevelamer carbonate treatment and 4 events in 3 patients during sevelamer hydrochloride treatment); and vomiting (2 events in 2 patients during sevelamer carbonate treatment and 1 event in 1 patient during sevelamer hydrochloride treatment).

Adverse events possibly or probably related to the study drug that occurred during the randomized Treatment Periods were also evaluated for the following subgroups: males, females, blacks or African Americans, other races, < 65 years of age, and > 65 years of age. In general, the treatment-related adverse events seen within each subgroup were consistent with the analysis of the overall population.

#### 7.1.6 Less Common Adverse Events

NA

#### 7.1.7 Laboratory Findings

Abnormal laboratory values were not analyzed in this study given the high frequency of chronically abnormal laboratory parameters in dialysis patients. However, changes in laboratory values that were clinically significant as assessed by the Investigator and for which a medical intervention was indicated were considered adverse events.

There was a small increase in serum phosphorus during sevelamer hydrochloride treatment (0.3 mg/dL), but not during the sevelamer carbonate treatment. There was no difference in the change in serum phosphorus between the treatment regimens. The mean serum phosphorus was within the KDOQI recommended range of 3.5-5.5 mg/dL at all times during both sevelamer carbonate and sevelamer hydrochloride treatments.

There was a small increase in calcium-phosphorus product during sevelamer hydrochloride treatment ( $3.18 \text{ mg}^2/\text{dL}^2$ ) but not during sevelamer carbonate treatment. There was no difference in the change in calcium-phosphorus product between the treatment regimens.

Median iPTH increased during both sevelamer carbonate treatment (38 pg/mL) and sevelamer hydrochloride treatment (25 pg/mL). The difference between treatment regimens was not clinically meaningful. There was a small increase in serum albumin during both sevelamer carbonate (0.07 g/dL) and sevelamer hydrochloride (0.04 g/dL) treatments. There was no difference in the change in serum albumin between the treatment regimens.

There was no change in serum calcium during either treatment or between the treatment regimens. These laboratory findings are shown on the following table.

Table 13: Serum Phosphorus, Calcium (Adjusted for Albumin), Calcium-Phosphorus Product, iPTH and Albumin

	Sevelamer Carbonate (N=73) [mean ± SD]	Sevelamer Hydrochloride (N=78) [mean ± SD]	P-Value*
<b>Serum Phosphorus (mg/dL)</b>			0.715
Baseline	4.6 ± 1.1	4.6 ± 1.1	
Final	4.8 ± 1.2	4.8 ± 1.2	
Change	0.2 ± 1.1	0.3 ± 1.2	
P-value	0.080	0.019	
<b>Serum Calcium (Adjusted for Albumin) (mg/dL)</b>			0.560
Baseline	9.3 ± 0.7	9.3 ± 0.7	
Final	9.3 ± 0.5	9.4 ± 0.7	
Change	0.0 ± 0.6	0.1 ± 0.6	
P-value	0.402	0.848	
<b>Calcium-Phosphorus Product (mg<sup>2</sup>dL<sup>2</sup>)</b>			0.539
Baseline	42.86 ± 10.19	42.38 ± 10.70	
Final	45.02 ± 11.40	45.57 ± 11.81	
Change	2.17 ± 11.08	3.18 ± 11.32	
P-value	0.075	0.006	
<b>iPTH(pg/mL)<sup>†</sup></b>			0.020
Baseline	245	249	
Final	297	258	
Change	38	25	
P-value	<0.001	0.024	
<b>Serum Albumin (g/dL)</b>			0.644
Baseline	3.82 ± 0.31	3.82 ± 0.31	
Final	3.89 ± 0.27	3.87 ± 0.30	
Change	0.07 ± 0.23	0.04 ± 0.22	
P-value	0.021	0.050	

Data source: Table 14.3.4.1, Table 14.3.4.2.1, Table 14.3.4.3, Table 14.3.4.4, Table 14.3.4.5.1

† iPTH presented as median

\*Wilcoxon signed rank test used to compare change from baseline between treatments.

A two-week Washout Period was included following the active treatment period. The original study design did not include the two-week Washout Period. As this change was implemented while the study was in progress, not all patients consented to participate in the Washout Period. Serum phosphorus, calcium and iPTH were also investigated during this Washout Period. The results for serum phosphorus, calcium and iPTH before and after the end of washout are shown in the following table and by treatment sequence.

