

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-318

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



sevelamer carbonate
Module 1: Administrative and Prescribing Information
Patent Information

1.3.5.1 Patent Information/FDA Form 3542a

Relevant method of use and composition patent information for sevelamer carbonate is provided on the following pages.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.
	NDA NUMBER 22-318
	NAME OF APPLICANT/NDA HOLDER Genzyme Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME) RENVELA	
ACTIVE INGREDIENT(S) Sevelamer Carbonate	STRENGTH(S) 2.4 g
DOSAGE FORM Powder, Sachet	

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

GENERAL

a. United States Patent Number 5,667,775	b. Issue Date of Patent 09/16/1997	c. Expiration Date of Patent 09/16/2014
d. Name of Patent Owner Genzyme Corporation	Address (of Patent Owner) 500 Kendall Street	
	City/State Cambridge, Massachusetts	
	ZIP Code 02142	FAX Number (if available) (617) 768-9736
	Telephone Number (617) 252-7500	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		

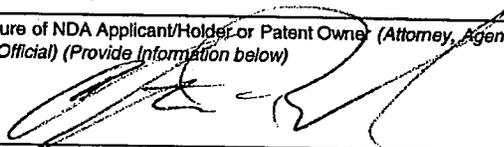
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
4. Method of Use	
<i>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
22	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Please see extended response.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

6 Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below) <div style="text-align: center; margin-top: 10px;">  </div>	Date Signed 02/01/2008
--	---------------------------

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Christopher M. Beck	
Address Genzyme Corporation 153 Second Avenue	City/State Waltham, MA
ZIP Code 02451	Telephone Number (781) 434-3471
FAX Number (if available) (781) 895-4982	E-Mail Address (if available) Christopher.Beck@genzyme.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
 CDER (HFD-007)
 5600 Fishers Lane
 Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXTENDED RESPONSE: SECTION 4.2a

US 5,667,775

Claim 22

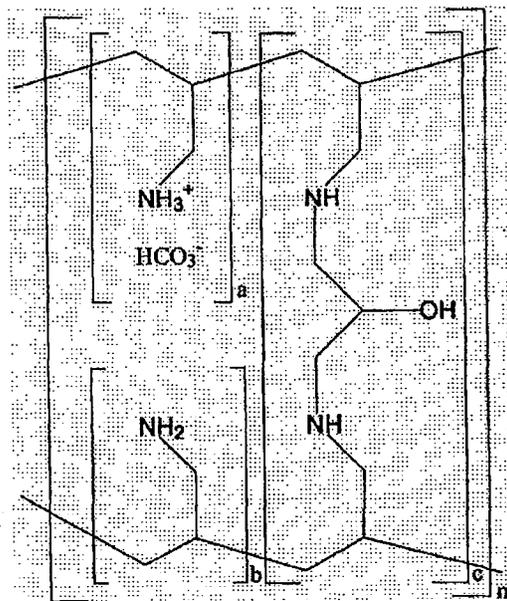
Claim 22 recites, *inter alia*, a method for removing phosphate from a patient by ion exchange, comprising orally administering to said patient a therapeutically effective amount of a composition comprising at least one hydrophilic cross-linked aliphatic amine polymer.

Section 11 of the proposed Renvela labeling states, in part, that:

Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt. Sevelamer carbonate is hygroscopic, but insoluble in water. The structure is represented

b(4)

Chemical Structure of Sevelamer Carbonate



a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
m = large number to indicate extended polymer network

As seen from the above passage, sevelamer carbonate is a hydrophilic cross-linked aliphatic amine polymer.

Finally, at Section 12.1, the proposed Renvela labeling states that

b(4)

Accordingly claim 22 of US 5,667,775 reads on the proposed Renvela labeling.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 22-318	
		NAME OF APPLICANT/NDA HOLDER Genzyme Corporation	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) RENVELA			
ACTIVE INGREDIENT(S) Sevelamer Carbonate		STRENGTH(S) 2.4 g	
DOSAGE FORM Powder, Sachet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
GENERAL			
a. United States Patent Number 5,496,545		b. Issue Date of Patent 03/05/1996	c. Expiration Date of Patent 08/11/2013
d. Name of Patent Owner Genzyme Corporation		Address (of Patent Owner) 500 Kendall Street	
		City/State Cambridge, Massachusetts	
		ZIP Code 02142	FAX Number (if available) (617) 768-9736
		Telephone Number (617) 252-7500	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) 1-13 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Please see extended response

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed
02/01/2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Christopher M. Beck	
Address Genzyme Corporation 153 Second Avenue	City/State Waltham, MA
ZIP Code 02451	Telephone Number (781) 434-3471
FAX Number (if available) (781) 895-4982	E-Mail Address (if available) Christopher.Beck@genzyme.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use; if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXTENDED RESPONSE: SECTION 4.2a

US 5,496,545

Claims 1-5

Claims 1-5 recite, *inter alia*, a method for removing phosphate from a patient by ion exchange comprising orally administering to said patient a therapeutically effective amount of a composition comprising at least one polymer characterized by a repeat unit having the formula:

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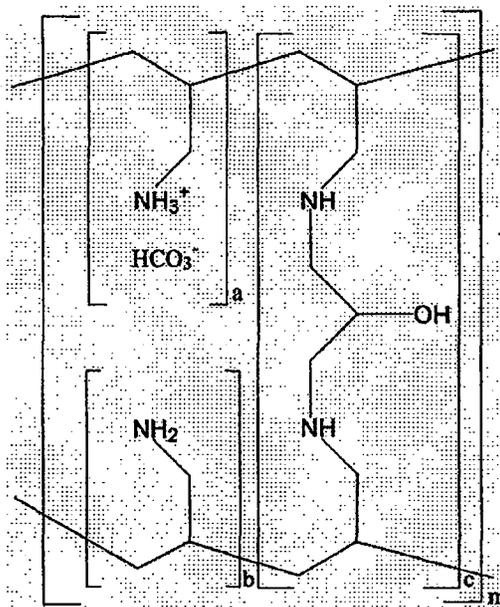
b(4)

└

or a copolymer thereof, wherein n is an integer and each R, independently, is H or a lower alkyl, alkylamino, or aryl group. Where R is hydrogen, the repeat unit defined by the above formula is that of allylamine.

Claims 2-5 are ultimately dependent upon claim 1, and further specify that the polymer or copolymer that is orally administered by the claimed method is crosslinked. For example, claim 2 requires that the crosslinker is present in an amount from 0.5% to 75% by weight of the composition and claim 3 requires that the crosslinker is present in an amount from about 2% to 20% by weight. Claim 4 and Claim 5 further define the crosslinker, which may be epichlorohydrin.

Section 11 of the proposed Renvela labeling states, in relevant part, that "Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt." This section goes on to describe the chemical structure of sevelamer carbonate as:



a, b = number of primary amine groups $a + b = 9$
 c = number of crosslinking groups $c = 1$
 m = large number to indicate extended polymer network

Finally, at Section 12.1, the proposed Renvela labeling states that _____ **b(4)**

Accordingly claims 1-5 of US 5,496,545, read on the methods described in the proposed Renvela labeling.

Claims 6-13

Claims 6-13 recite, *inter alia*, a method for removing phosphate from a patient by ion exchange comprising orally administering to said patient a therapeutically effective amount of a composition comprising at least one polymer characterized by a repeat unit having the formula:

b(4)

or a copolymer thereof, wherein n is an integer and each R, independently, is H or a lower alkyl, alkylamino, or aryl group, and each X⁻ is an exchangeable negatively charged counterion. Where R is hydrogen, the repeat unit defined by the above formula is that of a protonated allylamine, with X⁻ being an exchangeable negatively charged counterion.

Claims 7-9 are ultimately dependent upon claim 6, and further specify that the polymer or copolymer that is orally administered by the claimed method is crosslinked. For example, claim 7 requires that the crosslinker is present in an amount from 0.5% to 75% by weight of the composition, and claim 9 requires that the crosslinker is present in an amount from about 2% to 20% by weight. Claim 8 recites a group of species which may serve as the crosslinker (e.g., epichlorohydrin).

Claims 10-13 also depend upon claim 6 and further define the orally administered polymer as a copolymer further comprising a repeat unit having the formula:

b(4)

or a copolymer thereof, wherein n is an integer and each R, independently, is H or a lower alkyl, alkylamino, or aryl group. Where R is hydrogen, the repeat unit defined by the above formula is that of allylamine.

Claims 11-13 are ultimately dependent upon claim 10, and further specify that the polymer or copolymer that is orally administered by the claimed method is crosslinked. For example, claim 11 requires that the crosslinker is present in an amount from 0.5% to 75% by weight of the composition and claim 13 requires that the crosslinker is present in an amount from about 2% to 20% by weight. Claim 12 recites a group of species which may serve as the crosslinker (e.g., epichlorohydrin).

Section 11 of the proposed Renvela labeling states, in relevant part, that "Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt." This section goes on to describe the chemical structure of sevelamer carbonate as:

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.
	NDA NUMBER 22-318
	NAME OF APPLICANT/NDA HOLDER Genzyme Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME) RENVELA	
ACTIVE INGREDIENT(S) Sevelamer Carbonate	STRENGTH(S) 2.4 g

DOSAGE FORM
Powder, Sachet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

I. GENERAL

a. United States Patent Number 6,509,013	b. Issue Date of Patent 01/21/2003	c. Expiration Date of Patent 08/11/2013
d. Name of Patent Owner Genzyme Corporation	Address (of Patent Owner) 500 Kendall Street	
	City/State Cambridge, Massachusetts	
	ZIP Code 02142	FAX Number (if available) (617) 768-9736
	Telephone Number (617) 252-7500	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> No		

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

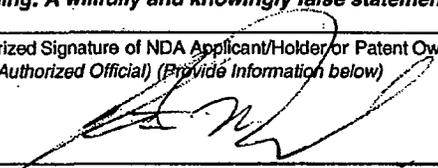
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication, or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed 02/01/2008</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Christopher M. Beck</p>	
<p>Address Genzyme Corporation 153 Second Avenue</p>	<p>City/State Waltham, MA</p>
<p>ZIP Code 02451</p>	<p>Telephone Number (781) 434-3471</p>
<p>FAX Number (if available) (781) 895-4982</p>	<p>E-Mail Address (if available) Christopher.Beck@genzyme.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

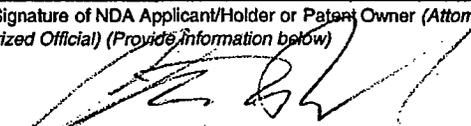
Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>			
		NDA NUMBER 22-318	
		NAME OF APPLICANT/NDA HOLDER Genzyme Corporation	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) RENVELA			
ACTIVE INGREDIENT(S) Sevelamer Carbonate		STRENGTH(S) 2.4 g	
DOSAGE FORM Powder, Sachet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
GENERAL			
a. United States Patent Number 6,858,203		b. Issue Date of Patent 02/22/2005	c. Expiration Date of Patent 08/11/2013
d. Name of Patent Owner Genzyme Corporation		Address (of Patent Owner) 500 Kendall Street	
		City/State Cambridge, Massachusetts	
		ZIP Code 02142	FAX Number (if available) (617) 768-9736
		Telephone Number (617) 252-7500	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
4. Method of Use	
<i>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1-9	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Please see attached extended response
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)</p> 	<p>Date Signed 02/01/2008</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Christopher M. Beck</p>	
<p>Address Genzyme Corporation 153 Second Avenue</p>	<p>City/State Waltham, MA</p>
<p>ZIP Code 02451</p>	<p>Telephone Number (781) 434-3471</p>
<p>FAX Number (if available) (781) 895-4982</p>	<p>E-Mail Address (if available) Christopher.Beck@genzyme.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXTENDED RESPONSE: SECTION 4.2a

US 6,858,203

Claims 1-8

Claims 1-8 recite, *inter alia*, a method for removing phosphate from a patient comprising orally administering to said patient a therapeutically effective amount of a composition comprising at least one polymer characterized by a repeat unit having the formula:

b(4)

or a copolymer thereof, wherein n is an integer and each R, independently, is H or a lower alkyl, alkylamino, or aryl group, and each X⁻ is a carbonate or bicarbonate anion.

Claims 2-4 are ultimately dependent upon claim 1, and further specify that the polymer or copolymer that is orally administered by the claimed method is crosslinked. For example, claim 2 requires that the crosslinker is present in an amount from 0.5% to 75% by weight of the composition, and claim 4 requires that the crosslinker is present in an amount from about 2% to 20% by weight. Claim 3 recites a group of species which may serve as the crosslinker (*e.g.*, epichlorohydrin).

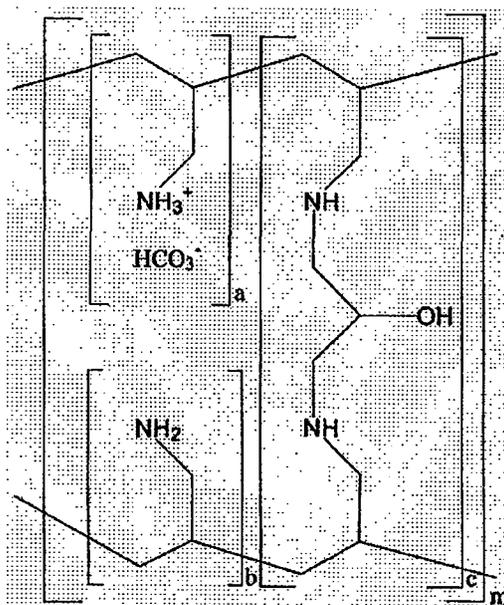
Claims 5-8 also depend upon claim 1 and further define the orally administered polymer as a copolymer further comprising a repeat unit having the formula:

b(4)

wherein n is an integer and each R, independently, is H or a lower alkyl, alkylamino, or aryl group. Where R is hydrogen, the repeat unit defined by the above formula is that of allylamine.

Claims 6-8 are ultimately dependent upon claim 5, and further specify that the polymer or copolymer that is orally administered by the claimed method is crosslinked. For example, claim 6 requires that the crosslinker is present in an amount from 0.5% to 75% by weight of the composition and claim 8 requires that the crosslinker is present in an amount from about 2% to 20% by weight. Claim 7 recites a group of species which may serve as the crosslinker (*e.g.*, epichlorohydrin).

Section 11 of the proposed Renvela labeling states, in relevant part, that "Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt." This section goes on to describe the chemical structure of sevelamer carbonate as:



a, b = number of primary amine groups a + b = 9
 c = number of crosslinking groups c = 1
 m = large number to indicate extended polymer network

Finally, at Section 12.1, the proposed Renvela labeling states that

b(4)

Accordingly claims 1-8 of US 6,858,203 read on the methods described in the proposed Renvela labeling.

Claim 9

Claim 9 recites, *inter alia*, a method for removing phosphate from a patient comprising orally administering to said patient a therapeutically effective amount of a composition comprising a copolymer characterized by a repeat unit having the formula:

┌

b(4)

└

and a second repeat unit having the formula:

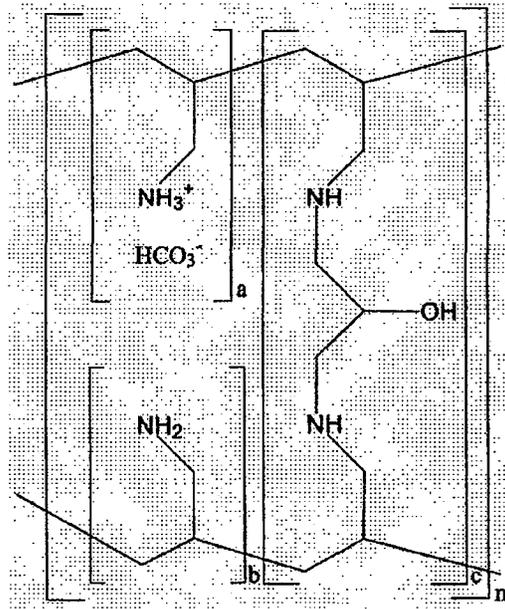
┌

b(4)

└

wherein said copolymer is crosslinked with epichlorohydrin, wherein the epichlorohydrin is present in said composition from about 2% to about 20% by weight and wherein each n is an integer, each R is H, and each X⁻ is a carbonate or bicarbonate anion.

Section 11 of the proposed Renvela labeling states, in relevant part, that "Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt." This section goes on to describe the chemical structure of sevelamer carbonate as:



a, b = number of primary amine groups a + b = 9
 c = number of crosslinking groups c = 1
 m = large number to indicate extended polymer network

Finally, at Section 12.1, the proposed Renvela labeling states that “_____”

b(4)

Accordingly claim 9 of US 6,858,203 reads on the methods described in the proposed Renvela labeling.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 22-318	
		NAME OF APPLICANT/NDA HOLDER Genzyme Corporation	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) RENVELA			
ACTIVE INGREDIENT(S) Sevelamer Carbonate		STRENGTH(S) 2.4 g	
DOSAGE FORM Powder, Sachet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
I. GENERAL			
a. United States Patent Number 7,014,846		b. Issue Date of Patent 03/21/2006	c. Expiration Date of Patent 08/11/2013
d. Name of Patent Owner Genzyme Corporation		Address (of Patent Owner) 500 Kendall Street,	
		City/State Cambridge, Massachusetts	
		ZIP Code 02142	FAX Number (if available) (617) 768-9736
		Telephone Number (617) 252-7500	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

b(4)

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) 9-12 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Please see extended response

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed 02/01/2008
---	---------------------------

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Christopher M. Beck	
Address 153 Second Avenue	City/State Waltham, MA
ZIP Code 02451	Telephone Number (781) 434-3471
FAX Number (if available) (781) 895-4982	E-Mail Address (if available) Christopher.Beck@genzyme.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXTENDED RESPONSE: SECTION 4.2a

US 7,014,846

Claims 9-12

Claim 9 recites, *inter alia*, a method of removing phosphate from a patient comprising orally administering to said patient a therapeutically effective amount of a composition comprising a crosslinked, water insoluble polyallylamine homopolymer, wherein said polyallylamine homopolymer comprises repeat units represented by the structural formula:

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b(4)

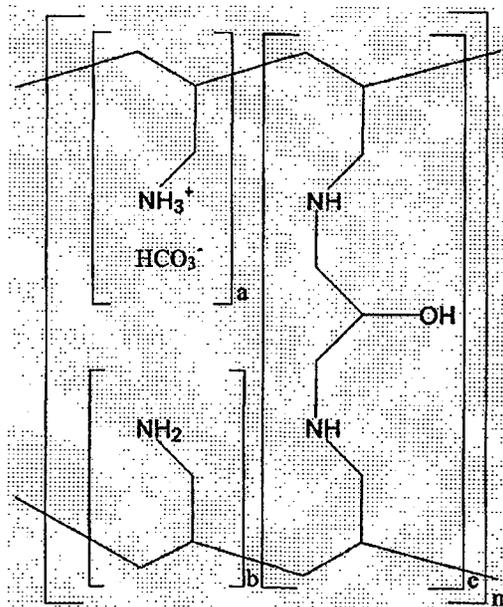
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wherein n is an integer, and wherein the homopolymer is fully protonated, partially protonated or unprotonated.

Claims 10 and 11 ultimately depend from claim 9 and further define the crosslinking of the composition recited in the claimed method. For example, claim 10 recites a polyallylamine homopolymer that is crosslinked with an epichlorohydrin crosslinking agent, and claim 11 further recites that this crosslinking agent is present in an amount from about 2% to about 20% by weight of the polymer.

Claim 12 depends from claim 9 and further defines the polyallylamine homopolymer as fully or partially protonated.

Section 11 of the proposed Renvela labeling states, in relevant part, that "Renvela (sevelamer carbonate) is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt." This section goes on to describe the chemical structure of sevelamer carbonate as:



a, b = number of primary amine groups $a + b = 9$
 c = number of crosslinking groups $c = 1$
 m = large number to indicate extended polymer network

The same section also describes sevelamer carbonate as “hygroscopic, but insoluble in water.”

Thus, sevelamer carbonate is a crosslinked, water insoluble polyallylamine homopolymer.

Finally, at Section 12.1, the proposed Renvela labeling states that “

b(4)

Accordingly claims 9-12 of US 7,014,846 read on the methods described in the proposed Renvela labeling.

EXCLUSIVITY SUMMARY

NDA # 22-318

SUPPL #

HFD # 110

Trade Name Renvela

Generic Name sevelamer carbonate

Applicant Name Genzyme Corporation

Approval Date, If Known August 12, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 022127

NDA# 021179

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

- 1) Cross-Over Study of Sevelamer Carbonate (Renvela) Powder and Sevelamer Hydrochloride (Renagel) Tablets
- 2) Once a Day Versus Three Times a Day Dosing

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- 1) Cross-Over Study of Sevelamer Carbonate (Renvela) Powder and Sevelamer Hydrochloride (Renegel) Tablets
- 2) Once a Day Versus Three Times a Day Dosing

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 71,878 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Anna Park
Title: Regulatory Project Manager
Date: August 12, 2009

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Division Director/ Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANNA J PARK
08/18/2009

NORMAN L STOCKBRIDGE
08/18/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-318 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Cardiovascular and Renal Products PDUFA Goal Date: 8/12/09 Stamp Date: 6/12/09

Proprietary Name: Renvela

Established/Generic Name: sevelamer carbonate

Dosage Form: powder

Applicant/Sponsor: Genzyme Corp

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):

(1) phosphate binder in patients with chronic kidney disease on dialysis

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: phosphate binder in patients with chronic kidney disease on dialysis

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):			
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	<hr style="width: 100px; border: 0.5px solid black;"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): <u>12/31/11</u>							

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

b(4)

+ Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	_____	_____	Yes <input type="checkbox"/>	No <input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	_____

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	_____	<input type="checkbox"/>	<input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

DDMAC
Paul
DARRTS



DEBARMENT CERTIFICATION

Certification Pursuant to 21 USC Section 306(k)(1)

Genzyme Corporation hereby certifies that it did not and will not use in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

GENZYME CORPORATION

Mary Beth Clarke
Mary Beth Clarke, Senior Director, Regulatory Affairs

2/5/08
Date



sevelamer carbonate
Module 1: Administrative and Prescribing Information
Financial Certification and Disclosure

1.3.4 Financial Certification and Disclosure

As required in 21 CFR 54.4(a)(1), attached for certain clinical investigators [as defined in 21 CFR 54.2(d)], is a completed Form FDA 3454, attesting to the absence of financial interests and arrangements described in 21 CFR 54.4(a)(3).

For the remaining clinical investigators [as defined in 21 CFR 54.2(d)], attached is a certification attesting to the sponsor's due diligence in attempting to obtain the information, and the reason why such information was not obtained.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

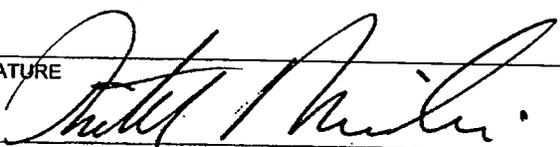
Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Refer to attached list.	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Richard Moscicki, MD	TITLE Chief Medical Officer and Senior Vice President, Biomedical and Regulatory Affairs
FIRM / ORGANIZATION	
SIGNATURE 	DATE 2/12/08

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

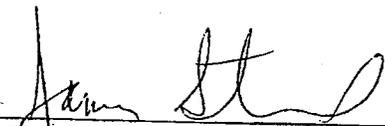


CERTIFICATION OF DUE DILIGENCE

Genzyme Corporation hereby certifies that it has acted with due diligence to obtain the financial information described in 21 CFR 54.4(a)(3), but has been unable to do so for four (4) co-investigators for Study No. SVCARB00205.

The names of the investigators and the reasons financial disclosure information was not received are included in the attached list.

GENZYME CORPORATION

By: 
James Streisand, MD
Vice President, Clinical Research

Date: 2/7/08



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Module 1: Administrative and Prescribing Information
Financial Certification and Disclosure

**Attachment to Genzyme Certification of Due Diligence
Study No. SVCARB00205**

Completed financial disclosure forms were not received from the following investigators:

Site No.	Site Name	Name	Responsibility	Reason
			Co-investigator	Initial Financial Disclosure form on file; Follow up form not received despite written and verbal requests.
			Co-investigator	Initial Financial Disclosure forms on file; Follow up forms not received despite written and verbal requests.
			Co-investigator	
			Co-investigator	

b(4)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION	
NDA # 22-318 BLA #	NDA Supplement # BLA STN #
If NDA, Efficacy Supplement Type: N/A	
Proprietary Name: Renvela Powder Established/Proper Name: Sevelamer carbonate Dosage Form: powder	Applicant: Genzyme Corporation Agent for Applicant (if applicable): N/A
RPM: Anna Park	Division: Cardiovascular and Renal Products
<p>NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)	August 12, 2009
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)	<input type="checkbox"/> None _____ <div style="text-align: right;">CR 4/17/09</div>
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	<input type="checkbox"/> Received

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	December 3, 2008
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR- 1/28/09 CR - 4/17/09
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	08/04/09
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	08/07/09
• Original applicant-proposed labeling	June 12, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Tablet label
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	August 11, 2009
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	August 11, 2009
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	March 31, 2008
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Tablet formulation
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	August 11, 2009
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP December 31, 2008; July 14, 2009 <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD
❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	N/A
Administrative / Regulatory Documents	
Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	included
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) • Incoming submissions/communications 	
❖ Postmarketing Commitment (PMC) Studies	<input type="checkbox"/> None (Pediatrics)
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

• Incoming submission documenting commitment	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	3/12/09; 4/20/09; 5/5/09
❖ Internal memoranda, telecons, etc.	1/14/09; 5/21/09
❖ Minutes of Meetings	
• PeRC (<i>indicate date; approvals only</i>)	<input type="checkbox"/> Not applicable 12/3/08
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg December 4, 2007
• EOP2 meeting (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 12, 2009
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 7, 2009
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	January 7, 2009
• Clinical review(s) (<i>indicate date for each review</i>)	December 1, 2008
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	Clinical review (page 38)
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	see Clinical review (page 8)
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) • REMS Memo (<i>indicate date</i>) • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 11, 2008
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 10, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/27/09
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 09/19/08,12/17/08; 1/27/09; 4/15/09; 8/4/09
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	N/A
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	January 27, 2009

<input checked="" type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	January 27, 2009
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	<div style="background-color: #cccccc; height: 20px;"></div>
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	Date completed: January 27, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22318	ORIG 1		RENVELA

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/s/

ANNA J PARK
08/19/2009

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§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: DMEPA,

Attention: Lori Cantin

FROM: Anna Park, Project Manager

OND/ Division of Cardiovascular and Renal Products (DCRP)

301-796-1129

DATE

June 30, 2009

IND NO.

NDA NO.

22-318

TYPE OF DOCUMENT

Electronic

DATE OF DOCUMENT

June 12, 2009

NAME OF DRUG

Sevelamer carbonate powder

PRIORITY CONSIDERATION

standard

CLASSIFICATION OF DRUG

Phosphate binder

DESIRED COMPLETION DATE

July 30, 2009

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input checked="" type="checkbox"/> FINAL PRINTED LABELING |
| <input checked="" type="checkbox"/> NEW CORRESPONDENCE | <input checked="" type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the labeling for this original NDA. The draft labeling is in the EDR at the following link: \\CDSESUB1\EVSPROD\NDA022318\0014

PDUFA Goal Date: August 12, 2009

SIGNATURE OF REQUESTER

Anna Park

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Anna Park

6/30/2009 04:30:02 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-318

Genzyme Corporation
Attention: Jamie MacPherson, Pharm.D., RAC
Manager, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

We acknowledge receipt on of your June 12, 2009 resubmission to your new drug application for Renvela (sevelamer carbonate) for oral suspension, 2.4 grams.

We consider this a complete, class 1 response to our April 17, 2009 action letter. Therefore, the user fee goal date is August 12, 2009.

If you have any questions, please contact:

Ms. Anna Park, R.Ph.
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
6/17/2009 10:49:52 AM

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§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-318
Genzyme Corporation
Attention: Jamie MacPherson, Pharm.D., RAC
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renvela (sevelamer carbonate) for Oral Suspension, 2.4 grams.

We also refer to your 4/10/09 submission which included [redacted] and the draft carton and container labeling.

b(4)

We have reviewed the referenced material with the Division of Medication Errors and Analysis (DMEPA) and have the following comments. Reference is also made to the teleconference that was held on April 23, 2009 with you and your request to place our recommendations in a letter.

The [redacted] and the sevelamer dosage is in milligram.

1. [redacted]

b(4)

2. [redacted]

b(4)

3. [redacted] we recommend conducting stability data of the 800 mg packet and considering commercializing this strength in addition to the 2.4 gram packet.

If you have any questions, please call:
Anna Park, R.Ph.
Regulatory Health Project Manager
301-796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
5/5/2009 12:31:39 PM

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): DMEPA			FROM (Name, Office/Division, and Phone Number of Requestor): Anna Park/DCRP/301-796-1129	
DATE 04/15/09	IND NO.	NDA NO. 22-318	TYPE OF DOCUMENT electronic	DATE OF DOCUMENT April 10, 2009
NAME OF DRUG Sevelamer carbonate powder	PRIORITY CONSIDERATION routine	CLASSIFICATION OF DRUG Phosphate binder	DESIRED COMPLETION DATE April 30, 2009	
NAME OF FIRM: Genzyme Corporation				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input checked="" type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input checked="" type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input checked="" type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT			
II. BIOMETRICS				
<input type="checkbox"/> PRIORITY P NDA REVIEW	<input type="checkbox"/> CHEMISTRY REVIEW			
<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> PHARMACOLOGY			
<input type="checkbox"/> CONTROLLED STUDIES	<input type="checkbox"/> BIOPHARMACEUTICS			
<input type="checkbox"/> PROTOCOL REVIEW	<input type="checkbox"/> OTHER (SPECIFY BELOW):			
<input type="checkbox"/> OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE			
<input type="checkbox"/> BIOAVAILABILITY STUDIES	<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS			
<input type="checkbox"/> PHASE 4 STUDIES	<input type="checkbox"/> IN-VIVO WAIVER REQUEST			
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY			
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE			
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)	<input type="checkbox"/> POISON RISK ANALYSIS			
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL	<input type="checkbox"/> NONCLINICAL			
COMMENTS / SPECIAL INSTRUCTIONS: Please see the attached link. \\CDSESUB1\EVSPROD\NDA022318\0011. Also, CMC has placed their review into DFS as a Memo to File.				
SIGNATURE OF REQUESTOR Anna Park			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

Anna Park

4/15/2009 06:24:18 PM

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

White Oak
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

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Meeting Confirmation

Date: May 8, 2009
Time: 09:00 AM – 10:30 AM, EST
Application: NDA 22-318
Drug: Sevelamer powder for oral suspension
Sponsor: Genzyme Corp.
Meeting Purpose: _____
Date of Request: March 18, 2009
Date of Confirmation: March 23, 2009
Meeting Type: C

b(4)

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
Gail Moreschi, M.D., MPH	Medical Officer, DCRP
Shen Xiao, M.D.	Medical Officer, DCRP
Melanie Blank, M.D.	Medical Officer, DCRP
Aliza Thompson, M.D.	Medical Officer, DCRP
Shona Pendse, M.D.	Medical Officer, DCRP
Nancy Xu, M.D.	Medical Officer, DCRP
James Hung, Ph.D.	Director, Division of Biometrics I, Office of Biostatistics
Ququan (Cherry) Liu, Ph.D.	Statistician
Angelica Dorantes, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Robert Kumi, Ph.D.	Clinical Pharmacologist
Islam Younis, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Edward Fromm, R.Ph.	Chief, Project Management Staff, DCRP
Anna Park, R.Ph.	Regulatory Project Manager

**Location: Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Conference Room 1315
Silver Spring, MD 20993-0002**

Our internal meeting is scheduled for April 14, 2009. We will send a written response to your questions approximately three days after our internal meeting. You have the option of canceling your meeting if you feel our written response adequately addresses your questions.

Please email me in Word version the list of meeting attendees and the list of specific questions from the briefing document, when available.

Archival copies of the briefing document should be officially submitted in triplicate to the Document Control Room no later than 4 weeks prior to the meeting. In addition to the triplicate copies, please send 20 Desk Copies of the briefing document to the following address:

**Food and Drug Administration
10903 New Hampshire Ave.
Attention: Anna Park
Room 4167
Silver Spring, MD 20993-0002**

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/s/

Anna Park-Hong
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-318

Genzyme Corporation
Attention: Jamie MacPherson, PharmD, RAC
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

We acknowledge receipt on February 18, 2009 of your February 18, 2009 resubmission to your new drug application for Renvela (sevelamer carbonate) for oral suspension, 2.4 grams.

We consider this a complete, class I response to our January 28, 2009 action letter. Therefore, the user fee goal date is April 18, 2009.

If you have any questions, please call:

Anna Park-Hong, R.Ph.
Regulatory Project Manager
(301) 796-1129.

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management staff
Division of Cardiovascular and Renal
Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Edward Fromm
3/12/2009 11:10:33 AM

7 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Teleconference Minutes

Date: January 9, 2009
Application: NDA 22-318
Drug: sevelamer carbonate powder
Sponsor: Genzyme Corporation
Meeting Purpose: Discuss dose titration with the powder formulation

FDA Attendees:

Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
Anna Park-Hong, R.Ph.	Regulatory Project Manager, DCRP
Lori Wachter, RN	Regulatory Project Manager, DCRP

Genzyme Corporation Attendees:

Jamie MacPherson, PharmD	Manager, Regulatory Affairs
Melanie Govignon	Associate II, Regulatory Affairs
Mary Beth Clarke	Sr. Director, Regulatory Affairs
Nicole Oliynyk	Director, Regulatory Affairs, CMC
Maria Iacovelli	Manager, Regulatory Affairs, CMC
Alicia Jeannotte	Senior Associate, Regulatory Affairs, CMC
Maureen Dillon	Senior Director, Clinical Research
Sunita Goyal, M.D.	Medical Director, Clinical Research
Nancy Mulrow, M.D.	Senior Director Pharmacovigilance and Medical Information
Melissa Plone	Manager, Medical Writing
Diane Silva	Director, Program Management

Background:

Genzyme Corporation submitted a New Drug Application for a new formulation of Renvela (sevelamer carbonate) powder to control serum phosphorous in patients with chronic kidney disease on dialysis on March 31, 2008. This powder formulation is a 2.4-gram powder packet for oral suspension. The tablet formulation of Renvela was approved on October 19, 2007 under NDA 22-127.

After further review of the NDA application, it was determined that the single dose available (2.4 grams) of the powder formulation appears too coarse to allow for usual dose titration. A teleconference was requested with Genzyme to further discuss this _____

b(4)

Meeting:

After brief introductions, Dr. Karkowsky initiated the meeting noting the Division's concern of a non-titratable dose with the 2.4-gram powder packet. The sponsor acknowledged the powder formulation was developed as an alternative dosage form for patients maintained on the 2.4-gram dose. Patients would be initiated on the tablet formulation, titrated to an effective dose then switched to the powder formulation, as an option. As plasma levels were measured instead of drug effect, Dr. Karkowsky explained equivalency was not demonstrated between the tablet and powder formulation, disallowing substitution.

Although both study designs were similar, the tablet formulation provided for dose titration unlike the powder. Alternative solutions were proposed to include:

1. Development of the 800-mg powder packet

b(4)

Moreover, because of the higher frequency of drop outs with once-daily administration of sevelamer carbonate 2.4-gram powder packets and to avoid the intake of additional packets by patients for optimal control, the Division recommends administering sevelamer carbonate in equally divided doses with meals.

Minutes preparation: *{See appended electronic signature page}*
Anna Park-Hong

Concurrence, Chair: *{See appended electronic signature page}*
Abraham Karkowsky, M.D., Ph.D.

Drafted-1/12/09; Final-1/13/09

Reviewed: A. Karkowsky- 1/13/09
N. Stockbridge-1/13/09

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/s/

Anna Park-Hong
1/13/2009 09:28:01 AM
CSO

Abraham Karkowsky
1/14/2009 12:54:52 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-318 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Renvela Powder
Established Name: Sevelamer Powder
Strengths: 2.4 gram sachet powder

Applicant: Genzyme Corporation
Agent for Applicant (if applicable):

Date of Application: March 31, 2008
Date of Receipt: March 31, 2008
Date clock started after UN: N/A
Date of Filing Meeting: May 12, 2008
Filing Date: June 6, 2008
Action Goal Date (optional):

User Fee Goal Date: January 31, 2009

Indication(s) requested: Phosphate binder in CKD on dialysis

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: new indication 10/19/2010 and new salt exclusivity 10/19/2010

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

- 3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers:
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) December 4, 2007 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 12, 2008

NDA #: 22-318

DRUG NAMES: Sevelamer carbonate 2.4 gram sachet powder

APPLICANT: Genzyme Corporation

BACKGROUND:

Genzyme is seeking marketing approval for sevelamer carbonate powder for oral suspension as a phosphate binder for use in controlling serum phosphorus in patients with chronic kidney disease (CKD) on dialysis. Sevelamer carbonate powder is being developed as an alternative formulation to sevelamer carbonate tablets. Sevelamer carbonate tablets (NDA 22-127) was approved on October 19, 2007.

ATTENDEES:

Norman Stockbridge
Ellis Unger
Abraham Karkowsky
Gail Moreschi
Charles Resnick
Donghao Lu
Joseph Xavier
Angelica Dorantes
Ququan Liu
Kasturi Srinivasachar
James Hung
Islam Younis
Divya Menon-Andersen
Russell Fortney
Anna Park-Hong

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization

Reviewer

Medical:	Gail Moreschi
Secondary Medical:	N/A
Statistical:	James Hung
Pharmacology:	Joseph Xavier
Statistical Pharmacology:	N/A
Chemistry:	Donghao Lu
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Robert Kumi
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	Anna Park-Hong
Other Consults:	DMETS, DDMAC

Per reviewers, are all parts in English or English translation?

YES NO

If no, explain:

CLINICAL

FILE

REFUSE TO FILE

- Clinical site audit(s) needed?

YES NO

If no, explain: not needed

- Advisory Committee Meeting needed?

YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY

N/A

FILE

REFUSE TO FILE

STATISTICS

N/A

FILE

REFUSE TO FILE

BIOPHARMACEUTICS

FILE

REFUSE TO FILE

- Biopharm. study site audits(s) needed?

YES NO

PHARMACOLOGY/TOX

N/A

FILE

REFUSE TO FILE

- GLP audit needed?

YES NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection?

YES NO

- Sterile product?

YES NO

If yes, was microbiology consulted for validation of sterilization?

YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Anna Park-Hong
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Anna Park-Hong
1/6/2009 10:00:47 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-318

INFORMATION REQUEST LETTER

Genzyme Corporation
Attention: Jamie MacPherson, Pharm.D., RAC
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

Please refer to your March 31, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renvela (sevelamer carbonate) Oral Suspension.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1. [redacted] is used at the unit ratio of [redacted] for the [redacted] process while [redacted] is used at the unit ratio of [redacted] for the [redacted] process as stated in this NDA. b(4)
However, it is noted that [redacted] was used at the unit ratio of [redacted] for the [redacted] process in NDA 22-127 (as stated in Amendment 006). Clarify this discrepancy. Provide data to support the proposed change for [redacted] from [redacted]. b(4)
2. You propose to [redacted] the retest period from [redacted] to [redacted] for sevelamer carbonate drug substance material manufactured by [redacted] process and [redacted] process. This is not acceptable. The stability data from the batches manufactured at Genzyme K1 facility using [redacted] process support a retest period of [redacted]. However, the stability data from the batches manufactured at the K23 facility using [redacted] process did not support a retest period of [redacted]. For example, the levels of [redacted] were out of specification at the [redacted] time point for several of the test batches manufactured at the K23 facility using the [redacted] process. b(4)
3. Provide the suppliers' COAs for propylene glycol alginate, sucralose and ferric oxide.
4. It is noted that the registration lots did not contain the 2.4 g package size. Provide CoAs for the drug product packaged in the to-be-marketed 2.4 g package size.
5. In the drug product stability studies, it was adequate that you had a bracketing approach for the drug products containing different lots of bulk drug substance manufactured by [redacted] and Genzyme K23. However, none of the drug products contained the drug substance manufactured using the [redacted] process. We recommend that the first 3 commercial production batches studied under post-approval stability protocol include the product batches manufactured using the drug substance from [redacted] process as well. b(4)
6. The product should be named as "Renvela (sevelamer carbonate) for oral suspension" (deleting "Powder", in both label and labeling text). For the sachet label, the words "For oral suspension" should be moved up just below the established name. Remove the text "[redacted]" from the "How Supplied" section of the package insert. b(4)

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

Ramesh Sood
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Don Henry
11/6/2008 08:42:54 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): Raanan (Ron) Bloom, OPS/PARS, 301-796-2185		FROM (Name, Office/Division, and Phone Number of Requestor): Donghao (Robert) Lu, Ph.D., Division of Pre-Marketing Assessment I, Off. of New Drug Quality Assessment through Scott N. Goldie		
DATE September 27, 2008	IND NO.	NDA NO. 22-318	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT March 31, 2008
NAME OF DRUG Renvela	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE December 31, 2008	
NAME OF FIRM: Novartis Pharma				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> RESUBMISSION	<input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT			
II. BIOMETRICS				
<input type="checkbox"/> PRIORITY P NDA REVIEW	<input type="checkbox"/> CHEMISTRY REVIEW			
<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> PHARMACOLOGY			
<input type="checkbox"/> CONTROLLED STUDIES	<input type="checkbox"/> BIOPHARMACEUTICS			
<input type="checkbox"/> PROTOCOL REVIEW	<input type="checkbox"/> OTHER (SPECIFY BELOW):			
<input type="checkbox"/> OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE			
<input type="checkbox"/> BIOAVAILABILITY STUDIES	<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS			
<input type="checkbox"/> PHASE 4 STUDIES	<input type="checkbox"/> IN-VIVO WAIVER REQUEST			
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY			
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE			
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)	<input type="checkbox"/> POISON RISK ANALYSIS			
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL	<input type="checkbox"/> NONCLINICAL			
COMMENTS / SPECIAL INSTRUCTIONS: Environmental Assessment Review - electronic Submission in EDR \\CDSesub1\EVSPROD\NDA022318\0000 . Genzyme Corporation Inc. provided an environmental assessment (EA) in support of NDA 22-318. This NDA was submitted to seek approval for the development of powder for oral suspension dosage form containing 2.4 g sevelamer carbonate. A related environmental assessment was previously submitted to the FDA by Genzyme Corporation Inc. for Renvela (NDA 22-127, tablet). Please review and advise.				
SIGNATURE OF REQUESTOR {see attached signature page}		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

Scott Goldie
9/27/2008 02:10:48 PM

Donghao Lu
10/10/2008 01:48:58 PM

Ramesh Sood
10/10/2008 03:28:07 PM

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/s/

Anna Park-Hong
7/3/2008 12:12:19 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-318

Genzyme Corporation
Attention: Jamie MacPherson, Pharm.D., RAC
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renvela (Sevelamer Carbonate) Powder for Suspension.

We also refer to your submission dated May 30, 2008, containing a Proposed Pediatric Study Request.

We have reviewed the referenced material and have the following comments and recommendations.

1. For the initial study, "Randomized, Double-blind, Fixed-dose, Placebo Controlled, Dose-ranging Study," we agree that your proposed study is acceptable.
2. Regarding your second study, "Single-arm, Open-Label, Dose Titration Study to Investigate the Safety and Tolerability of Sevelamer Carbonate in Pediatric Patients with Chronic Kidney Disease," we recommend the addition of a two-week randomized withdrawal period.

If you have any questions, please call Anna Park-Hong, Project Manager, at 301-796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
6/27/2008 10:51:10 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-318

Genzyme Corporation
Attention: Jamie MacPherson, PharmD, RAC
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

Please refer to your new drug application (NDA) dated March 31, 2008, received March 31, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Renvela (sevelamer carbonate) Powder for Oral Suspension.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is January 31, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients from 18 years of age.

b(4)

If you have any questions, please call Anna Park-Hong, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
6/6/2008 07:16:19 AM

REQUEST FOR CONSULTATION

TO (Office/Division): Pediatric and Maternal Health Staff

FROM (Name, Office/Division, and Phone Number of Requestor):
Anna Park-Hong/DCRP/ 301-796-1129

DATE
June 3, 2008

IND NO.

NDA NO.
NDA-22-318
NDA 22-127
NDA 21-179

TYPE OF DOCUMENT
electronic

DATE OF DOCUMENT
May 30, 2008

NAME OF DRUG
Sevelamer carbonate powder

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
Phosphate binder

DESIRED COMPLETION DATE

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Genzyme is seeking feedback from the Division on their proposed official pediatric plan to NDA 22-318. The Renvela tablet (NDA 22-127) was submitted with a deferral for pediatrics studies. NDA 22-127 was approved on October 19, 2007.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Anna Park-Hong
6/3/2008 02:53:14 PM



NDA 22-318

NDA ACKNOWLEDGMENT

Genzyme Corporation
Attention: Jamie MacPherson, Pharm.D., RAC
Manager, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Renvela® Powder for Oral Suspension (sevelamer carbonate)

Date of Application: March 31, 2008

Date of Receipt: March 31, 2008

Our Reference Number: NDA 22-318

Please note that the receipt date of the submission, March 31, 2008 has been verified through core-id from the incoming gateway submission. This letter supersedes the previous acknowledgement letter of April 8, 2008.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 31, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Ms. Anna Park-Hong, R.Ph.
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm

5/30/2008 03:25:32 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-318

NDA ACKNOWLEDGMENT

Genzyme Corporation
Attention: Jamie MacPherson, Pharm.D., RAC
Manager, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. MacPherson:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Renvela® Powder for Oral Suspension (sevelamer carbonate)

Date of Application: March 31, 2008

Date of Receipt: April 1, 2008

Our Reference Number: NDA 22-318

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 1, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review

NDA 22-318

Page 2

without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Ms. Anna Park-Hong, R.Ph.
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
4/8/2008 11:40:41 AM

Meeting Minutes

Date: December 4, 2007
Application: IND 71,878
Drug: Renvela
Sponsor: Genzyme
Meeting Purpose: Pre-NDA
Meeting Type: B

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader
Gail Moreschi, M.D., M.P.H.	Medical Officer
Robert Kumi, Ph.D.	Clinical Pharmacology
Xavier Joseph, Ph.D.	Pharmacology
Edward Fromm, R.Ph.	Chief, Project Management Staff
Russell Fortney, R.Ph.	Regulatory Project Manager
Anna Park-Hong, R.Ph.	Regulatory Project Manager

Genzyme Attendees:

Scott Chasen-Taber, Ph.D.	Senior Director, Biostatistics
Mary Beth Clarke	Senior Director, Regulatory Affairs
Maureen Dillon	Senior Director, Clinical Research
Jeff Goldberg	Director, Program Management
Jeremy Heaton, M.D.	Medical Director, Clinical Research
Jamie MacPherson	Manager, Regulatory Affairs
Nancy J. Mulrow, M.D.	Senior Director, Pharmacovigilance and Medical Information
Jim Streisand, M.D.	Vice President, Clinical Research
Pamela Williamson	Senior Vice President, Regulatory Affairs and Corporate Quality

Background:

On December 20, 2006, Genzyme submitted NDA 22-127 for sevelamer carbonate tablets and the NDA was approved on October 19, 2007. Genzyme would like to seek marketing approval for sevelamer carbonate powder for oral suspension as a phosphate binder for use in controlling serum phosphate in patients with chronic kidney disease on dialysis.

b(4)

Meeting:

1. As discussed at the May 22, 2005 pre-IND meeting (IND 71,878) the sevelamer carbonate powder NDA will be based on the results from a clinical study comparing sevelamer carbonate powder and sevelamer hydrochloride tablets dosed three times per day (SVCARB00205, submitted to IND 71,878 as serial number 0008 on June 8, 2006). The results of this study show equally effective serum phosphorus

control using sevelamer carbonate powder as compared to sevelamer hydrochloride tablets dosed three times per day. A synopsis for SVCARB00205 is included in the briefing package.
Does the Agency agree with this approach?

FDA response: No. The metric of interest is the effect of the drug on serum phosphate concentration, and not serum phosphate concentrations per se. The drug effect is the difference between phosphate levels on and off therapy. The demonstration of equivalent effects of the two treatments should be supported by the usual bioequivalence criteria. Other information, such as *in vitro* binding, might be supportive of an approval if the bioequivalence margins are not quite met.

Additional discussion during meeting: Dr. Stockbridge reiterated that the final phosphate level was not a measure of drug effect, and said that the sponsor should address this issue in their submission. He said the sponsor should also address "regression to the mean" and intra-subject variability.

2. The final package insert will contain information from the approved sevelamer carbonate tablet label resulting in a combined label for both dosage forms of sevelamer carbonate (i.e. tablet and powder). The sevelamer carbonate powder NDA will include a draft of this combined package insert, based upon the sevelamer carbonate tablet label (NDA 22-127).
Does the Agency agree with this approach?

FDA response: In principle we think your proposal is acceptable; however, this will be a review issue. If there are substantial differences in dose range or adverse events that require clarification, a single unified label may not be appropriate.

Additional discussion during meeting: Dr. Stockbridge noted that a combined label appears likely, but will be a review issue.

3. The Dosing and Administration section of the draft Package Insert will indicate that sevelamer carbonate 800 mg tablets be used as the starting dosage option and for titration. The powder dosage form will be included as an option for patients who have already reached their maintenance dose and will provide an option for patients who prefer not to swallow a large number of tablets. Therefore, the commercial size of the powder sachets will be intended for patients whose serum phosphorus levels are maintained with at least 2.4 grams three times per day (7.2 g/day).
Does the Agency agree with this approach?