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Table 14: Serum Phosphorus, Calcium, and iPTH Before and After End of Washout

	Overall (N=40) [mean ± SD]	Sequence 1 (Carbonate/ Hydrochloride) (N=19) [mean ± SD]	Sequence 2 (Hydrochloride/ Carbonate) (N=21) [mean ± SD]
<b>Serum Phosphorus (mg/dL)</b>			
Week 16	5.0 ± 1.3	4.6 ± 1.2	5.3 ± 1.4
Week 18	6.5 ± 1.9	6.3 ± 1.8	6.6 ± 2.0
Change	1.5 ± 1.9	1.7 ± 1.5	1.3 ± 2.2
P-Value	<0.001	<0.001	0.022
<b>Serum Calcium (Adjusted for Albumin) (mg/dL)</b>			
Week 16	9.3 ± 0.7	9.4 ± 0.8	9.2 ± 0.6
Week 18	9.0 ± 0.6	9.0 ± 0.6	9.1 ± 0.7
Change	-0.3 ± 0.6	-0.5 ± 0.5	-0.1 ± 0.7
P-Value	0.001	<0.001	0.425

	Overall (N=40) [mean ± SD]	Sequence 1 (Carbonate/ Hydrochloride) (N=19) [mean ± SD]	Sequence 2 (Hydrochloride/ Carbonate) (N=21) [mean ± SD]
<b>iPTH (pg/mL)<sup>†</sup></b>			
Week 16	197	292	304
Week 18	245	436	492
Change	172	128	41
P-Value	<0.001	<0.001	0.049

Data source: Table 14.2.1.3, Table 14.3.4.2.2, Table 14.3.4.5.2 and Listing 16.2.7.1.2.

† iPTH presented as median

At the end of the treatment period, the serum phosphorus was  $5.0 \pm 1.3$  mg/dL in all FAS patients participating in the washout. Following the two-week Washout Period, the serum phosphorus level increased significantly ( $1.5 \pm 1.9$  mg/dL;  $p < 0.001$ ). This increase in serum phosphorus during the Washout Period was seen regardless of the salt form of sevelamer prescribed immediately preceding the Washout. In patients treated with sevelamer carbonate prior to washout, serum phosphorus increased  $1.3 \pm 2.2$  mg/dL (from  $5.3 \pm 1.4$ ,  $p = 0.022$ ) and in patients treated with sevelamer hydrochloride immediately preceding the washout, serum phosphorus increased  $1.7 \pm 1.5$  mg/dL (from  $4.6 \pm 1.2$ ,  $p < 0.001$ ).

At the end of the treatment period, the serum calcium was  $9.3 \pm 0.7$  mg/dL in all FAS patients participating in the washout. Following the two-week Washout Period, the serum calcium level decreased ( $-0.3 \pm 0.6$  mg/dL). This decrease in serum calcium during the Washout Period was different for each of the salt forms of sevelamer prescribed immediately preceding the washout. In patients treated with sevelamer hydrochloride prior to washout, serum calcium decreased  $-0.5 \pm 0.5$  mg/dL (from  $9.4 \pm 0.8$  mg/dL), but there was no change in patients treated with sevelamer carbonate immediately preceding the washout.

At the end of the treatment period, the median iPTH was 292 pg/mL in all FAS patient participating in the washout. Following the two-week Washout Period, the serum iPTH level increased (128 pg/mL). This increase in iPTH during the Washout Period was seen regardless of the salt form of sevelamer prescribed immediately preceding the washout. In patients treated with sevelamer carbonate prior to Washout, median iPTH increased 128 pg/mL (from 292

pg/mL) and in patients treated with sevelamer hydrochloride immediately preceding the washout, median iPTH increased 41 pg/mL (from 304 pg/mL).

#### Serum Chemistry:

There was a decrease in serum chloride during sevelamer carbonate treatment, but no change during sevelamer hydrochloride treatment. There was an increase in serum carbon dioxide during sevelamer carbonate treatment but not during sevelamer hydrochloride treatment. There were no significant changes in the other serum chemistry parameters for either treatment regimen or no significant differences in the change in these parameters between the treatment regimens.

#### Hematology:

There was an increase in hemoglobin for sevelamer carbonate but not for sevelamer hydrochloride. There was no significant difference in the change in hemoglobin between the treatments. There was an increase in monocytes for sevelamer carbonate but not for sevelamer hydrochloride. There was no significant difference in the change in monocytes between the treatments. There were no significant change in the other hematology measures for either treatment regimen and no significant difference in the change in these parameters between the treatments.

#### 7.1.8 Vital Signs

There were no significant changes in the vital signs for either treatment regimen. There were no significant differences in the change in these parameters between the treatments.

#### 7.1.10 Immunogenicity

NA

#### 7.1.11 Human Carcinogenicity

NA

#### 7.1.12 Special Safety Studies

NA

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

NA

#### 7.1.14 Human Reproduction and Pregnancy Data

NA

#### 7.1.15 Assessment of Effect on Growth

NA

#### 7.1.16 Overdose Experience

NA

#### 7.1.17 Postmarketing Experience

### 7.2 Adequacy of Patient Exposure and Safety Assessments

Adverse events occurring during the study were consistent with the patients' underlying renal disease. The frequency of adverse events was similar between sevelamer carbonate and sevelamer hydrochloride. The highest frequency of treatment emergent adverse events occurred in the gastrointestinal tract, with 25 events in 15 (20.5%) patients during sevelamer carbonate treatment and 45 events in 28 (35.9%) patients during sevelamer hydrochloride treatment. The majority of adverse events were mild or moderate in severity.

Severe AEs occurred in 5 (6.8%) patients during sevelamer carbonate treatment and 6 (7.7%) patients during sevelamer chloride treatment. A total of 20 events in 12 (16.4%) patients during sevelamer carbonate treatment and 33 events in 15 (19.2%) patients during sevelamer hydrochloride treatment were considered by the Investigator to be treatment-related. All treatment-related adverse events were mild or moderate in severity.