FDA response: The difference in dose size may be problematic. Although the intent of providing the powder for patients who require at least 7.2 g daily is clear, there will be patients who prefer the powder over the tablets, but use only a partial or divided dose of the powder. Some patients may store reconstituted powder for later use. Thus, we expect that the NDA will address the issue of formulation stability, not only before reconstitution, but also after reconstitution.

Additional discussion during meeting: Dr. Stockbridge asked if it would be appropriate to consume a fraction of the sachet if the dose was not a multiple of 2.4 grams. The sponsor reiterated that the sachets are for patients stabilized on the 2.4-gram dose, or for patients who would prefer to combine powder and tablets as necessary for the appropriate dose. The sponsor noted that the powder/water mixture is stable for _____ after mixing. Dr. Karkowsky requested additional stability data so that it is known exactly when the drug settles out.

4. The sevelamer carbonate powder NDA was originally planned to be supported by clinical study SVCARB00205 (comparing sevelamer hydrochloride tablets dosed three times per day with meals and sevelamer carbonate powder dosed three times per day with meals) and propose three times per day

b(4)

dosing only.

b(4)

Due to a change in timing, this powder NDA will be supported by both SVCARB00205 and GD3-199-301. GD3-199-301

b(4)

Overall, AEs occurring during the study were consistent with the patients' underlying renal disease, however, a larger percentage of treatment-related upper gastrointestinal disorders were noted in patients dosed with sevelamer carbonate powder QD.

b(4)

b(4)

A synopsis for GD3-199-301 is included in the briefing package.

Does the Agency agree with this approach?

FDA response: This will be a review issue. We can provide further discussion at the meeting.

Additional discussion during meeting:

b(4)

5. In the FDA response dated March 9, 2006 to our request for a meeting to discuss pediatric studies, we were encouraged to discuss obtaining a Written Request at the time of submitting our NDA for sevelamer carbonate tablets. The NDA for sevelamer carbonate tablets contained a request for deferral of pediatric studies until the powder formulation was available. In a letter dated February 21, 2007, FDA stated that they agreed that a deferral was justified and to further discuss our plans in the powder

formulation NDA. Genzyme plans to conduct a pediatric study with sevelamer carbonate powder

b(4)

As agreed to by FDA in an e-mail correspondence dated May 18, 2007, a full pediatric plan will not be included in this NDA at the time of initial filing and will be

b(4)

FDA response:

Additional discussion during meeting: No additional discussion.

6. Genzyme will not be including an integrated summary of safety or efficacy where datasets from multiple studies are pooled then reanalyzed for sevelamer carbonate powder. As was true for not including these analyses with the sevelamer carbonate tablet NDA, it would not be appropriate to pool data from the two sevelamer carbonate powder studies given the different duration (4 versus 24 weeks) and dosing regimen (three times per day versus once per day), or to pool data from the powder studies with the previous sevelamer clinical studies.

FDA response: Your proposal is acceptable.

Additional discussion during meeting: No additional discussion.

Additional Preliminary Comments from Clinical Pharmacology and Biopharmaceutics:

To ensure comparability of the sevelamer carbonate powder to tablet you should conduct in vitro studies at different pHs and ionic strengths.

Additional discussion during meeting: No additional discussion.

Minutes preparation: *{See appended electronic signature page}*
Anna Park-Hong

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Drafted-12/11/07; Final-12/17/07

Reviewed: E.Fromm-12/11/07
X.Joseph-12/11/07
R.Kumi-12/14/07
G.Moreschi-12/13/07
A.Karkowsky-12/13/07
N.Stockbridge-12/14/07

Linked Applications

Sponsor Name

Drug Name

IND 71878

GENZYME
CORPORATION

SEVELAMER CARBONATE (GT 335 012)

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/s/

ANNA J PARK-HONG
12/17/2007

NORMAN L STOCKBRIDGE
12/17/2007

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm					
1. APPLICANT'S NAME AND ADDRESS GENZYME CORP Mary Beth Clarke 500 Kendall Street Cambridge MA 02142 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 022318			
2. TELEPHONE NUMBER 617-768-6907		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
3. PRODUCT NAME Renvela (Sevelamer Carbonate)		6. USER FEE I.D. NUMBER PD3008108			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
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2.7.3 Summary of Clinical Efficacy – Control Serum Phosphorus

The proposed indication for sevelamer carbonate powder is the same as the approved indication for sevelamer carbonate tablets [New Drug Application (NDA) 022127] and is as follows:

“Sevelamer carbonate is indicated for the control of serum phosphorus in chronic kidney disease (CKD) patients on dialysis”.

2.7.3.1 Background and Overview of Clinical Efficacy

2.7.3.1.1 Background

In CKD the system for maintaining phosphorus balance is altered by the progressive loss of functioning nephrons. In early CKD, serum phosphorus levels are maintained at near normal levels by enhanced phosphorus excretion by the residual nephrons, resulting in preservation of net phosphorus excretion. As renal failure progresses the glomerular filtration rate (GFR) decreases, resulting in the loss of preservation or balance of net phosphorus excretion and the subsequent development of hyperphosphataemia.

Hyperphosphataemia in patients with CKD can lead to secondary hyperparathyroidism and has been associated with arterial calcification and renal osteodystrophy (Delmez, 1992, *Am J Kidney Dis*; Young, 2005, *Kidney Int*; Slinin, 2005, *J Am Soc Nephrol*).

Control of serum phosphorus is critical to prevent metastatic calcification, a condition where calcium and phosphate precipitate in soft tissues. Hyperphosphataemia has also emerged as one of the more important risk factors for mortality in CKD patients (Lowrie, 1990, *Am J Kidney Dis*; Block, 1998, *Am J Kidney Dis*; Block, 2004, *J Am Soc Nephrol*; Young, 2005, *Kidney Int*; Slinin, 2005, *J Am Soc Nephrol*).

Dietary phosphorus restriction and/or dialysis are usually insufficient to adequately control serum phosphorus levels in patients with CKD. Therefore, a major component of hyperphosphataemia management is use of phosphate binders to decrease the intestinal absorption of dietary phosphorus (Hercz, 1987, *Kidney Int*; Schaefer, 1993, *J Nephrol*). The currently available phosphate binders include calcium acetate (PhosLo[®]), calcium carbonate, aluminium hydroxide, lanthanum carbonate (Fosrenol[®]), sevelamer hydrochloride (Renagel[®]) and sevelamer carbonate (Renvela[®]). Each of these phosphate



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binders is only available in a solid dosage form and the majority of patients require multiple large tablets to attain serum phosphorus control.

Difficulty swallowing tablets and capsules is common, and the availability of a non-tablet form of binder may benefit patients who require multiple tablets with each meal or those who dislike or have difficulty using solid dosage forms of medications. In a survey of 792 patients conducted by community pharmacists, approximately 60% of the patients reported experiencing difficulties swallowing solid dosage forms and 69% admitted skipping a dose of medication due to swallowing difficulties (Strachan, *Pharm Pract*, 2005). Approximately one-quarter (26%) reported problems swallowing tablets in a survey of more than 6000 patients seen by general practitioners (Anderson, *Tidsskrift Nor Laegeforen*, 1995). The size, texture and taste were the most frequent complaints described in this survey. Age-related physiological changes, including age-related declines in salivary gland function and swallowing reflexes, may contribute to swallowing difficulties. Medical conditions such as Parkinson's disease, stroke and cancer can also lead to swallowing difficulties.

A phosphate binder formulated as a powder which can be mixed with water provides an alternative dosage form that may benefit patients who require multiple tablets with each meal or those who dislike or have difficulty using solid dosage forms of medications. A powder for oral suspension also provides a more suitable formulation than tablets for a broad range of paediatric patients. Paediatric trials will be designed using the powder formulation.

2.7.3.1.2 Overview of Clinical Program to Evaluate the Efficacy of Sevelamer Carbonate

Genzyme has developed Renvela[®] (sevelamer carbonate) as both a tablet and a powder formulation. The powder formulation is for oral suspension. A NDA (NDA 022127) for sevelamer carbonate tablets was approved for marketing on October 19, 2007. Sevelamer carbonate tablets are indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. In NDA 022127, the efficacy of sevelamer carbonate tablets was demonstrated to be equivalent to the efficacy of sevelamer hydrochloride tablets in haemodialysis patients allowing the use of the sevelamer hydrochloride data to support the NDA for sevelamer carbonate tablets. Therefore, NDA 022127 included



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clinical studies conducted with sevelamer hydrochloride in addition to the study conducted with sevelamer carbonate tablets.

The current submission requests marketing approval for sevelamer carbonate powder for the control of serum phosphorus in patients with chronic kidney disease on dialysis. In support of this NDA, *in vitro* studies have been conducted and demonstrate equivalent phosphate binding with sevelamer carbonate powder, sevelamer carbonate tablets and sevelamer hydrochloride tablets.

Genzyme has also conducted a clinical study to compare sevelamer carbonate powder to sevelamer hydrochloride tablets. SVCARB00205 was a randomised, open-label, cross-over design study comparing the safety and efficacy of sevelamer carbonate powder dosed three times per day (TID) with sevelamer hydrochloride tablets dosed TID in CKD patients on haemodialysis with a serum phosphorus ≥ 1.76 mmol/L (≥ 5.5 mg/dL) following a phosphate binder washout. The study demonstrated that sevelamer carbonate powder and sevelamer hydrochloride tablets, each dosed TID with meals, were equivalent in controlling serum phosphorus levels and had similar safety profiles.

To demonstrate that the efficacy of sevelamer carbonate powder dosed TID is similar to sevelamer carbonate tablets dosed TID, this summary of clinical efficacy will include a comparative assessment of the serum phosphorus and LDL cholesterol results for sevelamer carbonate powder from SVCARB00205 with the results for sevelamer carbonate tablets from clinical study GD3-163-201. GD3-163-201 was a randomised, double-blind, cross-over design study comparing sevelamer carbonate tablets dosed TID with sevelamer hydrochloride tablets dosed TID in CKD patients on haemodialysis. This study demonstrated that sevelamer carbonate tablets and sevelamer hydrochloride tablets, each dosed TID with meals, were equivalent in controlling serum phosphorus levels. GD3-163-201 was submitted in NDA 022127 (Sequence 0000, 2006-12-20) as the pivotal sevelamer carbonate tablet study.

This summary of clinical efficacy will also include information from clinical study GD3-199-301, a study exploring once daily (QD) dosing of sevelamer carbonate powder. GD3-199-301 was a randomised, open-label, parallel-design study to evaluate the safety and efficacy of sevelamer carbonate powder dosed QD with the largest meal compared to sevelamer hydrochloride tablets dosed TID with meals in CKD patients on



Table 2.7.3-1: Sevelamer Carbonate Studies that Provide Efficacy Data

Study ID	Number of Study Centres Location(s)	Study Start Enrolment Status, Date Total Enrolment/Enrolment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/Arm Treated/Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
SVCARB00205	7 sites in the United Kingdom	Started: 31 Jan 2006 Completed: 21 Mar 2007 Screened: 75 enrolled/ 75 planned Randomised: 31 enrolled/ 24 planned	Randomised, open-label, cross-over	Sevelamer carbonate powder for oral suspension 800 mg sachets Sevelamer hydrochloride 800 mg tablets The binder dose at the end of the sevelamer hydrochloride run-in was replaced gram per gram by study drug. The dose was to be maintained throughout the treatment periods. Both to be taken orally TID with meals. Mean actual dose (Safety Set) Sevelamer carbonate: 5.9 ± 2.7 g/day Sevelamer hydrochloride: 6.5 ± 3.3 g/day	Compare the safety and efficacy of sevelamer carbonate powder with sevelamer hydrochloride tablets, each dosed TID	Treated: 31 (31 patients received sevelamer carbonate powder and 28 patients received sevelamer hydrochloride tablets) Completed both treatments: 24	15 weeks: 2-week washout period; 4-week sevelamer hydrochloride run-in period; two 4-week randomised treatment periods; 1-week follow-up period.	68%/ 32% 53 years (27-80 years)	Haemo-dialysis patients	Time weighted average of serum phosphorus

Table 2.7.3-1: Sevelamer Carbonate Studies that Provide Efficacy Data

Study ID	Number of Study Centres Location(s)	Study Start Enrolment Status, Date Total Enrolment/Enrolment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/Arm Treated/Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
GD3-163-201	13 sites in the United States	Started: 30 Mar 2005 Completed: 15 Mar 2006 Screened: 101 enrolled/120 planned Randomised: 79 enrolled/80 planned	Randomised, double-blind, cross-over	Sevelamer carbonate 800 mg tablets Sevelamer hydrochloride 800 mg tablets The total binder dose the patient entered the study on was replaced by study drug in a pill for pill exchange. The dose was to be maintained throughout the treatment periods. Both taken orally TID with meals. Mean actual dose (Safety Set) Sevelamer carbonate tablets: 5.8 ± 2.8 g/day Sevelamer hydrochloride: 5.6 ± 2.9 g/day	Compare the safety and efficacy of sevelamer carbonate tablets with sevelamer hydrochloride tablets, each dosed TID	Treated: 78 (73 patients received sevelamer carbonate tablets and 78 patients received sevelamer hydrochloride tablets) Completed both treatments: 69 Completed washout: 40	23 weeks: 5-week sevelamer hydrochloride run-in period, two 8-week randomised treatment periods, 2-week washout period	51%/49% 58 years (29-88 years)	Haemo-dialysis patients	Time weighted average of serum phosphorus

Table 2.7.3-1: Sevelamer Carbonate Studies that Provide Efficacy Data

Study ID	Number of Study Centres Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/ Arm Treated/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
GD3-199-301	29 sites in the United States	Started: 27 Jan 06 Completed: 16 Mar 07 Screened: 396 enrolled/ 280 planned Randomised: 217 (144 sevelamer carbonate powder QD; 73 sevelamer hydrochloride tablets TID) enrolled/ 207 (138 sevelamer carbonate powder QD; 69 sevelamer hydrochloride tablets TID) planned	Randomised, open-label, parallel	Sevelamer carbonate powder for oral suspension 2.4 g sachets Sevelamer hydrochloride 800 mg tablets The starting dose was 4.8 g/day of either sevelamer carbonate powder or sevelamer hydrochloride tablets. The dose was to be titrated to reach a serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.76 mmol/L). Sevelamer carbonate powder was to be taken QD with the largest meal. Sevelamer hydrochloride tablets were to be taken TID with the meals. Mean actual dose (Safety Set) Sevelamer carbonate powder dosed QD: 6.2 ± 2.6 g/day Sevelamer hydrochloride tablets dosed TID: 6.7 ± 3.0 g/day	Compare the safety and efficacy of sevelamer carbonate powder dosed QD with the largest meal to sevelamer hydrochloride tablets dosed TID with meals	Sevelamer carbonate powder QD: 141 treated/ 93 completed Sevelamer hydrochloride tablets TID: 72 treated/ 62 completed	26 weeks: 2-week washout period, 24-week randomised treatment period	61% / 39% 58 years (20-85 years)	Haemo-dialysis patients	Change in serum phosphorus



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2.7.3.2.1 Brief Narrative of the Sevelamer Carbonate Studies**2.7.3.2.1.1 SVCARB00205: A Randomised, Cross-Over Study to Demonstrate Equivalence of Sevelamer Carbonate Powder and Sevelamer Hydrochloride Tablets Dosed Three Times Per Day in Haemodialysis Patients**

The full report for this study is located in Module 5, Section 5.3.5.1.

Objectives

The primary objectives of this study were to demonstrate the equivalence of sevelamer carbonate powder to sevelamer hydrochloride tablets on the control of serum phosphorus when dosed TID and to compare the safety and tolerability of sevelamer carbonate and sevelamer hydrochloride in hyperphosphataemic CKD patients on haemodialysis. The secondary objectives of this study were to evaluate the effects of sevelamer carbonate powder and sevelamer hydrochloride tablets dosed TID on calcium-phosphorus product and serum lipids in hyperphosphataemic CKD patients on haemodialysis.

Study Design

This was a randomised, open-label, cross-over design study of sevelamer carbonate powder TID versus sevelamer hydrochloride tablets TID in hyperphosphataemic CKD patients on haemodialysis. The study began with a two-week phosphate binder washout period. Patients who were hyperphosphataemic (serum phosphorus ≥ 1.76 mmol/L or 5.5 mg/dL) following the washout period continued into a four-week sevelamer hydrochloride run-in period. Patients were then randomised to one of two treatment sequences: 1) sevelamer carbonate powder TID with meals for four weeks followed by sevelamer hydrochloride tablets TID for four weeks or 2) sevelamer hydrochloride tablets TID for four weeks followed by sevelamer carbonate powder TID with meals for four weeks. The total binder dose the patient was on at the end of the sevelamer hydrochloride run-in period was replaced by study drug in a gram per gram exchange. The dose was to be maintained at this level throughout the treatment periods. At the end of the second treatment period the patients were instructed to return to their pre-study phosphate binder. The study ended with a one-week follow-up period. The study schematic is presented in Figure 2.7.3-1.

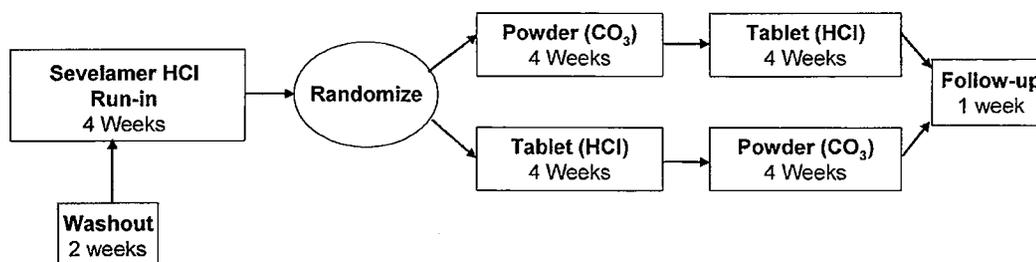


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Clinical Summary – Summary of Clinical Efficacy – Control Serum Phosphorus

Figure 2.7.3-1: SVCARB00205 Study Schematic



Statistical Methods

The effects of sevelamer carbonate powder and sevelamer hydrochloride tablets on the control of serum phosphorus were determined using equivalence testing. The log-transformed time-weighted mean of the measurements from the last 2 weeks in each treatment period were used in the analysis. The analysis of variance (ANOVA) included subject, sequence, period, and treatment. The two 1-sided hypotheses were tested at the 5% level of significance for log-transformed serum phosphorus by constructing 90% confidence intervals for the ratio of sevelamer carbonate to sevelamer hydrochloride geometric means. Sevelamer carbonate was considered to be equivalent to sevelamer hydrochloride if the 90% CI for the ratio of geometric mean serum phosphorus was within the range of 0.80 to 1.25. The equivalence analysis was based on a comparison of serum phosphorus control from the Per Protocol Set (PPS) as this is the standard population for equivalence testing. Confirmatory analyses were performed on the Full Analysis Set (FAS) population.

To assess the differences between sevelamer carbonate powder and sevelamer hydrochloride tablets, each dosed TID with meals, on serum calcium-phosphorus product, total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels, a 2x2 ANOVA model based on natural-log transformed data with a random subject effect and fixed sequence, period, and treatment effects was used. Comparisons between the treatment regimens were tested at the 5% level. In addition, the geometric least squares mean ratio and corresponding 90% confidence intervals were derived as described for the primary efficacy parameter to provide a relative sense of magnitude of any difference that



was observed. These secondary analyses were performed using the FAS, as this is generally recommended per ICH E.9., with supporting analysis using the PPS.

The study was designed to assess whether gram-per gram switching from sevelamer hydrochloride tablets to sevelamer carbonate powder could be expected to provide equivalent serum phosphorus control. The pre-treatment washout established that patients entering the study were hyperphosphataemic in the absence of effective phosphate binder treatment. In a run-in period, patients' serum phosphorus was then controlled with sevelamer hydrochloride. It follows that any loss of efficacy on sevelamer carbonate relative to sevelamer hydrochloride during the randomised treatment period would be reflected in increased serum phosphorus during sevelamer carbonate treatment.

Previous studies of sevelamer hydrochloride and sevelamer carbonate have found that on average patients return to pre-study washout serum phosphorus levels following a two week post-treatment washout period. Given this, and as defined in the study protocol, the randomised treatment drug effect was measured using the time-weighted average of serum phosphorus measurements during the third and fourth week of treatment. This approach demonstrates serum phosphorus did not increase during sevelamer carbonate treatment. As requested by FDA, a post-hoc assessment of the change in serum phosphorus from post-washout to the end of each treatment period was calculated to demonstrate a reduction in serum phosphorus levels. As a sensitivity analysis, the change from post-washout to the time-weighted serum phosphorus was also calculated to confirm that use of time-weighted average as a metric is representative of the patients' outcome in terms of phosphorus.

Results and Discussion

A total of 31 patients were randomised: 17 patients were randomised to the carbonate/hydrochloride sequence and 14 patients were randomised to the hydrochloride/carbonate sequence. A total of 24 patients completed both randomised treatment periods.

The Safety Set comprised the 31 patients (31 patients received sevelamer carbonate powder treatment and 28 patients received sevelamer hydrochloride tablet treatment). The FAS consisted of 30 patients (30 patients received sevelamer carbonate powder



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treatment and 28 patients received sevelamer hydrochloride tablet treatment) and the PPS consisted of 21 patients (all 21 patients received both treatment regimens).

In the PPS, the mean serum phosphorus was 1.61 ± 0.49 mmol/L (5.0 ± 1.5 mg/dL) during sevelamer carbonate powder treatment and 1.67 ± 0.35 mmol/L (5.2 ± 1.1 mg/dL) during sevelamer hydrochloride tablet treatment. For assessing phosphorus equivalence, the treatment response across sequences was pooled since the 2x2 ANOVA model sequence p-value was not significant ($p=0.93$). The geometric least square mean ratio (sevelamer carbonate powder/sevelamer hydrochloride tablets) was 0.95 with a corresponding 90% confidence interval of 0.87-1.03. The confidence interval is within the interval of 0.80-1.25, indicating that sevelamer carbonate powder and sevelamer hydrochloride tablets are equivalent in controlling serum phosphorus. The results of a confirmatory analysis conducted with the FAS corroborated the PPS analysis.

Table 2.7.3-2 presents the results of the equivalence tests for both the PPS and FAS.

Table 2.7.3-2:
Serum Phosphorus Equivalence Tests in SVCARB00205 (PPS and FAS)

Analysis Set	Sevelamer Carbonate Powder TID [mean \pm SD]	Sevelamer Hydrochloride Tablets TID [mean \pm SD]	Geometric LS Mean Ratio	90% CI of Ratio
mmol/L				
Per Protocol Set	N=21 1.61 ± 0.49	N=21 1.67 ± 0.35	0.95	0.87-1.03
Full Analysis Set	N=25 1.62 ± 0.47	N=28 1.66 ± 0.35	0.96	0.88-1.05
mg/dL				
Per Protocol Set	N=21 5.0 ± 1.5	N= 21 5.2 ± 1.1	0.95	0.87-1.03
Full Analysis Set	N=25 5.0 ± 1.5	N= 28 5.1 ± 1.1	0.96	0.88-1.05

Source: SVCARB00205 CSR Table 14.2.1.1.1, Table 14.2.1.2.1, Table 14.2.1.1.2 and Table 14.2.1.2.2.



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A post-hoc assessment of the change in serum phosphorus from post-washout to the end of each treatment period was performed to demonstrate a reduction in serum phosphorus levels (see Section 2.7.3.6). In the PPS, the mean change from post-washout baseline to the end of each treatment period was -0.84 ± 0.91 mmol/L (-2.61 ± 2.82 mg/dL) during sevelamer carbonate powder treatment and -0.74 ± 0.64 mmol/L (-2.30 ± 1.97 mg/dL) during sevelamer hydrochloride tablet treatment. The difference in least square mean change from baseline was -0.11 mmol/L (-0.35 mg/dL) and the 90% confidence interval was -0.33 to 0.10 mmol/L (-1.03 to 0.32 mg/dL). This indicates that phosphorus levels at the end of each treatment period tended to be slightly more reduced from post-washout levels during sevelamer carbonate powder treatment compared to the sevelamer hydrochloride tablet treatment. Similar results were seen with the FAS.

As a sensitivity analysis to the analysis performed above, the change in serum phosphorus from post-washout baseline to the time-weighted average values was also calculated (see Section 2.7.3.6). The results for the time-weighted average values are similar to that seen using the last phosphorus assessment values. In the PPS, the mean change from post-washout baseline was -0.78 ± 0.82 mmol/L (-2.41 ± 2.54 mg/dL) in the sevelamer carbonate powder group and -0.71 ± 0.65 mmol/L (-2.21 ± 2.00 mg/dL) in the sevelamer hydrochloride tablet group. The least square mean difference was -0.06 mmol/L (-0.18 mg/dL) and the 90% confidence interval was -0.20 to 0.08 mmol/L (-0.63 to 0.26 mg/dL). Consistent with that seen for the last phosphorus assessment analysis, the reduction from post-washout for the time-weighted average values in each period tended to be slightly greater during sevelamer carbonate powder treatment. Similar results were seen with the FAS.

The dose prescribed to each patient is a marker for the patient's degree of hyperphosphataemia. A post-hoc analysis of the time-weighted average serum phosphorus levels was performed by dose group and is presented in Table 2.7.3-3. The phosphorus levels for both sevelamer carbonate and sevelamer hydrochloride are similar regardless of dose prescribed indicating that sevelamer carbonate powder and sevelamer hydrochloride tablets provide similar serum phosphorus control regardless of the degree of hyperphosphataemia and dose administered.



**Table 2.7.3-3:
Serum Phosphorus by Dose Group in SVCARB00205 (FAS)**

Prescribed Daily Dose (grams)	Sevelamer Carbonate Powder TID	Sevelamer Hydrochloride Tablets TID
mmol/L		
≤ 4.8		
N	7	8
Median	1.19	1.68
> 4.8 to < 9.6		
N	6	6
Median	1.84	1.78
≥ 9.6		
N	12	14
Median	1.61	1.65
mg/dL		
≤ 4.8		
N	7	8
Median	3.7	5.2
> 4.8 to < 9.6		
N	6	6
Median	5.7	5.5
≥ 9.6		
N	12	14
Median	5.0	5.1

Note: No inferential statistics were calculated due to the small sample size.

Table 2.7.3-4 presents the calcium-phosphorus product and lipid results for the FAS. No statistically significant or clinically meaningful differences were observed between sevelamer carbonate powder and sevelamer hydrochloride tablets dosed TID with regards to calcium-phosphorus product or lipid levels at the end of each treatment period. The results for the PPS are similar.



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**Table 2.7.3-4:
Serum Calcium-Phosphorus Product and Lipids at End of Treatment in
SVCARB00205 (FAS)**

Laboratory Parameter	Sevelamer Carbonate Powder TID	Sevelamer Hydrochloride Tablets TID	P-value
SI Units			
Calcium-Phosphorus Product (mmol ² /L ²)			0.749
N	25	28	
Mean ± SD	3.69 ± 1.11	3.69 ± 0.81	
Median	3.8	3.8	
Total Cholesterol (mmol/L)			0.218
N	22	27	
Mean ± SD	3.50 ± 0.70	3.34 ± 0.82	
Median	3.4	3.3	
LDL Cholesterol (mmol/L)			0.109
N	22	27	
Mean ± SD	1.82 ± 0.48	1.75 ± 0.66	
Median	1.7	1.7	
HDL Cholesterol (mmol/L)			0.537
N	22	27	
Mean ± SD	1.15 ± 0.46	1.13 ± 0.36	
Median	1.1	1.1	
Triglycerides (mmol/L)			0.992
N	22	27	
Mean ± SD	2.18 ± 1.58	2.13 ± 1.49	
Median	1.6	1.6	
US Units			
Calcium-Phosphorus Product (mg ² /dL ²)			0.747
N	25	28	
Mean ± SD	45.9 ± 13.8	45.8 ± 10.0	
Median	46.6	46.9	
Total Cholesterol (mg/dL)			0.229
N	22	27	
Mean ± SD	135.4 ± 26.9	129.1 ± 31.6	
Median	132	127	



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**Table 2.7.3-4:
Serum Calcium-Phosphorus Product and Lipids at End of Treatment in
SVCARB00205 (FAS)**

Laboratory Parameter	Sevelamer Carbonate Powder TID	Sevelamer Hydrochloride Tablets TID	P-value
LDL Cholesterol (mg/dL)			0.094
N	22	27	
Mean ± SD	70.4 ± 18.3	67.7 ± 25.4	
Median	67	65	
HDL Cholesterol (mg/dL)			0.584
N	22	27	
Mean ± SD	44.5 ± 17.7	43.7 ± 13.9	
Median	43	42	
Triglycerides (mg/dL)			0.997
N	22	27	
Mean ± SD	192.7 ± 139.6	188.9 ± 131.9	
Median	144	142	

Source: SVCARB00205 CSR Table 14.2.2.2.1, Table 14.2.2.2.2, Table 14.2.3.2.1, Table 14.2.3.2.2, Table 14.2.4.2.1, Table 14.2.4.2.2, Table 14.2.5.2.1, Table 14.2.5.2.2, Table 14.2.6.2.1, and Table 14.2.6.2.2

P-value determined using 2x2 ANOVA model

Evaluations of various safety assessments monitored during this study suggest that sevelamer carbonate powder was safe and well tolerated. Refer to Summary of Clinical Safety (Section 2.7.4).

Conclusion

The results of this study show that sevelamer carbonate powder TID and sevelamer hydrochloride tablets TID are equivalent in controlling serum phosphorus in patients with CKD on haemodialysis. There were no significant differences between the treatment groups in serum calcium-phosphorus product or lipid profiles.



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Clinical Summary – Summary of Clinical Efficacy – Control Serum Phosphorus

2.7.3.2.1.2 GD3-163-201: A Double-Blind, Cross-Over Design Study of Sevelamer Hydrochloride (Renagel[®]) and Sevelamer Carbonate in Chronic Kidney Disease Patients on Hemodialysis

The full report for this study is located in Module 5, Section 5.3.5.1.

Objectives

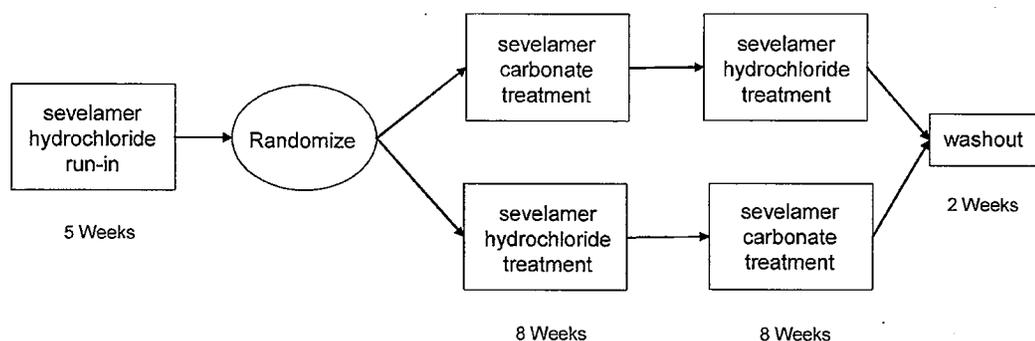
The primary objectives of this study were to compare the effects of sevelamer carbonate tablets and sevelamer hydrochloride tablets, each dosed TID, on the control of serum phosphorus in CKD patients on haemodialysis and to compare the safety and tolerability of sevelamer carbonate and sevelamer hydrochloride in CKD patients on haemodialysis. The secondary objective of this study was to compare the effects of sevelamer carbonate and sevelamer hydrochloride on serum lipid profiles in CKD patients on haemodialysis.

Study Design

This was a randomised, double-blind, cross-over study of sevelamer carbonate tablets versus sevelamer hydrochloride tablets in CKD patients on haemodialysis. Patients completed a five-week sevelamer hydrochloride run-in period. Patients were then randomised to one of two treatment sequences: 1) sevelamer carbonate tablets dosed TID for eight weeks followed by sevelamer hydrochloride tablets dosed TID for eight weeks or 2) sevelamer hydrochloride tablets dosed TID for eight weeks followed by sevelamer carbonate tablets dosed TID for eight weeks. The study ended with a two-week post-treatment phosphate binder washout period. The study schematic is presented in Figure 2.7.3-2.



Figure 2.7.3-2: GD3-163-201 Study Schematic



Statistical Methods

The effects of sevelamer carbonate tablets and sevelamer hydrochloride tablets on the control of serum phosphorus were determined using equivalence testing. The log-transformed time-weighted mean of the measurements from the last 2 weeks in each treatment period were used in the analysis. The ANOVA included subject, sequence, period, and treatment. The two 1-sided hypotheses were tested at the 5% level of significance for log-transformed serum phosphorus by constructing 90% confidence intervals for the ratio of sevelamer carbonate to sevelamer hydrochloride geometric means. Sevelamer carbonate was considered to be equivalent to sevelamer hydrochloride if the 90% CI for log-transformed serum phosphorus was within the range of 0.80 to 1.25. The equivalence analysis was based on a comparison of serum phosphorus control from the PPS as this is the standard population for equivalence testing. Confirmatory analyses were performed on the FAS population.

To assess the differences between sevelamer carbonate and sevelamer hydrochloride dosing on total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels, a 2x2 ANOVA model based on natural-log transformed data with a random subject effect and fixed sequence, period, and treatment effects was used. The mean of the measurements from two assessments in each treatment period were used. Comparisons between the treatment regimens were tested at the 5% level. Serum lipids were analysed using the FAS as the primary population.



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Results and Discussion

A total of 79 patients were randomised, 40 were randomised to the carbonate/hydrochloride sequence and 39 were randomised to the hydrochloride/carbonate sequence. A total of 69 patients completed both randomised treatment periods. 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 opted to participate in the washout period. A total of 47 patients entered the washout period and 40 patients completed the washout period.

The Safety Set and FAS consisted of 78 patients (73 patients received sevelamer carbonate tablet treatment and 78 patients received sevelamer hydrochloride tablet treatment) and the PPS consisted of 56 patients (all 56 patients received both treatment regimens).

The mean serum phosphorus was 1.49 ± 0.3 mmol/L (4.6 ± 0.9 mg/dL) during sevelamer carbonate treatment and 1.52 ± 0.3 mmol/L (4.7 ± 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 FAS are similar.

Post-hoc analyses were performed to understand the results across dose level as a marker for degree of underlying hyperphosphataemia. 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 Table 2.7.3-5. 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.



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**Table 2.7.3-5:
Serum Phosphorus by Dose Group in GD3-163-201**

Prescribed Daily Dose (grams)	N	Geometric LS Mean Ratio	90% Confidence Interval of Ratio
≤ 4.8	22	0.97	0.91-1.04 ¹
> 4.8 to < 9.6	14	0.95	0.85-1.05 ¹
≥ 9.6	20	1.04	0.98-1.10 ¹

Data source: GD3-163-201 CSR Post-hoc Table 3

¹ 90% CI for the ratio is within the interval (0.8, 1.25).

A two-week phosphate binder washout period was included following the active treatment period to confirm that the patients enrolled in this trial were hyperphosphataemic. At the end of the treatment period the serum phosphorus was 1.61 ± 0.42 mmol/L (5.0 ± 1.3 mg/dL) in all patients completing in the washout (N=40). Following the two-week washout period, the serum phosphorus level increased significantly [0.48 ± 0.61 mmol/L (1.5 ± 1.9 mg/dL) to 2.10 ± 0.61 mmol/L (6.5 ± 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 (N=21), serum phosphorus increased 0.42 ± 0.71 mmol/L (1.3 ± 2.2 mg/dL) [from 1.71 ± 0.45 mmol/L (5.3 ± 1.4 mg/dL) to 2.13 ± 0.65 mmol/L (6.6 ± 2.0 mg/dL), $p = 0.022$] and in patients treated with sevelamer hydrochloride immediately preceding the washout (N=19), serum phosphorus increased 0.55 ± 0.48 mmol/L (1.7 ± 1.5 mg/dL) [from 1.49 ± 0.39 (4.6 ± 1.2 mg/dL) to 2.03 ± 0.58 mmol/L (6.3 ± 1.8 mg/dL), $p < 0.001$].

The mean total cholesterol was 3.72 ± 0.88 mmol/L (144.0 ± 33.9 mg/dL) during sevelamer carbonate treatment and 3.59 ± 0.87 mmol/L (139.0 ± 33.6 mg/dL) during sevelamer hydrochloride treatment. These values were statistically different ($p = 0.009$), but the difference is not clinically meaningful. As a post-hoc test to understand the magnitude of this difference, the geometric least square mean ratio (sevelamer carbonate/sevelamer hydrochloride) and corresponding 90% confidence interval were calculated (ratio=1.04; CI: 1.01-1.06) and observed to be well within the traditional equivalence boundary, 0.80-1.25. The results of an analysis conducted with the PPS are similar.



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The mean LDL cholesterol was 1.54 ± 0.64 mmol/L (59.5 ± 24.9 mg/dL) during sevelamer carbonate treatment and 1.45 ± 0.60 mmol/L (56.0 ± 23.3 mg/dL) during sevelamer hydrochloride treatment. These values were statistically different ($p=0.035$), but the difference is not clinically meaningful. As a post-hoc test to understand the magnitude of this difference, the geometric least square mean ratio (sevelamer carbonate/sevelamer hydrochloride) and corresponding 90% confidence interval were calculated (ratio=1.07; CI: 1.01-1.12) and observed to be well within the traditional equivalence boundary, 0.80-1.25. In the PPS, the mean LDL cholesterol was 1.49 ± 0.62 mmol/L (57.5 ± 24.1 mg/dL) during sevelamer carbonate treatment and 1.41 ± 0.55 mmol/L (54.4 ± 21.4 mg/dL) during sevelamer hydrochloride treatment. These values were not statistically different. The geometric least square mean ratio (sevelamer carbonate/sevelamer hydrochloride) and corresponding 90% confidence interval were calculated (ratio=1.04; CI: 0.99-1.10) and observed to be well within the traditional equivalence boundary, 0.80-1.25.

The mean HDL cholesterol was 1.29 ± 0.46 mmol/L (50.0 ± 17.7 mg/dL) during sevelamer carbonate treatment and 1.27 ± 0.39 mmol/L (49.2 ± 15.2 mg/dL) during sevelamer hydrochloride treatment. These values were not statistically different. The results of an analysis conducted with the PPS are similar.

The mean triglycerides were 1.99 ± 1.24 mmol/L (176.0 ± 109.5 mg/dL) during sevelamer carbonate treatment and 1.91 ± 1.17 mmol/L (169.1 ± 104.1 mg/dL) during sevelamer hydrochloride treatment. These values were not statistically different. The results of an analysis conducted with the PPS are similar.

Evaluations of various safety assessments monitored during this study suggest that sevelamer carbonate and sevelamer hydrochloride were safe and well tolerated. Refer to the Summary of Clinical Safety (Section 2.7.4).

Conclusion

In patients with CKD on haemodialysis, the results of this study show that sevelamer carbonate tablets and sevelamer hydrochloride tablets are equivalent in controlling serum phosphorus. There were no clinically significant differences between treatment regimens in lipid profiles.



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Clinical Summary – Summary of Clinical Efficacy – Control Serum Phosphorus

2.7.3.2.1.3 GD3-199-301: A Randomized, Parallel, Open-Label Study to Compare Once Per Day Sevelamer Carbonate Dosing with Three Times Per Day Sevelamer Hydrochloride Tablet Dosing in Chronic Kidney Disease Patients on Hemodialysis

The full report for this study is located in Module 5, Section 5.3.5.1.

Objectives

The primary objectives of this study were to evaluate the efficacy of sevelamer carbonate powder dosed QD with the largest meal compared to sevelamer hydrochloride tablets dosed TID with meals on the control of serum phosphorus and to compare the safety and tolerability of sevelamer carbonate powder and sevelamer hydrochloride tablets in hyperphosphataemic CKD patients on haemodialysis. The secondary objectives of this study were to evaluate the effects of sevelamer carbonate powder dosed QD and sevelamer hydrochloride tablets dosed TID on calcium-phosphorus product and serum lipids in hyperphosphataemic CKD patients on haemodialysis.

Study Design

This was a randomised, open-label, parallel design study in CKD patients on haemodialysis to evaluate the safety and efficacy of sevelamer carbonate powder, dosed QD with the largest meal, compared to sevelamer hydrochloride tablets, dosed TID with meals. Patients completed a two-week phosphate binder washout period. Hyperphosphatemic (serum phosphorus ≥ 1.76 mmol/L or 5.5 mg/dL) patients were then randomised to one of two treatment groups in a 2:1 fashion: 1) sevelamer carbonate powder dosed QD with the largest meal or 2) sevelamer hydrochloride tablets dosed TID with meals for the 24-week treatment period. The starting dose was 4.8 g/day of either sevelamer carbonate powder or sevelamer hydrochloride tablets. The dose was to be titrated as needed to reach a target serum phosphorus level of ≥ 1.13 and ≤ 1.78 mmol/L (≥ 3.5 and ≤ 5.5 mg/dL). The study schematic is presented in Figure 2.7.3-3.

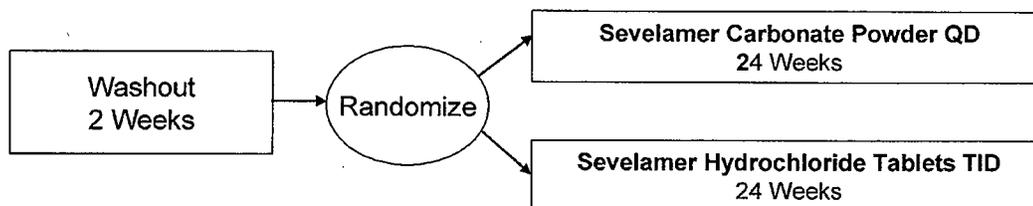


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Clinical Summary – Summary of Clinical Efficacy – Control Serum Phosphorus

Figure 2.7.3-3: GD3-199-301 Study Schematic



Statistical Methods

The primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 24/ET. Specifically, a two-sided 95% confidence interval was estimated for the difference in mean serum phosphorus change between treatment groups (diff = sevelamer carbonate powder QD – sevelamer hydrochloride tablets TID). If the upper confidence bound (one sided 97.5% upper confidence bound) was less than 0.32 mmol/L (1 mg/dL), then non-inferiority was to be concluded. Serum phosphorus was analysed using the PPS as the primary analysis population as this is appropriate for non-inferiority testing.

Results and Discussion

A total of 217 patients were randomised: 144 patients were randomised to the sevelamer carbonate powder QD group and 73 patients were randomised to the sevelamer hydrochloride TID tablet group. One hundred and fifty five patients completed the study: 93 (64.6%) sevelamer carbonate powder QD patients and 62 (84.9%) sevelamer hydrochloride tablet TID patients.

The Safety Set and FAS included 213 patients [141 sevelamer carbonate powder QD, 72 sevelamer hydrochloride tablets TID] and the PPS included 148 patients [97 sevelamer carbonate powder QD, 51 sevelamer hydrochloride tablets TID].

Table 2.7.3-6 presents the change from baseline to Week 24/ET for serum phosphorus for both the PPS and the FAS.



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**Table 2.7.3-6:
Change in Serum Phosphorus in GD3-199-301 (PPS and FAS)**

	Sevelamer Carbonate Powder QD [mean ± SD]	Sevelamer Hydrochloride Tablets TID [mean ± SD]	2-sided 95% CI†
Serum Phosphorus (mmol/L)			
Per Protocol Set	N=97	N=51	
Pre-washout	1.68 ± 0.37	1.72 ± 0.32	
Baseline	2.36 ± 0.43	2.45 ± 0.41	
Week 24/ET	1.71 ± 0.45	1.50 ± 0.32	
Change	-0.66 ± 0.57	-0.96 ± 0.42	0.12, 0.48
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	1.70 ± 0.36	1.72 ± 0.31	
Baseline	2.34 ± 0.44	2.39 ± 0.41	
Week 24/ET	1.73 ± 0.46	1.58 ± 0.38	
Change	-0.61 ± 0.54	-0.82 ± 0.50	0.06, 0.36
P-value [^]	< 0.001	< 0.001	
Serum Phosphorus (mg/dL)			
Per Protocol Set	N=97	N=51	
Pre-washout	5.2 ± 1.1	5.3 ± 1.0	
Baseline	7.3 ± 1.3	7.6 ± 1.3	
Week 24/ET	5.3 ± 1.4	4.6 ± 1.0	
Change	-2.0 ± 1.8	-2.9 ± 1.3	0.39, 1.50
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	5.3 ± 1.1	5.3 ± 1.0	
Baseline	7.3 ± 1.4	7.4 ± 1.3	
Week 24/ET	5.4 ± 1.4	4.9 ± 1.2	
Change	-1.9 ± 1.7	-2.5 ± 1.6	0.19, 1.12
P-value [^]	< 0.001	< 0.001	

Data source: GD3-199-301 CSR Table 14.2.1.1; Table 14.2.1.2; Table 14.2.1.3; and Table 14.2.1.4

[^]P-value is from Wilcoxon Signed Rank Test

† 95% CI on difference = sevelamer carbonate powder QD – sevelamer hydrochloride tablet TID. If upper confidence bound is < 1 then non-inferiority was to be concluded.

Note: The number of observations varies in the statistics shown. Please refer to the tables in the GD3-199-301 CSR for details.



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In the PPS, the mean serum phosphorus pre-washout was 1.68 ± 0.37 mmol/L (5.2 ± 1.1 mg/dL) for the sevelamer carbonate powder QD group and 1.72 ± 0.32 mmol/L (5.3 ± 1.0 mg/dL) for the sevelamer hydrochloride tablet TID group. Following the two week phosphate binder washout, the mean serum phosphorus was 2.36 ± 0.43 mmol/L (7.3 ± 1.3 mg/dL) for the sevelamer carbonate powder QD group and 2.45 ± 0.41 mmol/L (7.6 ± 1.3 mg/dL) for the sevelamer hydrochloride tablet TID group confirming that this population was hyperphosphatemic. At Week 24/ET, the mean serum phosphorus was 1.71 ± 0.45 mmol/L (5.3 ± 1.4 mg/dL) for the sevelamer carbonate powder QD group and 1.50 ± 0.32 mmol/L (4.6 ± 1.0 mg/dL) for the sevelamer hydrochloride tablet TID group, which represented statistically significant changes (both $p < 0.001$) from baseline of -0.66 ± 0.57 mmol/L (-2.0 ± 1.8 mg/dL) and -0.96 ± 0.42 mmol/L (-2.9 ± 1.3 mg/dL) for both groups, respectively. The upper confidence bound was 0.48 mmol/L (1.50 mg/dL); therefore non-inferiority of sevelamer carbonate powder QD compared to sevelamer hydrochloride tablets TID based on a pre-specified non-inferiority margin of 0.32 mmol/L (1 mg/dL) was not demonstrated. The FAS results were comparable, thus confirming these findings.

The percentage of patients responding to therapy [serum phosphorus between 1.13 and 1.78 mmol/L (3.5 and 5.5 mg/dL), inclusive] was summarised by treatment group. The response rate was 56% in the sevelamer carbonate QD group and 73% in the sevelamer hydrochloride TID group.

Results for calcium-phosphorus product and lipids were similar to those presented for serum phosphorus. These endpoints are not presented since this study will not be used to support the posology in the package insert. Please refer to the clinical study report in Module 5 for a full discussion of these results.

Evaluations of various safety assessments monitored during this study suggest that overall adverse events occurring during the study were consistent with the patients' underlying renal disease; however, a larger percentage of treatment-related upper gastrointestinal disorders were noted in patients dosed with sevelamer carbonate powder QD. Refer to the Summary of Clinical Safety (Section 2.7.4).



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Conclusion

Sevelamer carbonate powder for oral suspension when dosed once per day with the largest meal is not non-inferior compared to sevelamer hydrochloride tablets when dosed three times per day with meals based on the primary efficacy analysis of a change in serum phosphorus levels from baseline to Week 24/ET among the PPS.

2.7.3.3 Comparison and Analyses of Results Across Studies

In the sections that follow, we will compare the sevelamer carbonate experience in SVCARB00205 and GD3-163-201. Since the dosing regimen in GD3-199-301 (QD) was different than the dosing regimen (TID) employed in the studies, SVCARB00205 and GD3-163-201, that will be used to support the posology in the package insert, GD3-199-301 is not included in the comparative assessment.

2.7.3.3.1 Study Populations

In SVCARB00205 (summarised in Section 2.7.3.2.1.1), a cross-over study of sevelamer carbonate powder and sevelamer hydrochloride tablets, each dosed TID, 31 haemodialysis patients received sevelamer carbonate powder TID with meals.

In GD3-163-201 (summarised in Section 2.7.3.2.1.2), a cross-over study of sevelamer carbonate tablets and sevelamer hydrochloride tablets, each dosed TID, 73 haemodialysis patients received sevelamer carbonate tablets TID with meals.

2.7.3.3.1.1 Demographic and Baseline Characteristics

The demographics and renal history of the patients in SVCARB00205 and GD3-163-201 are summarised in Table 2.7.3-7. SVCARB00205 and GD3-163-201 are cross-over studies so the demographics and renal history information apply to both treatment regimens.

The distribution of age and gender were similar in both studies. The distribution of race groups varied according to the geographical region in which the study was performed. In SVCARB00205 which was conducted in the United Kingdom, the most common race group was Caucasian; whereas in GD3-163-201 which was conducted in the United States, a higher proportion of African-American patients was studied. The most common primary causes of chronic renal failure were “other,” glomerulonephritis and diabetes in



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SVCARB00205. Of the 15 patients with “other” cited as the primary cause in SVCARB00205, the aetiology of CKD was recorded as unknown in 5 patients, IgA nephropathy in 2 patients, and interstitial nephritis, congenital, renovascular disease, reflux nephropathy, road traffic accident, hereditary nephritis, Goodpasture syndrome and Alport’s syndrome in 1 patient each. Diabetes, hypertension and “other” were the most common primary causes of chronic renal failure in GD3-163-201. As sevelamer alone or in combination was required per protocol in SVCARB00205 and GD3-163-201, the most frequently prescribed pre-study phosphate binders were sevelamer or sevelamer in combination with calcium. Approximately 80% of patients in both studies were using oral active vitamin D, IV active vitamin D or a combination of oral and IV active vitamin D at screening. The duration on dialysis was longer in SVCARB00205 than in GD3-163-201. In general, the patients are reflective of the CKD on dialysis patient population.