One serious adverse event of faecoloma was considered by the Investigator to be possibly related to sevelamer hydrochloride treatment during the Run-In Period. The event was assessed by the Investigator as mild, and the patient recovered without sequelae.

During the randomized treatment period, a total of 17 serious adverse events occurred in 8 (11.0%) patients during sevelamer carbonate treatment and 17 serious adverse events occurred in 11 (14.1%) patients during sevelamer hydrochloride treatment. All SAEs during the randomized treatment periods were assessed by the Investigator as not related to study treatment. The most frequently occurring serious adverse event was coronary artery disease: 2 events in 2 patients during sevelamer carbonate treatment and 2 events in 2 patients during sevelamer hydrochloride treatment. Serious adverse events occurred across system organ classes and were consistent with patients' underlying renal disease and hemodialysis status.

Two patients died during the study, one patient in during each treatment regimen. Both deaths were secondary to complications of pre-existing diseases and were assessed by the Investigator as not related to study treatment. A total of 6 patients discontinued due to adverse events during sevelamer hydrochloride treatment. The most common adverse event that led to discontinuation was renal transplant.

There were no clinically significant changes observed for safety laboratory parameters. Additionally, no clinically significant changes in vital signs were observed during the randomized treatment periods.

The results from this study demonstrate sevelamer carbonate and sevelamer hydrochloride have a similar safety and tolerability profile.

### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

NA

### 7.4 General Methodology

NA

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

NA

### 8.2 Drug-Drug Interactions

NA

### 8.4 Pediatrics

The Sponsor is planning on submitting a powder formulation in the future, therefore a pediatric waiver was granted.

### 8.5 Advisory Committee Meeting

NA

### 8.6 Literature Review

NA

## 8.7 Postmarketing Risk Management Plan

NA

## 8.8 Other Relevant Materials

NA

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

Sevelamer carbonate was developed as a pharmaceutical alternative to sevelamer hydrochloride (Renagel®). Sevelamer carbonate is an anion exchange resin with the same polymeric structure as sevelamer hydrochloride in which carbonate replaces chloride as the counterion. Since the active moiety is the same and the counterion does not play a role in the binding of phosphate, equivalent phosphate binding activity is expected with both salt forms of sevelamer.

This clinical study demonstrates that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus in chronic kidney disease patients on hemodialysis. Overall, the adverse event profiles for sevelamer carbonate and sevelamer hydrochloride were similar. Deaths occurring in patients during this study were rare (one death during each treatment) and were assessed by the Investigator as not related to study drug. Serious adverse events were consistent with the patients' underlying renal disease and assessed by the investigator as not related to the study treatment. The most common adverse event leading to early discontinuation was renal transplant, which is not unexpected in this chronic kidney disease population.

In patients with chronic kidney disease on hemodialysis, the results of this study demonstrate that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus. Sevelamer carbonate and sevelamer hydrochloride have a similar safety and tolerability profile.

## 9.2 Recommendation on Regulatory Action

Approve

## 9.3 Recommendation on Postmarketing Actions

None

### 9.3.1 Risk Management Activity

None

### 9.3.2 Required Phase 4 Commitments

None

### 9.3.3 Other Phase 4 Requests

None

### 9.4 Labeling Review

The label review will be completed separately and combined with NDA 21,179/S020 for peritoneal dialysis.

### 9.5 Comments to Applicant

None

## 10 APPENDICES

NA

### 10.1 Review of Individual Study Reports

NA

### 10.2 Line-by-Line Labeling Review

Will be reviewed separately with NDA 21,179/S020.

## REFERENCES

NA

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## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### *Divisional Memorandum*

**NDA:** 22-179 (sevelamer hydrochloride)

**Sponsor:** Genzyme

**Review date:** 19 October 2007

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

**Distribution:** NDA 22-138  
DCaRP/Crowley/Moreschi  
OB/Liu

Sevelamer hydrochloride is approved for the treatment of hyperphosphatemia in patients on hemodialysis. The current application seeks approval for use in the setting of peritoneal dialysis. This memo is based upon the reviews of Drs. Moreschi (medical) and Liu (statistics) dated 28 June 2007.

In support of this use, the sponsor performed REN-003-04, an open-label, parallel comparison of Renagel and calcium acetate, at reasonable doses, for 12 weeks, in 143 patients on peritoneal dialysis. Subjects were washed out of their prior treatment for 2 weeks. No inspection was performed and the data were deemed of adequate quality by the reviewers.

Adverse events were somewhat more common on Renagel, but the only particular event of note higher on Renagel was peritonitis (8% vs 4%), a non-statistically significant difference that seems improbably related to treatment.

The same study provided evidence that Renagel lowered serum phosphate in peritoneal dialysis patients, but this was never an issue.

We have taken this opportunity to get labeling in PLR format and addressed some open issues with regard to labeling, including removal of the identity of the positive control in studies that led to the original approval.

I concur with the reviewers that the application should be approved.

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