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Table 2.7.3-7: Summary of Demographic Characteristics and Renal History in GD3-163-201 and SVCARB00205 (Safety Set)

Characteristic	SVCARB00205 Sevelamer Carbonate Powder TID (N=31)	GD3-163-201 Sevelamer Carbonate Tablets TID (N=78) [†]
Age (years) [Mean ±SD]	52.9 ± 13.2	58.1 ±12.3
Gender [n (%)]		
Male	21 (68)	40 (51)
Female	10 (32)	38 (49)
Race [n (%)]		
Caucasian	22 (71)	21 (27)
Black or African-American	3 (10)	52 (67)
Asian	6 (19)	0 (0)
Other	0 (0)	5 (6)
Primary Cause of ESRD [n (%)]		
Hypertension	1 (3)	18 (23)
Glomerulonephritis	8 (26)	7 (9)
Diabetes	4 (13)	33 (42)
Pyelonephritis	1 (3)	0 (0)
Polycystic Kidneys	2 (7)	2 (3)
Other	15 (48)	18 (23)
Pre-Study Phosphate Binder Use [n (%)]		
Sevelamer Hydrochloride	18 (58)	72 (92)
Sevelamer Hydrochloride and Calcium	11 (36)	6 (8)
Other	2 (7)	0 (0)
Using Vitamin D* [n (%)]	25 (81)	67 (86)
Duration of Dialysis (years)		
Median	4.4	2.4
Range	0.2-30.3	0.3-23.4

[†] In GD3-163-201, demographics were summarized for all patients who received either study drug (sevelamer carbonate or sevelamer hydrochloride). Five of the patients who received sevelamer hydrochloride discontinued prior to receiving sevelamer carbonate.

* Oral vitamin D, IV vitamin D or a combination of oral and IV vitamin D

Data Source: SVCARB00205 CSR Table 14.1.3.3 and Table 14.1.4.3; GD3-163-201 CSR Table 14.1.3.3 and Table 14.1.4.3



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2.7.3.3.2 Comparison of Efficacy Results of All Studies

The primary efficacy analysis in both SVCARB00205 and GD3-163-201 was based on a comparison of the effect of sevelamer carbonate and sevelamer hydrochloride on the control of serum phosphorus using equivalence testing. In this section, serum phosphorus results in SVCARB00205 and GD3-163-201 will be compared.

Previous studies have demonstrated that sevelamer (both hydrochloride and carbonate) has an effect on LDL cholesterol (NDA 022127). A secondary efficacy parameter in SVCARB00205 and GD3-163-201 was serum LDL cholesterol. A discussion of the results for serum LDL cholesterol in SVCARB00205 and GD3-163-201 is also presented. This discussion will parallel the analysis presented for serum phosphorus.

2.7.3.3.2.1 Primary Efficacy Parameter-Serum Phosphorus

Table 2.7.3-8 presents the results of the equivalence tests for both SVCARB00205 and GD3-163-201. The table indicates the time weighted average of serum phosphorus measurements for the last two weeks of each treatment arm and the resulting statistical analysis.



**Table 2.7.3-8:
Serum Phosphorus Equivalence Tests in SVCARB00205 and GD3-163-201 (PPS)**

Study	Sevelamer Carbonate [mean ± SD]	Sevelamer Hydrochloride [mean ± SD]	Geometric LS Mean Ratio	90% CI of Ratio
Serum phosphorus (mmol/L)				
SVCARB00205	N=21 1.6 ± 0.5	N=21 1.7 ± 0.4	0.95	0.87-1.03
GD3-163-201	N= 56 1.5 ± 0.3	N=56 1.5 ± 0.3	0.99	0.95-1.03
Serum phosphorus (mg/dL)				
SVCARB00205	N=21 5.0 ± 1.5	N=21 5.2 ± 1.1	0.95	0.87-1.03
GD3-163-201	N=56 4.6 ± 0.9	N=56 4.7 ± 0.9	0.99	0.95-1.03

Note: SVCARB00205 studied sevelamer carbonate powder while GD3-163-201 study sevelamer carbonate tablets; both studies used sevelamer hydrochloride tablets as the referent.

Data source: SVCARB00205 CSR Table 14.2.1.1.1 and Table 14.2.1.1.2; GD3-163-201 CSR Table 14.2.1.1

Note: GD3-163-201 CSR Table 14.2.1.1 presents mg/dL only. To convert to mmol/L multiply by 0.3229. SD = Standard deviation

In both SVCARB00205 and GD3-163-201, the confidence interval was within the interval of 0.80-1.25, indicating that sevelamer carbonate as either the powder or tablet formulation and sevelamer hydrochloride tablets are equivalent in controlling serum phosphorus.

K/DOQI clinical practice guideline for bone metabolism and disease in chronic kidney disease recommend that in CKD patients on haemodialysis serum phosphorus should be maintained between 1.13 to 1.78 mmol/L (3.5-5.5 mg/dL) (National Kidney Foundation, 2003, *Am J Kidney Dis*, Vol. 42). In both SVCARB00205 and GD3-163-201 serum phosphorus was maintained within the recommended levels.



2.7.3.3.2.2 Secondary Efficacy Parameter-LDL Cholesterol

SVCARB00205 and GD3-163-201 were cross-over studies with no washout periods and a sevelamer hydrochloride run-in period. The objective was to assess whether LDL levels were maintained at similar levels after sevelamer carbonate versus sevelamer hydrochloride treatment. Table 2.7.3-9 presents the LDL cholesterol results in SVCARB00205 and GD3-163-201. No clinically meaningful differences were observed between sevelamer carbonate and sevelamer hydrochloride dosed TID with regards to LDL cholesterol levels.

**Table 2.7.3-9:
LDL Cholesterol at End of Treatment in SVCARB00205 and GD3-163-201 (FAS)**

Laboratory Parameter	Sevelamer Carbonate Powder mean ± SD	Sevelamer Hydrochloride Tablets mean ± SD	P-value
mmol/L			
SVCARB00205	N=22 1.8 ± 0.5	N=27 1.8 ± 0.7	0.109
GD3-163-201	N=72 1.5 ± 0.6	N=76 1.4 ± 0.6	0.035
mg/dL			
SVCARB00205	N=22 70.4 ± 18.3	N=27 67.7 ± 25.4	0.094
GD3-163-201	N=72 59.5 ± 24.9	N=76 56.0 ± 23.3	0.035

Note: SVCARB00205 studied sevelamer carbonate powder while GD3-163-201 study sevelamer carbonate tablets; both studies used sevelamer hydrochloride tablets as the referent.

Data source: SVCARB00205 CSR Table 14.2.4.2.1 and Table 14.2.4.2.2; GD3-163-201 CSR

Table 14.2.3.2

Note: GD3-163-201 CSR Table 14.2.3.2 presents mg/dL only. To convert to mmol/L multiply by 0.02586.

SD = Standard deviation

P-values determined using 2x2 ANOVA model.

The National Kidney Foundation (NKF) Task Force on Cardiovascular Disease concluded that the incidence of acute cardiovascular disease is higher in patients with CKD compared to the general population and recommended that patients with CKD should be considered to be in the highest risk category, i.e., a coronary heart disease risk equivalent, for risk factor management of lipid abnormalities (National Kidney



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Foundation, 2003, *Am J Kidney Dis*, Vol. 41). Thus, KDOQI guidelines (which are aligned with National Cholesterol Educational Program guidelines) recommend LDL < 1.81 mmol/L (< 70 mg/dL) in this patient population (National Kidney Foundation, 2005, *Am J Kidney Dis*). In both SVCARB00205 and GD3-163-201, the LDL cholesterol levels following sevelamer carbonate treatment were on average at or below 1.81 mmol/L (70 mg/dL).

2.7.3.3.3 Comparison of Results in Sub-populations

A study evaluating sevelamer hydrochloride in peritoneal dialysis patients was described in NDA 022127. In this study, the effect of sevelamer hydrochloride on serum phosphorus and LDL cholesterol was found to be similar in CKD patients receiving peritoneal dialysis as compared to CKD patients on haemodialysis. Refer to NDA 022127, Sequence 000, 2006-12-20, summary-clinical-efficacy-control-serum-phosphorus.pdf, Section 2.7.3.3.3, page 96 for the discussion of the results in peritoneal dialysis patients. A study of sevelamer carbonate powder in peritoneal dialysis patients has not been performed. However, since sevelamer is the active moiety in both sevelamer hydrochloride and sevelamer carbonate and equivalent phosphorus control has been shown with both treatments in SVCARB00205 and GD3-163-201, similar efficacy in peritoneal dialysis patients is expected with sevelamer carbonate. The approved indication for sevelamer carbonate tablets is for the control of serum phosphorus in patients with CKD on dialysis. The same indication is being proposed for sevelamer carbonate powder.

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

In SVCARB00205, each patient's phosphate binder was replaced with an equivalent dose of sevelamer hydrochloride for a 4-week Run-In Period. Following the Run-In Period, patients were randomised to one of two treatment sequences: 1) sevelamer carbonate powder dosed TID with meals for four weeks followed by sevelamer hydrochloride tablets dosed TID with meals for four weeks or 2) sevelamer hydrochloride tablets dosed TID with meals for four weeks followed by sevelamer carbonate powder dosed TID with meals for four weeks. Throughout the randomised treatment period, patients were to remain on the same dose of sevelamer carbonate powder and sevelamer hydrochloride



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tablets as the last sevelamer hydrochloride tablet dose prescribed during the Run-In Period.

In the PPS, the mean prescribed daily dose during the randomised treatment periods was 7.4 ± 3.1 g/day sevelamer carbonate powder and 7.5 ± 3.1 g/day sevelamer hydrochloride tablets. The mean actual daily dose was 6.0 ± 3.1 g/day of sevelamer carbonate powder and 6.4 ± 3.3 g/day of sevelamer hydrochloride tablets. The maximum average actual daily dose of sevelamer carbonate was 12.3 g/day. Compliance was similar with both sevelamer carbonate powder (86%) and sevelamer hydrochloride tablets (84%).

Efficacy analyses found that serum phosphorus control with sevelamer carbonate powder and sevelamer hydrochloride tablets dosed TID were equivalent. Therefore, the dosing recommendations proposed for sevelamer carbonate powder are consistent with the package labelling for sevelamer carbonate tablets and sevelamer hydrochloride tablets.

As previously discussed with the Agency, Genzyme plans to provide a combined label for both dosage forms (tablets and powder) of sevelamer carbonate.

The Dosing and Administration section of the draft Package Insert will indicate that sevelamer carbonate 800 mg tablets be used as the starting dosage form and for titration. The powder dosage form will be included as an option for patients who have already reached their maintenance dose of at least 2.4 grams three times per day (7.2 g/day).

The suggested package labelling for sevelamer carbonate states:

General Dosing Information

f
L

7
J

b(4)



Sevelamer Carbonate Powder Preparation Instructions

b(4)

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

Long term studies up to 52 weeks evaluating sevelamer hydrochloride were described in NDA 022127. In these studies, control of serum phosphorus was maintained with long-term treatment. Refer to NDA 022127, Sequence 000, 2006-12-20, summary-clinical-efficacy-control-serum-phosphorus.pdf, Section 2.7.3.5, page 100 for the discussion of persistence of efficacy and/or tolerance effects.

Long-term studies with sevelamer carbonate powder dosed TID have not been performed. However, since sevelamer is the active moiety in both sevelamer hydrochloride and sevelamer carbonate and equivalent phosphorus control has been shown with both powder and tablets in SVCARB00205 and GD3-163-201, respectively, either can be administered for prolonged period without loss of its effectiveness in reducing serum phosphorus concentrations.

2.7.3.6 Appendix

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Post-hoc Table 1.1
Serum Phosphorus (mg/dL) Change from Post-Washout Baseline
Per-protocol Set

Statistics	Sequence 1 (N=19)				Sequence 2 (N=8)			
	Overall (N=21)	Sevelamer Hydrochloride Tablets (N=13)	Sevelamer Carbonate Powder (N=13)	Sevelamer Hydrochloride Tablets (N=13)	Sevelamer Carbonate Powder (N=8)	Sevelamer Hydrochloride Tablets (N=8)	Sevelamer Carbonate Powder (N=8)	Sevelamer Hydrochloride Tablets (N=8)
Time-weighted average [1]								
n	21	21	13	13	8	8	8	8
Mean	-2.41	-2.21	-2.41	-2.16	-2.40	-2.29	-2.40	-2.29
Std	2.54	2.00	2.47	1.80	2.82	2.42	2.82	2.42
Median	-2.6	-2.2	-3.1	-2.5	-1.8	-2.1	-1.8	-2.1
Min-Max								
LS Mean [3]	-2.41	-2.22						
LS Mean Difference (C-H) [3]	-0.18							
90% CI of Difference (C-H) [3]	-0.63, 0.26							
Last phosphorus assessment [2]								
n	21	21	13	13	8	8	8	8
Mean	-2.61	-2.30	-2.68	-2.47	-2.51	-2.01	-2.51	-2.01
Std	2.82	1.97	2.86	1.64	2.94	2.52	2.94	2.52
Median	-3.1	-2.4	-3.4	-3.0	-2.9	-1.4	-2.9	-1.4
Min-Max								
LS Mean [3]	-2.59	-2.24						
LS Mean Difference (C-H) [3]	-0.35							
90% CI of Difference (C-H) [3]	-1.03, 0.32							

b(4)

b(4)

Data Version: 07JAN2008
Data sets used: PERPAT1, BYPER1, LABS1, LABS1;
PT-1PHOS.SAS Execution: 10JAN2008 14:53

[1] The time-weighted mean value (of the non-missing assessments from the last two weeks in each treatment period).
[2] The last non-missing assessment from the last two weeks in each treatment period.
[3] The ANOVA model includes factors of a random subject effect and fixed sequence, period, and treatment effects.

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Post-hoc Table 1.2
Serum Phosphorus (mg/dL) Change from Post-Washout Baseline
Full Analysis Set

Statistics	Sequence 1 (N=16)				Sequence 2 (N=14)			
	Sevelamer Carbonate Powder (N=30)	Sevelamer Hydrochloride Tablets (N=28)	Sevelamer Carbonate Powder (N=16)	Sevelamer Hydrochloride Tablets (N=14)	Sevelamer Carbonate Powder (N=14)	Sevelamer Hydrochloride Tablets (N=14)	Sevelamer Carbonate Powder (N=14)	Sevelamer Hydrochloride Tablets (N=14)
Time-weighted average [1]								
n	25	28	14	14	11	11	14	14
Mean	-2.33	-2.20	-2.28	-2.21	-2.40	-2.40	-2.20	-2.20
Std	2.63	2.00	2.42	1.74	2.99	2.99	2.29	2.29
Median	-2.4	-2.1	-2.9	-2.6	-1.6	-1.6	2.2	2.2
Min-Max								
LS Mean [3]	-2.32	-2.20						
LS Mean Difference (C-H) [3]		-0.11						
90% CI of Difference (C-H) [3]		-0.55, 0.32						
Last phosphorus assessment [2]								
n	25	28	14	14	11	11	14	14
Mean	-2.51	-2.17	-2.57	-2.99	-2.44	-2.44	-1.96	-1.96
Std	2.80	2.10	2.78	1.60	2.95	2.95	2.55	2.55
Median	-3.0	-1.9	-3.3	-3.0	-2.1	-2.1	-1.7	-1.7
Min-Max								
LS Mean [3]	-2.45	-2.17						
LS Mean Difference (C-H) [3]		-0.28						
90% CI of Difference (C-H) [3]		-0.82, 0.27						

Data Version: 07JAN2008
 Data sets used: PERPAT1, BYPER1, LABS1;
 [1] The time-weighted mean value (of the non-missing assessments from the last two weeks in each treatment period).
 [2] The last non-missing assessment from the last two weeks in each treatment period.
 [3] The ANOVA model includes factors of a random subject effect and fixed sequence, period, and treatment effects.



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2.7.4 Summary of Clinical Safety

In chronic kidney disease (CKD) the system for maintaining phosphorus balance is altered by the progressive loss of functioning nephrons. In early CKD, serum phosphorus levels are maintained at near normal levels by enhanced phosphorus excretion by the residual nephrons, resulting in preservation of net phosphorus excretion. As renal failure progresses the glomerular filtration rate (GFR) decreases, resulting in the loss of preservation or balance of net phosphorus excretion and the subsequent development of hyperphosphataemia. Hyperphosphataemia in patients with CKD can lead to secondary hyperparathyroidism and has been associated with arterial calcification and renal osteodystrophy (Delmez, 1992, *Am J Kidney Dis*; Young, 2005, *Kidney Int*; Slinin, 2005, *J Am Soc Nephrol*). Control of serum phosphorus is critical to prevent metastatic calcification, a condition where calcium and phosphate precipitate in soft tissues. Hyperphosphataemia has also emerged as one of the more important risk factors for mortality in CKD patients (Lowrie, 1990, *Am J Kidney Dis*; Block, 1998, *Am J Kidney Dis*; Block, 2004, *J Am Soc Nephrol*; Young, 2005, *Kidney Int*; Slinin, 2005, *J Am Soc Nephrol*).

Dietary phosphorus restriction and/or dialysis are usually insufficient to adequately control serum phosphorus levels in patients with CKD. Therefore, a major component of hyperphosphataemia management is use of phosphate binders to decrease the intestinal absorption of dietary phosphorus (Hercz, 1987, *Kidney Int*; Schaefer, 1993, *J Nephrol*). The currently available phosphate binders include calcium acetate (PhosLo[®]), calcium carbonate, aluminium hydroxide, lanthanum carbonate (Fosrenol[®]), sevelamer hydrochloride (Renagel[®]) and sevelamer carbonate (Renvela[®]). Each of these phosphate binders is only available in a solid dosage form and the majority of patients require ingestion of multiple tablets to attain serum phosphorus control.

Difficulty swallowing tablets and capsules is common, and the availability of a non-tablet form of binder may benefit patients who require multiple tablets with each meal or those who dislike or have difficulty using solid dosage forms of medications. In a survey of 792 patients conducted by community pharmacists, approximately 60% of the patients reported experiencing difficulties swallowing solid dosage forms and 69% admitted skipping a dose of medication due to swallowing difficulties (Strachan, *Pharm Pract*, 2005). Approximately one-quarter (26%) reported problems swallowing tablets in a



survey of more than 6000 patients seen by general practitioners (Anderson, *Tidsskrift Nor Laegeforen*, 1995). The size, texture and taste were the most frequent complaints described in this survey. Age-related physiological changes, including age-related declines in salivary gland function and swallowing reflexes, may contribute to swallowing difficulties. Medical conditions such as Parkinson's disease, stroke and cancer can also lead to swallowing difficulties. A phosphate binder formulated as a powder which can be mixed with water provides an alternative dosage form to CKD patients that may benefit patients who require multiple tablets with each meal or those who dislike or have difficulty using solid dosage forms of medications.

Genzyme has developed Renvela[®] (sevelamer carbonate) as both a tablet and a powder formulation. The powder formulation is for oral suspension. A New Drug Application (NDA 022127) for sevelamer carbonate tablets was approved for marketing on October 19, 2007. Sevelamer carbonate tablets are indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. NDA 022127 presented data from clinical study GD3-163-201 to demonstrate that the safety and efficacy of sevelamer carbonate tablets was similar to the safety and efficacy of sevelamer hydrochloride tablets in haemodialysis patients. In addition, NDA 022127 also included clinical studies conducted with sevelamer hydrochloride which showed that the benefits and risks of sevelamer carbonate were similar to sevelamer hydrochloride and allowed cross-reference to the sevelamer hydrochloride data.

The current submission requests marketing approval for sevelamer carbonate powder for the control of serum phosphorus in patients with chronic kidney disease on dialysis. In support of this NDA, *in vitro* studies have been conducted and demonstrate equivalent phosphate binding with sevelamer carbonate powder, sevelamer carbonate tablets and sevelamer hydrochloride tablets (Refer to Section 2.7.1).

Genzyme has also conducted a clinical study to compare sevelamer carbonate powder to sevelamer hydrochloride tablets. SVCARB00205, was a randomised, open-label, cross-over design study comparing the safety and efficacy of sevelamer carbonate powder dosed three times per day (TID) with sevelamer hydrochloride tablets dosed TID in CKD patients on haemodialysis. In this study, patients completed a two-week phosphate binder washout period. Hyperphosphatemic [serum phosphorus ≥ 1.76 mmol/L (≥ 5.5 mg/dL)] patients following the washout period continued into a four-week



sevelamer hydrochloride tablet run-in period. Patients were then randomised in a 1:1 fashion to one of two treatment sequences: 1) sevelamer carbonate powder dosed TID for four weeks followed by sevelamer hydrochloride tablets dosed TID for four weeks; or 2) sevelamer hydrochloride tablets dosed TID for four weeks followed by sevelamer carbonate powder dosed TID for four weeks. The study ended with a one-week follow-up period. A study narrative describing SVCARB00205 is provided in Section 2.7.3.2.1.1 and a complete description of the study results is provided in the final SVCARB00205 report located in Module 5.

In SVCARB00205, a total of 31 patients were randomised and received at least one dose of sevelamer carbonate powder. A similar proportion of patients experienced adverse events (AE) while on sevelamer carbonate powder (32.3%) and while on sevelamer hydrochloride tablets (42.9%). In general, adverse events were reported across system organ classes (SOCs) and during both treatment regimens the majority of AEs occurred as single events in single patients. The frequency of treatment related AEs was low. A total of 4 events in 3 (9.7%) patients were considered by the investigator to be treatment related. All treatment related AEs were reported with sevelamer carbonate powder and included 2 events of nausea, 1 event of constipation, and 1 event of vomiting. One severe AE (chest pain) was reported during sevelamer carbonate powder treatment and no severe AEs were reported during sevelamer hydrochloride tablet treatment. No patients died during the period from Screening through the end of the 1-week Follow-up Period. During the 30-day post-completion period, one patient experienced an SAE of brain stem haemorrhage with an outcome of death. The death was considered secondary to pre-existing co-morbid conditions and assessed as not related to sevelamer carbonate powder by the investigator. The frequency of serious adverse events (SAEs) was low in each treatment regimen. No SAEs were considered by the investigator to be related to study treatment. Three patients discontinued during sevelamer carbonate powder treatment and no patients discontinued during sevelamer hydrochloride tablet treatment. Three of the four events leading to discontinuation were non-serious AEs and coded to the MedDRA SOC Gastrointestinal Disorders. A small, but statistically significant, increase in serum bicarbonate and decrease in serum chloride levels were observed during treatment with sevelamer carbonate powder. These changes were not observed during treatment with sevelamer hydrochloride tablets.



To demonstrate that the safety profile of sevelamer carbonate powder dosed TID is similar to sevelamer carbonate tablets dosed TID, this summary of clinical safety will include a comparative assessment with the adverse events, clinical laboratory evaluations and vital signs for patients who received sevelamer carbonate tablets in GD3-163-201. GD3-163-201 was a randomised, double-blind, cross-over design study comparing sevelamer carbonate tablets dosed TID with sevelamer hydrochloride tablets dosed TID in CKD patients on haemodialysis. Patients completed a five-week sevelamer hydrochloride tablet run-in period. Patients were then randomised to one of two treatment sequences: 1) sevelamer carbonate tablets dosed TID for eight weeks followed by sevelamer hydrochloride tablets dosed TID for eight weeks or 2) sevelamer hydrochloride tablets dosed TID for eight weeks followed by sevelamer carbonate tablets dosed TID for eight weeks. The study ended with a two-week phosphate binder washout period. GD3-163-201 was submitted in NDA 022127 (Sequence 0000, 2006-12-20) as the pivotal sevelamer carbonate tablet study. A study narrative describing GD3-163-201 is provided in Section 2.7.3.2.1.2 and a complete description of the study results is provided in the GD3-163-201 clinical study report located in Module 5 of the above referenced NDA.

Overall, adverse events experienced in both studies were consistent with previous experience with sevelamer. In the comparative assessment, common adverse events in SVCARB00205 and GD3-163-201 included nausea and vomiting. In both SVCARB00205 and GD3-163-201, fluctuations in laboratory parameters were representative of co-morbidities in patients with CKD. Small, but statistically significant increases in serum bicarbonate and decreases in serum chloride levels were observed during treatment with sevelamer carbonate in both SVCARB00205 and GD3-163-201.

This summary of clinical safety will also include information from GD3-199-301, a study exploring once daily (QD) dosing of sevelamer carbonate powder. GD3-199-301 is included in the clinical summary of safety as it provides safety data on 141 patients treated for 24 weeks, but it should be viewed as supportive safety information only as the dosing regimen in this study (QD) was different than the dosing regimen (TID) employed in the studies that will be used to support the posology in the package insert. GD3-199-301 was a randomised, open-label, parallel-design study in CKD patients on haemodialysis to evaluate the safety and efficacy of sevelamer carbonate powder dosed



QD with the largest meal compared to sevelamer hydrochloride tablets dosed TID with meals. In this study, patients completed a two-week phosphate binder washout period. Hyperphosphatemic patients [serum phosphorus > 1.76 mmol/L (>5.5 mg/dL)] were then randomised to one of two treatment groups in a 2:1 fashion: 1) sevelamer carbonate powder dosed QD with the largest meal or 2) sevelamer hydrochloride tablets dosed TID with meals for the 24-week treatment period. A study narrative describing GD3-199-301 is provided in Section 2.7.3.2.1.3 and a complete description of the study results is provided in the final GD3-199-301 report located in Module 5.

In GD3-199-301, a total of 141 patients received sevelamer carbonate powder QD and 72 patients received sevelamer hydrochloride tablets TID for up to 24 weeks. A similar proportion of sevelamer carbonate powder QD patients (87.9%) and sevelamer hydrochloride tablet TID patients (91.7%) experienced adverse events. In both treatment groups, the highest frequency of treatment emergent AEs were coded to the MedDRA SOC Gastrointestinal Disorders and included nausea, diarrhoea, vomiting, constipation, and upper abdominal pain. The highest frequency of treatment related AEs in both groups were coded to the MedDRA SOC Gastrointestinal Disorders and included nausea, diarrhoea, vomiting, and constipation. Treatment related nausea and vomiting were more common during sevelamer carbonate powder QD treatment than during sevelamer hydrochloride tablet TID treatment. In general, SAEs coded to similar SOCs during sevelamer carbonate powder QD and sevelamer hydrochloride tablets TID treatment; the majority were assessed by the investigator as not related to study treatment. A higher percentage of sevelamer carbonate powder QD patients discontinued due to an AE (12.0% of patients on sevelamer carbonate powder QD; 5.6% patients on sevelamer hydrochloride tablets TID). In the sevelamer carbonate powder QD group, the majority of AEs leading to discontinuation were treatment related upper gastrointestinal disorders. The nature of the reasons for discontinuation suggest that the palatability of the powder formulation being dosed QD may have contributed to lower tolerability of sevelamer carbonate powder QD compared with TID dosing with sevelamer hydrochloride tablets.

In addition, the safety of sevelamer carbonate seen in studies SVCARB00205, GD3-163-201 and GD3-199-301 will be compared to the safety data from sevelamer hydrochloride post-marketing experience, which includes cumulative post-marketing safety data from initial approval on 30 October 1998 through 30 October 2007.



Safety Conclusions

Overall, sevelamer carbonate powder dosed TID was well tolerated in CKD patients on haemodialysis. In addition, a comparative assessment of safety data for sevelamer carbonate powder dosed TID and sevelamer carbonate tablets dosed TID showed the following:

- Adverse events were distributed across similar SOCs for both sevelamer carbonate powder and sevelamer carbonate tablets, and the majority were mild or moderate in intensity.
- The most common treatment emergent adverse events observed for sevelamer carbonate powder and sevelamer carbonate tablets were gastrointestinal events, specifically nausea and vomiting.
- For both sevelamer carbonate powder and sevelamer carbonate tablets, deaths were rare and were generally consistent with the patients' underlying disease.
- All SAEs observed during sevelamer carbonate treatment (powder and tablet) were assessed by the investigator as not related or unlikely related to study treatment.
- Fluctuations in laboratory parameters were representative of co-morbidities in patients with CKD. There were no clinically significant changes in safety laboratory parameters during sevelamer carbonate treatment, but statistically significant increases in serum bicarbonate and decreases in serum chloride levels were observed.
- Overall, adverse events seen during treatment with sevelamer carbonate powder and tablets were similar in nature to adverse events spontaneously received by Genzyme during sevelamer hydrochloride post-marketing surveillance.

In summary, the safety profile seen with sevelamer carbonate powder is similar to the established safety profile of sevelamer carbonate tablets and sevelamer hydrochloride, as represented in the sevelamer carbonate and sevelamer hydrochloride tablet studies, the sevelamer hydrochloride post-marketing safety profile, and the current sevelamer carbonate and sevelamer hydrochloride labels.



2.7.4.1 Exposure to the Drug

2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

Safety data from the following protocols are presented:

- SVCARB00205, titled *A Randomised, Cross-Over Study to Demonstrate Equivalence of Sevelamer Carbonate Powder and Sevelamer Hydrochloride Tablets Dosed Three Times Per Day in Haemodialysis Patients*
- GD3-163-201, titled *A Double-Blind, Cross-Over Design Study of Sevelamer Hydrochloride (Renagel®) and Sevelamer Carbonate in Chronic Kidney Disease Patients on Hemodialysis*
- GD3-199-301, titled *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 Chronic Kidney Disease Patients on Hemodialysis*

The safety information is presented as defined by the ICH guidance document M4E: The CTD-Efficacy.

A tabular listing of the sevelamer carbonate studies discussed in this section is provided in Table 2.7.4-1.



Table 2.7.4-1: Sevelamer Carbonate Studies that Provide Safety Data

Study ID	Number of Study Centres Location(s)	Study Start Enrolment Status, Date Total Enrolment/Enrolment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/ Arm Treated/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
SVCARB00205	7 sites in the United Kingdom	Started: 31 Jan 2006 Completed: 21 Mar 2007 Screened: 75 enrolled/ 75 planned Randomised: 31 enrolled/ 24 planned	Randomised, open-label, cross-over	Sevelamer carbonate powder for oral suspension 800 mg sachets Sevelamer hydrochloride 800 mg tablets The binder dose at the end of the sevelamer hydrochloride run-in was replaced gram per gram by study drug. The dose was to be maintained throughout the treatment periods. Both to be taken orally TID with meals. Mean actual dose (Safety Set) Sevelamer carbonate: 5.9 ± 2.7 g/day Sevelamer hydrochloride: 6.5 ± 3.3 g/day	Compare the safety and efficacy of sevelamer carbonate powder with sevelamer hydrochloride tablets, each dosed TID	Treated: 31 (31 patients received sevelamer carbonate powder and 28 patients received sevelamer hydrochloride tablets) Completed both treatments: 24	15 weeks: 2-week washout period; 4-week sevelamer hydrochloride run-in period; two 4-week randomised treatment periods; 1-week follow-up period.	68%/ 32% 53 years (27-80 years)	Haemo-dialysis patients	Time weighted average of serum phosphorus



Table 2.7.4-1: Sevelamer Carbonate Studies that Provide Safety Data

Study ID	Number of Study Centres Location(s)	Study Start Enrolment Status, Date Total Enrolment/Enrolment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/Arm Treated/Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
G03-163-201	13 sites in the United States	Started: 30 Mar 2005 Completed: 15 Mar 2006 Screened: 101 enrolled/120 planned Randomised: 79 enrolled/80 planned	Randomised, double-blind, cross-over	Sevelamer carbonate 800 mg tablets Sevelamer hydrochloride 800 mg tablets The total binder dose the patient entered the study on was replaced by study drug in a pill for pill exchange. The dose was to be maintained throughout the treatment periods. Both taken orally TID with meals. Mean actual dose (Safety Set) Sevelamer carbonate tablets: 5.8 ± 2.8 g/day Sevelamer hydrochloride: 5.6 ± 2.9 g/day	Compare the safety and efficacy of sevelamer carbonate tablets with sevelamer hydrochloride tablets, each dosed TID	Treated: 78 (73 patients received sevelamer carbonate tablets and 78 patients received sevelamer hydrochloride tablets) Completed both treatments: 69 Completed washout: 40	23 weeks: 5-week sevelamer hydrochloride run-in period, two 8-week randomised treatment periods, 2-week washout period	51%/49% 58 years (29-88 years)	Haemo-dialysis patients	Time weighted average of serum phosphorus

Table 2.7.4-1: Sevelamer Carbonate Studies that Provide Safety Data

Study ID	Number of Study Centres Location(s)	Study Start Enrolment Status, Date Total Enrolment/ Enrolment Goal	Design Control Type	Study & Control Drugs Dose and Regimen	Primary Study Objective	Subjects/ Arm Treated/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint
GD3-199-301	29 sites in the United States	Started: 27 Jan 06 Completed: 16 Mar 07 Screened: 396 enrolled/280 planned Randomised: 217 (144 sevelamer carbonate powder QD; 73 sevelamer hydrochloride tablets TID) enrolled/ 207 (138 sevelamer carbonate powder QD; 69 sevelamer hydrochloride tablets TID) planned	Randomised, open-label, parallel	Sevelamer carbonate powder for oral suspension 2.4 g sachets Sevelamer hydrochloride 800 mg tablets The starting dose was 4.8 g/day of either sevelamer carbonate powder or sevelamer hydrochloride tablets. The dose was to be titrated to reach a serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.76 mmol/L). Sevelamer carbonate powder was to be taken QD with the largest meal. Sevelamer hydrochloride tablets were to be taken TID with the meals. Mean actual dose (Safety Set) Sevelamer carbonate powder dosed QD: 6.2 ± 2.6 g/day Sevelamer hydrochloride tablets dosed TID: 6.7 ± 3.0 g/day	Compare the safety and efficacy of sevelamer carbonate powder dosed QD with the largest meal to sevelamer hydrochloride tablets dosed TID with meals	Sevelamer carbonate powder QD: 141 treated/ 93 completed Sevelamer hydrochloride tablets TID: 72 treated/ 62 completed	26 weeks: 2-week washout period, 24-week randomised treatment period	61%/ 39% 58 years (20-85 years)	Haemo-dialysis patients	Change in serum phosphorus



2.7.4.1.2 Overall Extent of Exposure

In SVCARB00205, 31 patients received sevelamer carbonate powder and 28 patients received sevelamer hydrochloride tablets. The mean prescribed dose during the randomised treatment periods was 7.7 ± 3.1 g/day of sevelamer carbonate powder taken TID and 7.8 ± 3.0 g/day of sevelamer hydrochloride tablets taken TID. The mean actual dose during the randomised treatment periods was 5.9 ± 2.7 g/day of sevelamer carbonate powder taken TID and 6.5 ± 3.3 g/day of sevelamer hydrochloride tablets taken TID. Mean percent compliance was similar between the sevelamer carbonate and sevelamer hydrochloride regimens: 81% for sevelamer carbonate powder and 83% for sevelamer hydrochloride tablets. The median number of weeks on study medication was 4.1 weeks on sevelamer carbonate powder and 4.4 weeks on sevelamer hydrochloride tablets.

In GD3-163-201, 73 patients received sevelamer carbonate tablets and 78 patients received sevelamer hydrochloride tablets. The mean prescribed dose during the randomised treatment periods was 7.2 ± 3.2 g/day of sevelamer carbonate tablets taken TID and 7.1 ± 3.3 g/day of sevelamer hydrochloride tablets taken TID. The mean actual daily dose during the randomised treatment periods was 5.8 ± 2.8 g/day of sevelamer carbonate tablets taken TID and 5.6 ± 2.9 g/day of sevelamer hydrochloride tablets taken TID. During the randomised treatment periods, mean percent compliance was similar between sevelamer carbonate tablet and sevelamer hydrochloride tablet treatment (82% for sevelamer carbonate and 83% for sevelamer hydrochloride). The median number of weeks was 8.1 weeks on sevelamer carbonate tablets and 8.0 weeks on sevelamer hydrochloride tablets.

In GD3-199-301, 141 patients received sevelamer carbonate powder QD and 72 patients received sevelamer hydrochloride tablets TID. The mean prescribed dose at the end of the treatment period was 8.8 ± 3.8 g/day of sevelamer carbonate powder taken QD and 8.9 ± 3.8 g/day of sevelamer hydrochloride tablets taken TID. The mean actual daily dose was 6.2 ± 2.6 g/day of sevelamer carbonate powder taken taken QD and 6.7 ± 3.0 g/day of sevelamer hydrochloride tablets taken TID. Mean percent compliance was similar between groups (86% for the sevelamer carbonate powder QD group and 85% for the sevelamer hydrochloride tablet TID group, respectively). The median treatment duration was 23.1 weeks of sevelamer carbonate powder QD and 23.3 weeks of sevelamer hydrochloride tablets TID.



The sevelamer carbonate exposure data for SVCARB00205, GD3-163-201, and GD3-199-301 are summarised in Table 2.7.4-2.

Table 2.7.4-2:
Sevelamer Carbonate Exposure in Studies
SVCARB00205, GD3-163-201, and GD3-199-301 (Safety Set)

	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=73)	GD3-199-301 24 Week Treatment Period Sevelamer Carbonate Powder QD (N=141)
Prescribed Dose (g/day)			
Mean ± SD ¹	7.7 ± 3.1	7.2 ± 3.2	8.8 ± 3.8
Range	2.4-12.0	1.6-14.4	0.0-14.4
Actual Dose² (g/day)			
Mean ± SD	5.9 ± 2.7	5.8 ± 2.8	6.2 ± 2.6
Range	1.8-12.3	1.2-14.1	1.5-14.4
Compliance³ (%)			
Mean ± SD	80.7 ± 21.5	82.4 ± 19.1	85.7 ± 16.4
Range	35.1-113.1	24.8-129.8	23.2-143.6
Treatment Duration (weeks)			
Median	4.1	8.1	23.1
Range	0.4-5.1	5.1-8.9	0.1-24.0

¹ Prescribed dose at the end of the treatment period.

² Actual daily dose is calculated as the total number of tablets or sachets multiplied by the dose divided by the number of days on study treatment.

³ Compliance is calculated as the total number of tablets or sachets taken divided by the total prescribed number of tablets or sachets.

Note: The number of observations varies in the statistics shown. Please refer to the tables in the SVCARB00205, GD3-163-201, and GD3-199-301 CSRs for details.

Data Source: SVCARB00205 CSR Table 14.3.8.3; GD3-163-201 CSR Table 14.3.7.3 and Post hoc Table 5; GD3-199-301 CSR Table 14.1.12.3.

SVCARB00205 had a 4 week treatment period, GD3-163-201 had an 8 week treatment period and GD3-199-301 had a 24 week treatment period. The mean prescribed dose, mean actual dose and compliance was similar between SVCARB00205 and



GD3-163-201. In GD3-199-301, while the mean actual dose was similar to the two studies investigating TID dosing of sevelamer carbonate, the mean prescribed dose at the end of treatment was higher (Table 2.7.4-2).

2.7.4.1.3 Demographic and Other Characteristics of Study Population

2.7.4.1.3.1 Demographics and Renal History

The demographics and renal history of the patients in SVCARB00205, GD3-163-201, and GD3-199-301 (sevelamer carbonate patients) are summarised in Table 2.7.4-3. SVCARB00205 and GD3-163-201 are cross-over studies so the demographics and renal history information applies to both treatment regimens. In GD3-199-301, the two treatment groups were generally well balanced with respect to demographics and renal history. The demographics and renal history of the sevelamer hydrochloride patients in GD3-199-301 can be found in the GD3-199-301 clinical study report in Module 5.

The distribution of age and gender were similar in all three studies. The distribution of race groups varied according to the geographical region in which the study was performed. In SVCARB00205, which was conducted in the United Kingdom, the most common race group was Caucasian; whereas in GD3-163-201 and GD3-199-301 which were conducted in the United States, a higher proportion of African-American patients was studied. The most common primary causes of chronic renal failure were “other,” glomerulonephritis and diabetes in SVCARB00205. Of the 15 patients with “other” cited as the primary cause in SVCARB00205, the aetiology of CKD was recorded as unknown in 5 patients, IgA nephropathy in 2 patients, and interstitial nephritis, congenital, renovascular disease, reflux nephropathy, road traffic accident, hereditary nephritis, Goodpasture syndrome and Alport’s syndrome in 1 patient each. Diabetes, hypertension and “other” were the most common primary causes of chronic renal failure in GD3-163-201 and GD3-199-301. As sevelamer alone or in combination was required per protocol in SVCARB00205 and GD3-163-201, the most frequently prescribed pre-study phosphate binder was either sevelamer or sevelamer in combination with calcium in these studies. In GD3-199-301, the most frequently prescribed pre-study phosphate binders were sevelamer (34%) and calcium based binders (26%). Approximately 80% of patients in all three studies were using oral vitamin D, IV vitamin D or a combination of oral and IV vitamin D prior to the study. The duration on dialysis was longer in

genzyme

sevelamer carbonate
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SVCARB00205 than in GD3-199-301 or GD3-163-201. In general, the patients are reflective of the CKD on dialysis patient population.

**Table 2.7.4-3:
Summary of Demographic Characteristics and Renal History in
SVCARB00205, GD3-163-201, and GD3-199-301-Safety Set**

Characteristic	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=78) [†]	GD3-199-301 24 Week Treatment Period Sevelamer Carbonate Powder QD (N=141)
Age (years) [Mean ±SD]	52.9 ± 13.2	58.1 ± 12.3	56.7 ± 14.2
Gender [n (%)]			
Male	21 (68)	40 (51)	87 (62)
Female	10 (32)	38 (49)	54 (38)
Race [n (%)]			
Caucasian	22 (71)	21 (27)	59 (42)
Black or African-American	3 (10)	52 (67)	76 (54)
Asian	6 (19)	0 (0)	0 (0)
Other	0 (0)	5 (6)	6 (4)
Primary Cause of ESRD [n (%)]			
Hypertension	1 (3)	18 (23)	41 (29)
Glomerulonephritis	8 (26)	7 (9)	15 (11)
Diabetes	4 (13)	33 (42)	57 (40)
Pyelonephritis	1 (3)	0 (0)	0 (0)
Polycystic Kidneys	2 (7)	2 (3)	2 (1)
Other	15 (48)	18 (23)	26 (18)

**Table 2.7.4-3:
Summary of Demographic Characteristics and Renal History in
SVCARB00205, GD3-163-201, and GD3-199-301-Safety Set**

Characteristic	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=78) [†]	GD3-199-301 24 Week Treatment Period Sevelamer Carbonate Powder QD (N=141)
Pre-Study Phosphate Binder Use [n (%)]			
Sevelamer Hydrochloride	18 (58)	72 (92)	68 (48)
Sevelamer Hydrochloride and Calcium	11 (36)	6 (8)	11 (8)
Sevelamer Hydrochloride and Lanthanum	NA	NA	2 (1)
Calcium	NA	NA	34 (24)
Calcium and Lanthanum	NA	NA	1 (1)
Lanthanum	NA	NA	13 (9)
Other	2 (7)	0 (0)	0 (0)
Unknown	NA	NA	12 (9)
Using Vitamin D* [n (%)]	25 (81)	67 (86)	120 (85)
Duration of Dialysis (years)			
Mean ± SD	7.2 ± 8.0	4.4 ± 4.9	3.8 ± 3.5
Median	4.4	2.4	2.6
Range	0.2-30.3	0.3-23.4	0.3-26.7

[†] In GD3-163-201, demographics were summarized for all patients who received either study drug (sevelamer carbonate or sevelamer hydrochloride). Five of the patients who received sevelamer hydrochloride discontinued prior to receiving sevelamer carbonate.

* Oral vitamin D, IV vitamin D or a combination of oral and IV vitamin D

Data Source: SVCARB00205 CSR Table 14.1.3.3 and Table 14.1.4.3; GD3-163-201 CSR Table 14.1.3.3 and Table 14.1.4.3; GD3-199-301 CSR Table 14.1.4.3 and Table 14.1.5.3.



2.7.4.2 Adverse Events

Adverse events included any undesirable physical, psychological, or behavioural effect experienced by a patient in conjunction with the study, whether or not product-related. Adverse events included, but were not limited to: subjective or objective symptoms spontaneously offered by the patient and/or observed by the investigator; clinically significant changes in physical exam as assessed by the investigator; and changes in laboratory abnormalities that were clinically relevant as assessed by the investigator and for which a medical intervention was initiated. Treatment emergent adverse events were defined as those adverse events that occurred after the initiation of study treatment.

Investigators assessed causality of adverse events in relation to study treatment as: not related, remotely/unlikely related, possibly related, or probably related (or definitely related in SVCARB00205 and GD3-199-301). Treatment related adverse events were defined as adverse events assessed as possibly or probably related to study treatment (or definitely related in SVCARB00205 and GD3-199-301). Additionally, investigators assessed the intensity of adverse events as: mild, moderate, or severe and determined if adverse events were serious using the definition of seriousness as described in the International Conference on Harmonisation (ICH E2A).

All adverse events presented in this summary of safety were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Data from SVCARB00205 and GD3-199-301 were coded using MedDRA version 9.1 and data from GD3-163-201 was coded using MedDRA version 8.1. The changes made to the MedDRA dictionary from version 8.1 to 9.1 at the preferred term level did not impact the coding of the adverse event data.

2.7.4.2.1 Analysis of Adverse Events

In the Analysis of Adverse Events, the adverse events from studies SVCARB00205, GD3-163-201, and GD3-199-301 will be discussed individually. The in-text tables are structured so that the presentation of percentages of patients experiencing an adverse event is taken directly from the adverse event presentation in the SVCARB00205, GD3-163-201 and GD3-199-301 clinical study reports. As all three studies compared sevelamer carbonate and sevelamer hydrochloride, the discussion of these studies will



include the adverse events during both the sevelamer carbonate and sevelamer hydrochloride treatment periods.

SVCARB00205 and GD3-163-201 were cross-over design studies comparing sevelamer carbonate dosed TID with sevelamer hydrochloride tablets TID. GD3-199-301 was 24 week parallel design study comparing sevelamer carbonate powder dosed QD with sevelamer hydrochloride tablets TID. A comparative assessment of the adverse events that occurred during sevelamer carbonate treatment in SVCARB00205 and GD3-163-201 will be presented in Section 2.7.4.2.1.1, Common Adverse Events. Since the dosing regimen (QD) and treatment duration (24 weeks) in GD3-199-301 were different than the dosing regimen (TID) and treatment duration employed in SVCARB00205 (4 weeks) and GD3-163-201 (8 weeks), this study is not included in the comparative assessment.

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Table 2.7.4-4 presents an overview of the number of patients with treatment emergent adverse events, treatment emergent severe adverse events and related treatment emergent adverse events in SVCARB00205.

**Table 2.7.4-4:
Overview of the Number of Patients with Treatment Emergent Adverse Events
During the Randomised Treatment Periods in SVCARB00205 (Safety Set)**

	Sevelamer Carbonate Powder TID (N=31) n (%)	Sevelamer Hydrochloride Tablets TID (N=28) n (%)
Any Treatment Emergent AEs	10 (32.3)	12 (42.9)
Treatment Emergent Severe AEs	1 (3.2)	0
Related Treatment Emergent AEs	3 (9.7)	0

Data source: SVCARB00205 CSR Table 14.3.1.3, Table 14.3.1.4, and Table 14.3.1.5.



Treatment Emergent Adverse Events in SVCARB00205

The overall frequency of AEs that occurred during the randomised treatment periods was similar between treatment regimens: 21 events in 10 (32.3%) patients during treatment with sevelamer carbonate powder and 26 events in 12 (42.9%) patients during treatment with sevelamer hydrochloride tablets.

Table 2.7.4-5 displays the most frequently occurring treatment-emergent AEs ($\geq 5\%$ patients [i.e., at least 2 patients]) regardless of causality by MedDRA SOC, during either randomised treatment regimen.

**Table 2.7.4-5:
Summary of Treatment Emergent AEs (All Causality) by MedDRA System
Organ Class that Occurred in $\geq 5\%$ of Patients During the Randomised
Treatment Periods in SVCARB00205 (Safety Set)**

System Organ Class	Sevelamer Carbonate Powder TID (N=31)		Sevelamer Hydrochloride Tablets TID (N=28)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any AE	21	10 (32.3)	26	12 (42.9)
Gastrointestinal Disorders	5	4 (12.9)	4	3 (10.7)
Skin and Subcutaneous Tissue Disorders	2	2 (6.5)	2	2 (7.1)
Infections and Infestations	2	2 (6.5)	1	1 (3.6)
Investigations	2	2 (6.5)	1	1 (3.6)
Vascular Disorders	2	2 (6.5)	1	1 (3.6)
General Disorders and Administration Site Conditions	1	1 (3.2)	5	4 (14.3)
Musculoskeletal and Connective Tissue Disorders	1	1 (3.2)	4	3 (10.7)
Surgical and Medical Procedures	1	1 (3.2)	3	3 (10.7)

Source: SVCARB00205 CSR Table 14.3.1.3.

In general, AEs coded to similar SOCs during sevelamer carbonate powder TID and sevelamer hydrochloride tablet TID treatment. In both treatment regimens, the most frequent events coded to the Gastrointestinal Disorders SOC, with 5 events in 4 (12.9%) patients during treatment with sevelamer carbonate powder, and 4 events in 3 (10.7%)



patients during treatment with sevelamer hydrochloride tablets. AEs occurred more frequently (i.e., at least a 3 patient difference) during sevelamer hydrochloride tablet treatment than during sevelamer carbonate powder treatment for the SOC General Disorders and Administration Site Conditions (14.3% vs. 3.2%).

A summary of the treatment-emergent AEs occurring in $\geq 5\%$ patients (i.e., at least 2 patients) in either treatment regimen during the open-label, randomised treatment period regardless of causality is presented in Table 2.7.4-6 by MedDRA preferred term.

**Table 2.7.4-6:
Summary of Treatment Emergent AEs (All Causality) by MedDRA Preferred
Term that Occurred in $\geq 5\%$ of Patients During the Randomised Treatment
Periods in SVCARB00205 (Safety Set)**

System Organ Class Preferred Term	Sevelamer Carbonate Powder TID (N=31)		Sevelamer Hydrochloride Tablets TID (N=28)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any AE	21	10 (32.3)	26	12 (42.9)
Gastrointestinal Disorders	5	4 (12.9)	4	3 (10.7)
Nausea	2	2 (6.5)	0	0
General Disorders and Administration Site Conditions	1	1 (3.2)	5	4 (14.3)
Fatigue	0	0	2	2 (7.1)
Surgical and Medical Procedures	1	1 (3.2)	3	3 (10.7)
Arteriovenous fistula operation	1	1 (3.2)	2	2 (7.1)

Source: SVCARB00205 CSR Table 14.3.1.3.

In general, AEs were reported across SOCs and during both treatment regimens the majority of AEs occurred as single events in single patients. The AE reported in more than one patient during sevelamer carbonate powder treatment was nausea (2 events in 2 [6.5%] patients). The events reported in more than one patient during sevelamer hydrochloride tablet treatment were fatigue and arteriovenous fistula operation, each reported as 2 events in 2 (7.1%) patients.

AEs that occurred during the randomised treatment periods were also analysed for the following demographic subgroups: males and females, Blacks and other races, and



< 65 years of age and \geq 65 years of age. Interpretation of the data is limited due to the small number of patients in some of the subgroups, but in general, the results showed that AEs occurring during the study were not influenced by gender, race or age. Please see SVCARB00205 CSR Table 14.3.1.7.1.1, Table 14.3.1.7.1.2, Table 14.3.1.7.2.1, Table 14.3.1.7.2.2, Table 14.3.1.7.3.1 and Table 14.3.1.7.3.2 for these results.

Treatment Emergent Adverse Events by Intensity in SVCARB00205

Based on the most severe occurrence of a particular treatment emergent AE during the randomised treatment periods, 4 (12.9%) patients during the sevelamer carbonate powder regimen and 8 (28.6%) patients during the sevelamer hydrochloride tablet regimen experienced a mild AE; 5 (16.1%) patients during the sevelamer carbonate powder regimen and 4 (14.3%) patients during the sevelamer hydrochloride tablet regimen experienced a moderate AE; and 1 (3.2%) patient during the sevelamer carbonate powder regimen and no patients during the sevelamer hydrochloride tablet regimen experienced a severe AE.

The one severe AE reported during the randomised treatment periods was an event of chest pain during sevelamer carbonate powder treatment that was considered by the investigator to be remote/unlikely related to sevelamer carbonate powder. The patient discontinued sevelamer carbonate powder due to the event of chest pain.

Treatment Related Adverse Events in SVCARB00205

During the randomised treatment periods, a total of 4 events in 3 (9.7%) patients were considered by the investigator to be treatment related to sevelamer carbonate powder. All were coded to the Gastrointestinal Disorders SOC and included (by MedDRA preferred term): nausea (2 events in 2 [6.5%] patients), constipation (1 event in 1 [3.2%] patient) and vomiting (1 event in 1 [3.2%] patient). All treatment related AEs were of mild or moderate intensity. No treatment related AEs were reported during treatment with sevelamer hydrochloride tablets during the randomised treatment periods.

Treatment related AEs that occurred during the randomised treatment periods were also evaluated for the following demographic subgroups: males and females, Blacks and other races, < 65 years of age and \geq 65 years of age. Analysis of the data is limited due to the low frequency of treatment related AEs reported during the study and the small number



of patients in the subgroups. The 4 treatment related AEs occurred in male patients, aged < 65 years and of other race (i.e., non-black), which is consistent with the demographic characteristics of the majority of the patients in the Safety Set and indicates that, in general, AEs reported during the study were not influenced by gender, race or age. Please see SVCARB00205 CSR Table 14.3.1.8.1.1, Table 14.3.1.8.1.2, Table 14.3.1.8.2.1, Table 14.3.1.8.2.2, Table 14.3.1.8.3.1 and Table 14.3.1.8.3.2 for these results.

GD3-163-201: A Double-Blind, Cross-Over Design Study of Sevelamer Hydrochloride (Renagel®) and Sevelamer Carbonate in Chronic Kidney Disease Patients on Hemodialysis

Table 2.7.4-7 presents an overview of the number of patients with treatment emergent adverse events, treatment emergent severe adverse events, and related treatment emergent adverse events in GD3-163-201.

**Table 2.7.4-7:
Overview of the Number of Patients with Treatment Emergent Adverse Events
During the Randomised Treatment Periods in GD3-163-201 (Safety Set)**

	Sevelamer Carbonate Tablets TID (N=73) N (%)	Sevelamer Hydrochloride Tablets TID (N=78) N (%)
Any Treatment Emergent AEs	60 (82.2)	65 (83.3)
Treatment Emergent Severe AEs	5 (6.8)	6 (7.7)
Related Treatment Emergent AEs	12 (16.4)	15 (19.2)

Data source: GD3-163-201 CSR Table 14.3.1.3, Table 14.3.1.4 and Table 14.3.1.5.

Treatment Emergent Adverse Events in GD3-163-201

The overall frequency of adverse events was similar between treatment regimens: 195 events in 60 (82.2%) patients during sevelamer carbonate tablet treatment and 226 events in 65 (83.3%) patients during sevelamer hydrochloride tablet treatment.

The most frequently occurring AEs ($\geq 10\%$ of randomised patients in either treatment regimen, all causality) by MedDRA System Organ Class are presented in Table 2.7.4-8.



**Table 2.7.4-8:
Treatment Emergent AEs (All Causality) that Occurred in $\geq 10\%$ of Patients
During the Randomised Treatment Periods by MedDRA System Organ Class
in GD3-163-201 (Safety Set)**

System Organ Class	Sevelamer Carbonate Tablets TID (N=73)		Sevelamer Hydrochloride Tablets TID (N=78)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	195	60 (82.2)	226	65 (83.3)
Gastrointestinal disorders	25	15 (20.5)	45	28 (35.9)
Infections and infestations	24	19 (26.0)	21	18 (23.1)
Injury, poisoning and procedural complications	26	16 (21.9)	20	16 (20.5)
Musculoskeletal and connective tissue disorders	18	12 (16.4)	24	16 (20.5)
Investigations	19	14 (19.2)	17	13 (16.7)
Metabolism and nutrition disorders	13	12 (16.4)	20	14 (17.9)
Nervous system disorders	12	12 (16.4)	15	13 (16.7)
Respiratory, thoracic and mediastinal disorders	16	12 (16.4)	20	13 (16.7)
General disorders and administration site conditions	14	10 (13.7)	17	13 (16.7)

Data source: GD3-163-201 CSR Table 14.3.1.3.

In general, adverse events coded to similar SOCs during sevelamer carbonate tablet and sevelamer hydrochloride tablet treatment. The highest frequency of treatment emergent AEs occurred in the MedDRA SOC of Gastrointestinal disorders, with 25 events in 15 (20.5%) patients during sevelamer carbonate tablet treatment, and 45 events in 28 (35.9%) patients during sevelamer hydrochloride tablet treatment.

A summary of the adverse events occurring in $\geq 5\%$ patients in either treatment regimen regardless of causality is presented in Table 2.7.4-9 by MedDRA preferred term.



**Table 2.7.4-9:
Treatment Emergent Adverse Events (All Causality) Occurring in $\geq 5\%$ of
Patients During the Randomised Treatment Periods in GD3-163-201
(Safety Set)[†]**

System Organ Class Preferred Term	Sevelamer Carbonate Tablets TID (N=73)		Sevelamer Hydrochloride Tablets TID (N=78)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	195	60 (82.2)	226	65 (83.3)
Gastrointestinal disorders	25	15 (20.5)	45	28 (35.9)
Nausea	9	7 (9.6)	13	10 (12.8)
Vomiting	7	6 (8.2)	8	8 (10.3)
Diarrhoea	3	2 (2.7)	6	5 (6.4)
Gastroesophageal reflux disease	1	1 (1.4)	5	4 (5.1)
General disorders and administration site conditions	14	10 (13.7)	17	13 (16.7)
Fatigue	1	1 (1.4)	4	4 (5.1)
Infections and infestations	24	19 (26.0)	21	18 (23.1)
Urinary tract infection	6	6 (8.2)	1	1 (1.3)
Injury, poisoning and procedural complications	26	16 (21.9)	20	16 (20.5)
Arteriovenous fistula thrombosis	3	3 (4.1)	9	9 (11.5)
Arteriovenous fistula site complication	6	5 (6.8)	2	1 (1.3)
Arteriovenous fistula site haemorrhage	5	4 (5.5)	2	2 (2.6)
Metabolism and nutrition disorders	13	12 (16.4)	20	14 (17.9)
Hypercalcaemia	7	6 (8.2)	2	2 (2.6)
Musculoskeletal and connective tissue disorders	18	12 (16.4)	24	16 (20.5)
Pain in extremity	4	3 (4.1)	7	6 (7.7)
Muscle spasms	4	4 (5.5)	4	3 (3.8)
Nervous system disorders	12	12 (16.4)	15	13 (16.7)
Dizziness	6	6 (8.2)	3	3 (3.8)
Headache	3	3 (4.1)	5	4 (5.1)
Respiratory, thoracic and mediastinal disorders	16	12 (16.4)	20	13 (16.7)
Cough	4	4 (5.5)	4	3 (3.8)

Data source: GD3-163-201 CSR Table 14.3.1.3.

[†] Adverse events coded to the System Organ Class Investigations are not included in this table. Please refer to Section 2.7.4.3.3.2 for a discussion of these events.



Across both treatment regimens, the most frequently occurring adverse events (>10% patients) were (by MedDRA preferred term): nausea (9 events in 7 [9.6%] patients during sevelamer carbonate tablet treatment and 13 events in 10 [12.8%] patients during sevelamer hydrochloride tablet treatment), vomiting (7 events in 6 [8.2%] patients during sevelamer carbonate tablet treatment and 8 events in 8 [10.3%] patients during sevelamer hydrochloride tablet treatment), and arteriovenous fistula thrombosis (3 events in 3 [4.1%] patients during sevelamer carbonate tablet treatment and 9 events in 9 [11.5%] patients during sevelamer hydrochloride tablet treatment).

Treatment Emergent Adverse Events by Intensity in GD3-163-201

The majority of adverse events were mild or moderate in intensity. Based on the most severe occurrence of a particular treatment-emergent adverse event during the randomised treatment periods, 29 (39.7%) patients during the sevelamer carbonate tablet regimen and 31 (39.7%) patients during the sevelamer hydrochloride tablet regimen experienced a mild adverse event; 26 (35.6%) patients during the sevelamer carbonate tablet regimen and 28 (35.9%) patients during the sevelamer hydrochloride tablet regimen experienced a moderate adverse event; and 5 (6.8%) patients during the sevelamer carbonate tablet regimen and 6 (7.7%) patients during the sevelamer hydrochloride tablet regimen experienced a severe adverse event.

A majority of severe events occurred in a single patient each during the randomised treatment periods. Severe adverse events occurring in more than one patient during sevelamer carbonate tablet treatment included (by MedDRA preferred term) coronary artery disease [2 (2.7%) patients]. Severe adverse events occurring in more than one patient during sevelamer hydrochloride tablet treatment included (by MedDRA preferred term) renal transplant [2 (2.6%) patients]. All severe events were assessed by the investigator as not related or unlikely related to study treatment.

Treatment Related Adverse Events in GD3-163-201

During the randomised treatment periods in GD3-163-201, the frequency of patients experiencing treatment related adverse events was similar between treatment regimens: 20 events in 12 (16.4%) patients during sevelamer carbonate tablet treatment and 33 events in 15 (19.2%) patients during sevelamer hydrochloride tablet treatment. All treatment related AEs were mild or moderate in severity. A summary of the treatment



related adverse events occurring in $\geq 2\%$ patients by MedDRA preferred term is presented in Table 2.7.4-10.

**Table 2.7.4-10:
Treatment Emergent Adverse Events Possibly or Probably Related
Occurring in $\geq 2\%$ of Patients During the Randomised Treatment Periods in
GD3-163-201 (Safety Set)[†]**

System Organ Class Preferred Term	Sevelamer Carbonate Tablets TID (N=73)		Sevelamer Hydrochloride Tablets TID (N=78)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	20	12 (16.4)	33	15 (19.2)
Gastrointestinal disorders	9	6 (8.2)	14	8 (10.3)
Nausea	2	2 (2.7)	5	2 (2.6)
Gastroesophageal reflux disease	1	1 (1.4)	4	3 (3.8)
Vomiting	2	2 (2.7)	1	1 (1.3)
Metabolism and nutrition disorders	2	2 (2.7)	4	4 (5.1)
Decreased appetite	0	0 (0.0)	2	2 (2.6)

Data source: GD3-163-201 CSR Table 14.3.1.4.

[†] Refer to Section 2.7.4.3.3.2 for discussion of laboratory abnormalities coding to the System Organ Class Investigations.

Treatment related adverse events in SOC Gastrointestinal Disorders included (by MedDRA preferred term): nausea (2 events in 2 [2.7%] patients during sevelamer carbonate tablet treatment and 5 events in 2 [2.6%] patients during sevelamer hydrochloride tablet treatment); gastroesophageal reflux disease (1 event in 1 [1.4%] patient during sevelamer carbonate tablet treatment and 4 events in 3 [3.8%] patients during sevelamer hydrochloride tablet treatment); and vomiting (2 events in 2 [2.7%] patients during sevelamer carbonate tablet treatment and 1 event in 1 [1.3%] patient during sevelamer hydrochloride tablet treatment).



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 Chronic Kidney Disease Patients on Hemodialysis

Table 2.7.4-11 presents an overview of the number of patients with treatment emergent adverse events, treatment emergent severe adverse events and related treatment emergent adverse events in GD3-199-301. GD3-199-301 is included as it provides safety data on 141 patients treated for 24 weeks, but it should be viewed as supportive safety information only as the dosing regimen in this study (QD) was different than the dosing regimen (TID) employed in the studies that will be used to support the posology in the package insert.

**Table 2.7.4-11:
Overview of the Number of Patients with Treatment Emergent Adverse Events in
GD3-199-301 (Safety Set)**

	Sevelamer Carbonate Powder QD (N=141) n (%)	Sevelamer Hydrochloride Tablets TID (N=72) n (%)
Any Treatment Emergent AEs	124 (87.9)	66 (91.7)
Treatment Emergent Severe AEs	22 (15.6)	19 (26.4)
Related Treatment Emergent AEs	43 (30.5)	13 (18.1)

Data source: GD3-199-301 CSR Table 14.3.1.1.1, Table 14.3.1.4.1, and Table 14.3.1.3.

Treatment Emergent Adverse Events in GD3-199-301

The overall percentage of patients with treatment emergent AEs was similar between treatment groups with 723 AEs in 124 (87.9%) sevelamer carbonate powder QD patients and 430 AEs in 66 (91.7%) sevelamer hydrochloride tablet TID patients. The most frequently occurring AEs ($\geq 10\%$ of randomised patients in either treatment group, all causality) by MedDRA SOC are presented in Table 2.7.4-12.



Table 2.7.4-12:
Summary of AEs (All Causality) that Occurred in $\geq 10\%$ of Patients by MedDRA System Organ Class in GD3-199-301 (Safety Set)

System Organ Class	Sevelamer Carbonate Powder QD (N = 141)		Sevelamer Hydrochloride Tablets TID (N = 72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	723	124 (87.9)	430	66 (91.7)
Gastrointestinal Disorders	147	66 (46.8)	75	35 (48.6)
Cardiac Disorders	30	19 (13.5)	23	12 (16.7)
Musculoskeletal and Connective Tissue Disorders	73	47 (33.3)	34	21 (29.2)
Injury, Poisoning, and Procedural Complications	66	44 (31.2)	55	32 (44.4)
Infections and Infestations	77	43 (30.5)	36	28 (38.9)
General Disorders and Administrative Site Conditions	63	37 (26.2)	48	27 (37.5)
Nervous System Disorders	41	29 (20.6)	27	18 (25.0)
Respiratory, Thoracic and Mediastinal Disorders	53	29 (20.6)	24	18 (25.0)
Metabolism and Nutrition Disorders	33	24 (17.0)	19	16 (22.2)
Vascular Disorders	28	22 (15.6)	31	20 (27.8)
Skin and Subcutaneous Tissue Disorders	24	21 (14.9)	19	14 (19.4)
Investigations	22	11 (7.8)	16	12 (16.7)

Data source: GD3-199-301 CSR Table 14.3.1.1.1, Listing 16.2.7.1.

In general, there was a similar incidence of AEs by SOC in the sevelamer carbonate powder QD and sevelamer hydrochloride tablet TID treatment groups. In both treatment groups, the highest frequency of treatment emergent AEs occurred in the MedDRA SOC of Gastrointestinal Disorders with 147 AEs in 66 (46.8%) sevelamer carbonate powder QD patients and 75 AEs in 35 (48.6%) sevelamer hydrochloride tablet TID patients.

A summary of the AEs occurring in $\geq 5\%$ patients in either treatment group regardless of causality is presented in Table 2.7.4-13 by MedDRA preferred term.



sevelamer carbonate
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**Table 2.7.4-13:
Treatment Emergent Adverse Events (All Causality) Occurring in ≥5% of Patients
in GD3-199-301 (Safety Set)**

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	723	124 (87.9)	430	66 (91.7)
Cardiac Disorders	30	19 (13.5)	23	12 (16.7)
Cardiac Failure Congestive	7	5 (3.5)	8	5 (6.9)
Gastrointestinal Disorders	147	66 (46.8)	75	35 (48.6)
Nausea	37	30 (21.3)	11	8 (11.1)
Diarrhoea	38	25 (17.7)	21	13 (18.1)
Vomiting	29	24 (17.0)	7	6 (8.3)
Constipation	6	6 (4.3)	8	8 (11.1)
Abdominal Pain Upper	5	5 (3.5)	6	4 (5.6)
General Disorders and Administration Site Conditions	63	37 (26.2)	48	27 (37.5)
Oedema Peripheral	13	6 (4.3)	6	5 (6.9)
Pyrexia	4	4 (2.8)	9	6 (8.3)
Infections and Infestations	77	43 (30.5)	36	28 (38.9)
Upper Respiratory Tract Infection	11	9 (6.4)	5	5 (6.9)
Urinary Tract Infection	11	10 (7.1)	3	2 (2.8)
Pneumonia	6	6 (4.3)	5	4 (5.6)
Arteriovenous Fistula Site Infection	2	2 (1.4)	5	4 (5.6)
Injury, Poisoning and Procedural Complications	66	44 (31.2)	55	32 (44.4)
Arteriovenous Fistula Thrombosis	12	8 (5.7)	19	13 (18.1)
Arteriovenous Fistula Site Complication	19	18 (12.8)	6	5 (6.9)
Arteriovenous Fistula Site Haemorrhage	3	3 (2.1)	5	5 (6.9)
Investigations	22	11 (7.8)	16	12 (16.7)
Heart Rate Irregular	5	2 (1.4)	4	4 (5.6)



**Table 2.7.4-13:
Treatment Emergent Adverse Events (All Causality) Occurring in $\geq 5\%$ of Patients
in GD3-199-301 (Safety Set)**

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Metabolism and Nutrition Disorders	33	24 (17.0)	19	16 (22.2)
Hyperkalaemia	7	6 (4.3)	4	4 (5.6)
Hypocalcaemia	4	3 (2.1)	5	4 (5.6)
Musculoskeletal and Connective Tissue Disorders	73	47 (33.3)	34	21 (29.2)
Muscle Spasms	28	20 (14.2)	9	4 (5.6)
Pain in Extremity	13	12 (8.5)	7	7 (9.7)
Back Pain	10	8 (5.7)	3	3 (4.2)
Arthralgia	7	4 (2.8)	4	4 (5.6)
Nervous System Disorders	41	29 (20.6)	27	18 (25.0)
Headache	20	15 (10.6)	10	8 (11.1)
Dizziness	12	9 (6.4)	10	8 (11.1)
Respiratory, Thoracic and Mediastinal Disorders	53	29 (20.6)	24	18 (25.0)
Dyspnoea	11	8 (5.7)	6	5 (6.9)
Cough	9	9 (6.4)	4	4 (5.6)
Skin and Subcutaneous Tissue Disorders	24	21 (14.9)	19	14 (19.4)
Pruritus	9	9 (6.4)	5	3 (4.2)
Vascular Disorders	28	22 (15.6)	31	20 (27.8)
Hypotension	12	9 (6.4)	12	8 (11.1)

Data source: GD3-199-301 CSR Table 14.3.1.1.1, Listing 16.2.7.1.

The most frequently occurring treatment emergent AEs ($>15\%$ patients) were (by MedDRA preferred term): nausea (37 events in 30 [21.3%] sevelamer carbonate powder QD patients and 11 events in 8 [11.1%] sevelamer hydrochloride tablet TID patients), diarrhoea (38 events in 25 [17.7%] sevelamer carbonate powder QD patients and 21 events in 13 [18.1%] sevelamer hydrochloride tablet TID patients), vomiting (29 events



in 24 [17.0%] sevelamer carbonate powder QD patients and 7 events in 6 [8.3%] sevelamer hydrochloride tablet TID patients), and arteriovenous fistula thrombosis (12 events in 8 [5.7%] sevelamer carbonate powder QD patients and 19 events in 13 [18.1%] sevelamer hydrochloride tablet TID patients).

In addition to the differences in nausea and vomiting described above, the following differences between treatment groups were noted. A higher number of patients on sevelamer carbonate powder QD experienced muscle spasms and urinary tract infections compared to patients on sevelamer hydrochloride tablets TID. Twenty eight events of muscle spasms occurred in 20 [14.2%] sevelamer carbonate powder QD patients and 9 events occurred in 4 [5.6%] sevelamer hydrochloride tablet TID patients. The events coding to MedDRA preferred term of muscle spasms varied with regard to the location of the muscle spasm and in general, constituted muscle cramps during dialysis. Eleven events of urinary tract infection occurred in 10 [7.1%] sevelamer carbonate powder QD patients and 3 events occurred in 2 [2.8%] sevelamer hydrochloride tablet TID patients. Patients who experienced urinary tract infections had a history of urinary tract infections or pre-existing conditions that pre-disposed patients to develop a urinary tract infection. A higher number of patients on sevelamer hydrochloride tablets TID experienced arteriovenous fistula thrombosis compared to patients on sevelamer carbonate powder QD. A total of 12 events occurred in 8 [5.7%] sevelamer carbonate powder QD patients and 19 events occurred in 13 [18.1%] sevelamer hydrochloride tablet TID patients. However, when all of the similar medical concepts in the SOC Injury, Poisoning and Procedural Complications are evaluated as a whole, there was no difference between the treatment regimens with regard to arteriovenous fistula problems.

Treatment-emergent AEs were also analysed for the following subgroups: males, females, African Americans, Non-African Americans, < 65 years of age, and ≥ 65 years of age. Differences in frequency between subgroups were noted for the following adverse events (by MedDRA preferred term): muscle spasms, oral administration complication, nausea, vomiting, stomach discomfort, and constipation. In depth review of these adverse events revealed that patients who experienced these adverse events had a medical history of the event or a pre-existing condition that pre-disposed them to the event. Furthermore, the events were all mild or moderate in intensity, and the majority of patients recovered without treatment, intervention or discontinuation of study medication.



Thus, the analysis of AEs by subgroup did not identify any new safety issues and indicates that AEs reported during the study were not influenced by gender, race or age. Please see GD3-199-301 CSR Table 14.3.1.1.2, Table 14.3.1.1.3, Table 14.3.1.1.4, Table 14.3.1.1.5, Table 14.3.1.1.6 and Table 14.3.1.1.7 for these results.

Treatment Emergent Adverse Events by Intensity in GD3-199-301

The majority of treatment-emergent AEs were mild or moderate in intensity. Based on the most severe occurrence of a particular treatment-emergent AE, 43 (30.5%) sevelamer carbonate powder QD patients and 17 (23.6%) sevelamer hydrochloride tablet TID patients experienced at least one mild treatment-emergent AE; 59 (41.8%) sevelamer carbonate powder QD patients and 30 (41.7%) sevelamer hydrochloride tablet TID patients experienced at least one moderate treatment-emergent AE; and 22 (15.6%) sevelamer carbonate powder QD patients and 19 (26.4%) sevelamer hydrochloride tablet TID patients experienced at least one severe AE.

The majority of severe treatment emergent events occurred in a single patient each during the randomised treatment period. The majority of severe events in the sevelamer carbonate powder QD group coded to the SOC Infections and Infestations. Severe AEs occurring in more than one patient in the sevelamer carbonate powder QD group included (by MedDRA preferred term): pneumonia [3 (2.1%) patients], catheter sepsis [2 (1.4%) patients], staphylococcal bacteraemia [2 (1.4%) patients], arteriovenous graft thrombosis [2 (1.4%) patients], hyperkalaemia [2 (1.4%) patients], and dyspnoea [2 (1.4%) patients]. The majority of severe events in the sevelamer hydrochloride tablet TID group coded to the SOC Vascular Disorders. Severe AEs occurring in more than one patient in the sevelamer hydrochloride tablet TID group included (by MedDRA preferred term): cardiac failure congestive [4 (5.6%) patients], coronary artery disease [2 (2.8%) patients], hyperkalaemia [2 (2.8%) patients] and hypertension [2 (2.8%) patients]. Two patients on sevelamer carbonate powder QD experienced a severe gastrointestinal event (MedDRA preferred terms: abdominal pain upper and diarrhoea) and one patient on sevelamer hydrochloride tablets TID experienced a severe gastrointestinal event (MedDRA preferred term: gastrointestinal haemorrhage).



Treatment Related Adverse Events in GD3-199-301

The percent of patients experiencing treatment related AEs was greater in the sevelamer carbonate powder QD group. There were a total of 72 treatment related events in 43 (30.5%) sevelamer carbonate powder QD patients and 26 treatment related events in 13 (18.1%) sevelamer hydrochloride tablet TID patients. Two patients experienced treatment related AEs that were severe in intensity. One patient who experienced severe diarrhoea in the sevelamer carbonate powder group and one patient who experienced severe hypocalcaemia in the sevelamer hydrochloride tablet group were assessed as treatment related by the Investigator. A summary of the treatment related AEs occurring in > 2% patients by MedDRA preferred term is presented in Table 2.7.4-14.



Table 2.7.4-14:
Treatment Emergent Adverse Events Possibly, Probably or Definitely Related
Occurring in >2% of Patients in GD3-199-301 (Safety Set)

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Treatment related Adverse Event	72	43 (30.5)	26	13 (18.1)
Gastrointestinal Disorders	58	32 (22.7)	18	8 (11.1)
Diarrhoea	17	12 (8.5)	5	4 (5.6)
Nausea	18	14 (9.9)	4	2 (2.8)
Vomiting	8	8 (5.7)	1	1 (1.4)
Constipation	1	1 (0.7)	4	4 (5.6)
Stomach Discomfort	5	3 (2.1)	1	1 (1.4)
General Disorders and Administration Site Conditions	6	6 (4.3)	0	0 (0)
Oral Administration Complication	6	6 (4.3)	0	0 (0)
Investigations	2	2 (1.4)	3	2 (2.8)
Carbon Dioxide Decreased	1	1 (0.7)	3	2 (2.8)
Metabolism and Nutrition Disorders	5	5 (3.5)	4	3 (4.2)
Hypocalcaemia	1	1 (0.7)	3	2 (2.8)

Data source: GD3-199-301 CSR Table 14.3.1.4.1, Listing 16.2.7.1.

Treatment related AEs were most frequently seen in the SOC of Gastrointestinal Disorders. The most frequently occurring (> 4% patients) treatment related AEs coding to the SOC of Gastrointestinal Disorders were (by MedDRA preferred term): diarrhoea (17 events in 12 [8.5%] sevelamer carbonate powder QD patients and 5 events in 4 [5.6%] sevelamer hydrochloride tablet TID patients), nausea (18 events in 14 [9.9%] sevelamer carbonate powder QD patients and 4 events in 2 [2.8%] sevelamer hydrochloride tablet TID patients), vomiting (8 events in 8 [5.7%] sevelamer carbonate powder QD patients and 1 event in 1 [1.4%] sevelamer hydrochloride tablet TID patient), and constipation (1 event in 1 [0.7%] sevelamer carbonate powder QD patient and 4 events in 4 [5.6%] sevelamer hydrochloride tablet TID patients). The most frequently occurring (>4% patients) treatment related AE coding to the SOC General Disorders and



Administrative Site Conditions was (by MedDRA preferred term): oral administration complication (6 events in 6 [4.3%] sevelamer carbonate powder QD patients and no events in the sevelamer hydrochloride tablet TID patients).

Treatment emergent AEs possibly or probably related to the study drug were also analysed for the following subgroups: males, females, African Americans, Non-African Americans, < 65 years of age, and ≥ 65 years of age. Differences in frequency between subgroups were noted for the following treatment related adverse events (by MedDRA preferred term): oral administration complication, nausea, vomiting, and constipation. In-depth review of these AEs revealed that patients who experienced these adverse events had a medical history of the event or a pre-existing condition that pre-disposed them to the event. Furthermore, the events were all mild or moderate in intensity, and the majority of patients recovered without sequelae. The analysis of treatment related AEs by subgroup did not identify any new safety issues and indicate that AEs reported during this study were not influenced by gender, race or age. Please see GD3-199-301 CSR Table 14.3.1.4.2, Table 14.3.1.4.3, Table 14.3.1.4.4, Table 14.3.1.4.5, Table 14.3.1.4.6 and Table 14.3.1.4.7 for these results.

2.7.4.2.1.1 Common Adverse Events

SVCARB00205 and GD3-163-201 were cross-over design studies comparing sevelamer carbonate dosed TID with sevelamer hydrochloride tablets TID. GD3-199-301 was a 24 week parallel design study comparing sevelamer carbonate powder dosed QD with sevelamer hydrochloride tablets TID. A comparative assessment of the adverse events that occurred during sevelamer carbonate treatment in SVCARB00205 and GD3-163-201 will be presented in this section. Since the dosing regimen and treatment duration (24 weeks) in GD3-199-301 (QD) were different than the dosing regimen (TID) and treatment duration employed in studies, SVCARB00205 (4 weeks) and GD3-163-201 (8 weeks), that will be used to support the posology in the package insert, GD3-199-301 is not included in the comparative assessment.

Due to differences in treatment duration in SVCARB00205 and GD3-163-201, treatment emergent adverse events assessed as common across studies were defined as the following:



- Events occurring in $\geq 5\%$ sevelamer carbonate patients for treatment emergent adverse events.
- Events in ≥ 2 sevelamer carbonate patients for treatment related adverse events.

Table 2.7.4-15 presents an overview of the number of patients with treatment emergent adverse events, treatment emergent severe events, and related treatment emergent adverse events in SVCARB00205 and GD3-163-201.

**Table 2.7.4-15:
Overview of the Number of Patients with Treatment Emergent Adverse Events
During Sevelamer Carbonate Treatment in SVCARB00205 and GD3-163-201
(Safety Set)**

	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=73)
	N (%)	N (%)
Any Treatment Emergent AEs	10 (32.3)	60 (82.2)
Treatment Emergent Severe AEs	1 (3.2)	5 (6.8)
Related Treatment Emergent AEs	3 (9.7)	12 (16.4)

Data source: SVCARB00205 CSR Table 14.3.1.3, Table 14.3.1.4, and Table 14.3.1.5;
GD3-163-201 CSR Table 14.3.1.3, Table 14.3.1.4 and Table 14.3.1.5.

2.7.4.2.1.1.1 Treatment Emergent Adverse Events

A summary of the adverse events occurring in $\geq 5\%$ patients during sevelamer carbonate treatment in patients enrolled in SVCARB00205 and GD3-163-201 is presented in Table 2.7.4-16 by MedDRA preferred term. There were 21 events in 10 (32.2%) patients in SVCARB00205 and 195 events in 60 (82.2%) patients in GD3-163-201.



Table 2.7.4-16:
**AEs Occurring in $\geq 5\%$ of Patients During Sevelamer Carbonate Treatment in
 SVCARB00205 or GD3-163-201[†] (Safety Set)**

System Organ Class Preferred Term	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)		GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=73)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Adverse Event	21	10 (32.3)	195	60 (82.2)
Cardiac Disorders	0	0 (0)	6	4 (5.5)
Gastrointestinal Disorders	5	4 (12.9)	25	15 (20.5)
Nausea	2	2 (6.5)	9	7 (9.6)
Vomiting	1	1 (3.2)	7	6 (8.2)
General Disorders and Administration Site Conditions	1	1 (3.2)	14	10 (13.7)
Infections and Infestations	2	2 (6.5)	24	19 (26.0)
Urinary Tract Infection	1	1 (3.2)	6	6 (8.2)
Injury, Poisoning and Procedural Complications	0	0 (0)	26	16 (21.9)
Arteriovenous Fistula Site Complication	0	0 (0)	6	5 (6.8)
Arteriovenous Fistula Site Haemorrhage	0	0 (0)	5	4 (5.5)
Metabolism and Nutrition Disorders	0	0 (0)	13	12 (16.4)
Hypercalcaemia	0	0 (0)	7	6 (8.2)
Musculoskeletal and Connective Tissue Disorders	1	1 (3.2)	18	12 (16.4)
Muscle Spasms	0	0 (0)	4	4 (5.5)
Nervous System Disorders	1	1 (3.2)	12	12 (16.4)
Dizziness	0	0 (0)	6	6 (8.2)
Psychiatric Disorders	0	0 (0)	5	5 (6.8)
Respiratory, Thoracic and Mediastinal Disorders	0	0 (0)	16	12 (16.4)
Cough	0	0 (0)	4	4 (5.5)



Table 2.7.4-16:
AEs Occurring in $\geq 5\%$ of Patients During Sevelamer Carbonate Treatment in
SVCARB00205 or GD3-163-201[†] (Safety Set)

System Organ Class Preferred Term	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)		GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=73)	
	Events N	Patients n (%)	Events N	Patients n (%)
Skin and Subcutaneous Tissue Disorders	2	2 (6.5)	5	4 (5.5)
Vascular Disorders	2	2 (6.5)	5	5 (6.8)

Data Source: SVCARB00205 CSR Table 14.3.1.3; GD3-163-201 CSR Table 14.3.1.3

[†] Adverse events coded to the System Organ Class Investigations are not included in this table. Please refer to Section 2.7.4.3.3.2 for a discussion of these events.

In SVCARB00205, the most frequently reported AEs coded to the SOC Gastrointestinal Disorders [5 events in 4 (12.9%) patients]. In GD3-163-201, the most frequently reported AEs coded to the SOCs Infections and Infestations [24 events in 19 (26.0%) patients], Injury, Poisoning and Procedural Complications [26 events in 16 (21.9%) patients] and Gastrointestinal Disorders [25 events in 15 (20.5%) patients]. The most frequently occurring gastrointestinal adverse events were (by MedDRA preferred term): nausea [2 events in 2 (6.5%) patients in SVCARB00205 and 9 events in 7 (9.6%) patients in GD3-163-201] and vomiting [1 event in 1 (3.2%) patient in SVCARB00205 and 7 events in 6 (8.2%) patients in GD3-163-201].

There was a higher frequency of treatment emergent adverse events in GD3-163-201 than SVCARB00205. The duration of treatment with sevelamer carbonate in GD3-163-201 was four weeks longer than SVCARB00205 therefore the patient exposure and time on sevelamer carbonate tablets was longer. Adverse events coding to the SOC Infections and Infestations were more frequent in GD3-163-201 than in SVCARB00205 (26.0% vs. 6.5%). The higher frequency of infections in GD3-163-201 can be attributed to the increased frequency of urinary tract infections. Patients who experienced urinary tract infections in GD3-163-201 had a history of urinary tract infections or pre-existing conditions that pre-disposed patients to develop a urinary tract infection.



Overall, common adverse events experienced were not unexpected and were consistent with patients' underlying renal disease and CKD status. In general, the adverse events experienced during sevelamer carbonate powder treatment and sevelamer carbonate tablet treatment were similar in nature.

2.7.4.2.1.1.2 Treatment Emergent Adverse Events by Intensity

In both SVCARB00205 and GD3-163-201 the majority of adverse events were mild or moderate in intensity during sevelamer carbonate treatment. In SVCARB00205, the one severe AE reported during the randomised treatment period was an event of chest pain during sevelamer carbonate powder treatment that was considered by the investigator to be remote/unlikely related to study treatment. The patient discontinued study treatment due to the event of chest pain.

In GD3-163-201, a total of 5 (6.8%) patients experienced a severe adverse event during sevelamer carbonate tablet treatment. Severe adverse events occurred in a single patient each with the exception of (by MedDRA preferred term) coronary artery disease [2 (2.7%) patients]. All severe events were assessed by the investigator as not related or unlikely related to study treatment.

2.7.4.2.1.1.3 Treatment Related Adverse Events

A summary of the treatment related adverse events occurring in ≥ 2 patients during sevelamer carbonate powder treatment in SVCARB00205 and sevelamer carbonate tablet treatment in GD3-163-201 is presented in Table 2.7.4-17 by MedDRA preferred term. The overall frequency of treatment related adverse events was slightly higher in the GD3-163-201 than in SVCARB00205. There were 20 treatment related events in 12 (16.4%) patients in GD3-163-201 and 4 treatment related events in 3 (9.7%) patients in SVCARB00205.



Table 2.7.4-17:
Treatment Emergent Adverse Events Possibly, Probably, or Definitely Related to Sevelamer Carbonate in ≥ 2 Patients in SVCARB00205 or GD3-163-201[†]

System Organ Class Preferred Term	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)		GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=73)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any Treatment related Adverse Event	4	3 (9.7)	20	12 (16.4)
Gastrointestinal Disorders	4	3 (9.7)	9	6 (8.2)
Nausea	2	2 (6.5)	2	2 (2.7)
Vomiting	1	1 (3.2)	2	2 (2.7)
Metabolism and Nutrition Disorders	0	0 (0)	2	2 (2.7)

Data source: SVCARB00205 CSR Table 14.3.1.4; GD3-163-201 CSR Table 14.3.1.4 and Listing 16.2.6.1.

[†] Adverse events coded to the System Organ Class Investigations are not included in this table. Please refer to Section 2.7.4.3.3.2 for a discussion of these events.

The most frequently occurring treatment related adverse event in both studies were (by MedDRA preferred term) nausea (2 events in 2 [6.5%] patients in SVCARB00205 and 2 events in 2 [2.7%] patients in GD3-163-201) and vomiting (1 event in 1 [3.2%] patients in SVCARB00205 and 2 events in 2 [2.7%] patients in GD3-163-201). Overall, common treatment related adverse events experienced in both studies were consistent with previous experience with sevelamer.

2.7.4.2.1.1.4 Overall Conclusion of the Common Adverse Events

In the comparative assessment, common adverse events coding to the SOC Gastrointestinal Disorders in SVCARB00205 and GD3-163-201 included nausea and vomiting. Overall, common adverse events experienced in both studies were consistent with previous experience with sevelamer.

2.7.4.2.1.2 Deaths

Deaths that occurred during SVCARB00205, GD3-163-201 and GD3-199-301 will be discussed individually. As all three studies compared sevelamer carbonate and sevelamer hydrochloride, the discussion of these studies will include the deaths that occurred during



both the sevelamer carbonate and sevelamer hydrochloride treatment periods. In Section 2.7.4.2.1.2.4, Comparative Assessment of Deaths, a listing of deaths occurring in SVCARB00205, GD3-163-201, and GD3-199-301 in patients exposed to sevelamer carbonate treatment is also provided.

2.7.4.2.1.2.1 Deaths in SVCARB00205

No patients died during the period from Screening through to the end of the 1-week Follow-up Period. During the 30-day post-completion period, one patient (Patient 0521) experienced an SAE of brain stem haemorrhage with an outcome of death. The patient, a 64 year old male with medical history significant for type II diabetes, hypertension, nephrolithiasis, peripheral vascular disease, and dyslipidaemia, had previously discontinued study treatment due to an SAE of chest pain (considered remote/unlikely related to study treatment) that occurred 4 days after starting sevelamer carbonate powder treatment (the patient had completed the sevelamer hydrochloride tablet Run-In and randomised treatment periods). Eight days after starting sevelamer carbonate powder, the patient withdrew from the study per his own request. Eight days after withdrawing from the study, the patient was brought unconscious to hospital and a computerised tomography scan of the head showed a brain stem bleed (MedDRA preferred term: brain stem haemorrhage). The patient died the same day. The investigator considered the event of brain stem haemorrhage with an outcome of death as not related to study treatment.

2.7.4.2.1.2.2 Deaths in GD3-163-201

Two patients died during GD3-163-201, one patient during each treatment regimen. The first patient (009-003), a 73 year old female with a medical history significant for type II diabetes, myocardial infarction resulting in ventricular tachycardia with reperfusion, angina, peripheral vascular disease, stroke, hypertensive cardiovascular disease, arteriosclerotic heart disease, and left ventricular hypertrophy, died of complications of worsening coronary artery disease approximately one month after starting sevelamer carbonate tablets. All SAEs experienced by this patient, including the event of worsening coronary artery disease with an outcome of death, were assessed by the investigator as not related to sevelamer carbonate tablets.



The second patient (010-001), a 40 year old female with a medical history significant for diabetes, hypertension, and hyperlipidaemia 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. All SAEs experienced by this patient, including the event of complications of diabetes mellitus with an outcome of death, were assessed by the investigator as not related to sevelamer hydrochloride. The patient was not exposed to sevelamer carbonate tablets during the study.

2.7.4.2.1.2.3 Deaths in GD3-199-301

A total of 2 (1.4%) sevelamer carbonate powder QD patients and 4 (5.6%) sevelamer hydrochloride tablet TID patients died during the randomised treatment period.

Table 2.7.4-18 provides a list of the patients who died during the randomised treatment period. All treatment-emergent deaths were assessed as not related to the study treatment by the investigators. The causes of death were all consistent with the patients' underlying renal disease and CKD status.

**Table 2.7.4-18:
Patient Deaths in GD3-199-301**

Treatment Group	Patient ID	Cause of Death	Relationship to Study Treatment
Sevelamer carbonate powder QD	505113	Cardiac arrest, cause unknown	Not Related
	516116	Withdrawal of renal replacement therapy	Not Related
Sevelamer hydrochloride tablets TID	505121	Cardiac arrest, cause unknown	Not Related
	508132	Septic shock	Not Related
		Staphylococcal pneumonia	Not Related
		Hypertensive cardiovascular disease	Not Related
510118	Septicaemia	Not Related	
514108	Intracranial bleed	Not Related	

Data Source: GD3-199-301 CSR Listing 16.2.7.2.

One additional patient (529-103) died approximately 10 weeks after discontinuing from the study. This event was reported to Genzyme and captured in the SAE database even though it occurred after the 30-day follow-up period was complete. Patient 529103 was a



75 year old female with CKD on haemodialysis with a medical history significant for diabetes mellitus, hypertension, congestive heart failure, and history of smoking. The patient was randomised to sevelamer carbonate powder QD, but discontinued from the study due to a prolonged hospitalisation for congestive heart failure. Approximately 10 weeks later the patient died. The primary cause of death was reported as cardiopulmonary arrest. The intensity of the cardiopulmonary arrest was reported as severe. The relationship between sevelamer carbonate and the adverse event cardiopulmonary arrest was reported as not related by the investigator.

2.7.4.2.1.2.4 Comparative Assessment of Deaths

A listing of deaths occurring in SVCARB00205, GD3-163-201 and GD3-199-301 in patients exposed to sevelamer carbonate is provided in Table 2.7.4-19. Overall, a total of 5 (2.0%) deaths occurred among 245 patients exposed to sevelamer carbonate. None of the deaths was assessed by the investigator to be related to sevelamer carbonate and all were considered secondary to pre-existing co-morbid conditions. The frequency of deaths and nature of deaths is similar to previous clinical trials with sevelamer.



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**Table 2.7.4-19:
 Deaths in Patients Exposed to Sevelamer Carbonate**

Study Number	Patient ID	Age/ Sex	Max Prescribed Daily Dose (g)	Duration of Exposure	Cause of Death	Relationship to Sevelamer Carbonate	Other Medical Conditions	Location of Narrative Description
SVCARB00205	0521	64 / M	2.4	8 days	Brain stem haemorrhage	Not Related	CKD on haemodialysis, type II diabetes, hypertension, nephrolithiasis, peripheral vascular disease, and dyslipidaemia	SVCARB00205 (Section 14.3.3)
GD3-163-201	009-003	73 / F	2.4	5 weeks	Worsening coronary artery disease	Not Related	CKD on haemodialysis, Type II diabetes, Myocardial infarction, Angina, Peripheral vascular disease, Stroke, Hypertensive cardiovascular disease, Arteriosclerotic heart disease, Ventricular tachycardia with reperfusion, Left ventricular hypertrophy, Hypertension, Pulmonary hypertension	GD3-163-201 (Section 14.3.3)
GD3-199-301	505113	41 / F	7.2	1 month	Cardiac arrest, cause unknown	Not Related	CKD on haemodialysis, anaemia, diabetes, hypertension, depression, and seizures	GD3-199-301 (Section 14.3.3)

**Table 2.7.4-19:
Deaths in Patients Exposed to Sevelamer Carbonate**

Study Number	Patient ID	Age/ Sex	Max Prescribed Daily Dose (g)	Duration of Exposure	Cause of Death	Relationship to Sevelamer Carbonate	Other Medical Conditions	Location of Narrative Description
GD3-199-301	516116	66 / M	14.4	3.5 months	Withdrawal of renal replacement therapy	Not Related	CKD on haemodialysis, diabetes mellitus type II, left leg cellulitis, hyperparathyroidism, hyperlipidaemia, hypotension, peripheral vascular disease, charcot foot changes, congestive heart failure, coronary artery disease, iron deficiency anaemia, history of smoking, neuropathy, hypercholesterolaemia, hypertension, and renal osteodystrophy	GD3-199-301 (Section 14.3.3)
GD3-199-301	529103	75 / F	4.8	3 months	Cardiopulmonary arrest	Not related	CKD on haemodialysis, diabetes mellitus, hypertension, congestive heart failure, and history of smoking.	GD3-199-301 (Section 14.3.3)

Data Source: SVCARB00205 CSR Section 14.3.3; GD3-163-201 CSR Section 14.3.3; GD3-199-301 CSR Section 14.3.3.



2.7.4.2.1.3 Other Serious Adverse Events

SAEs that occurred during SVCARB00205, GD3-163-201 and GD3-199-301 will be discussed individually. As all three studies compared sevelamer carbonate and sevelamer hydrochloride, the discussion of these studies will include the serious adverse events during both the sevelamer carbonate and sevelamer hydrochloride treatment periods. A comparative summary of SAEs occurring in SVCARB00205 and GD3-163-201 during sevelamer carbonate treatment is also provided.

2.7.4.2.1.3.1 Other Serious Adverse Events in SVCARB00205

In SVCARB00205, the frequency of SAEs was low in each treatment regimen during the randomised treatment periods: 2 events in 2 (6.5%) patients during sevelamer carbonate powder TID treatment and 2 events in 1 (3.6%) patient during sevelamer hydrochloride tablet TID treatment. Table 2.7.4-20 displays all treatment emergent SAEs that occurred during the randomised treatment periods by MedDRA preferred term.

**Table 2.7.4-20:
Serious Adverse Events Occurring in Patients During the Randomised
Treatment Periods in SVCARB00205 (Safety Set)**

System Organ Class Preferred Term	Sevelamer Carbonate Powder TID (N=31)		Sevelamer Hydrochloride Tablets TID (N=28)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any SAE	2	2 (6.5)	2	1 (3.6)
General Disorders and Administration Site Conditions	1	1 (3.2)	2	1 (3.6)
Chest pain	1	1 (3.2)	0	0
Catheter related complication	0	0	2	1 (3.6)
Infections and Infestations	1	1 (3.2)	0	0
Catheter sepsis	1	1 (3.2)	0	0

Data Source: SVCARB00205 CSR Table 14.3.2.2.

The SAEs (MedDRA preferred term) of catheter-related complication (both events in one individual patient) and catheter sepsis were considered by the investigator to be of moderate intensity and not related to study treatment. The SAE of chest pain was



considered by the investigator to be of severe intensity and remote/unlikely related to study treatment; the patient was discontinued from the study due to the event.

SAEs starting or worsening during the randomised treatment periods were also analysed for the following demographic subgroups: males and females, Blacks and other races, < 65 years of age and ≥ 65 years of age. Interpretation of the data is limited due to the low frequency of SAEs during the study and the small number of patients in the subgroups, but in general the results showed that the SAEs occurring during the study were not influenced by gender, race or age. Please see SVCARB00205 CSR Table 14.3.2.3.1.1, Table 14.3.2.3.1.2, Table 14.3.2.3.2.1, Table 14.3.2.3.2.2, Table 14.3.2.3.3.1 and Table 14.3.2.3.3.2.

2.7.4.2.1.3.2 Other Serious Adverse Events in GD3-163-201

A similar proportion of patients in each treatment regimen experienced serious adverse events during the randomised treatment period: 17 events in 8 (11.0%) patients during sevelamer carbonate tablet treatment and 17 events in 11 (14.1%) patients during sevelamer hydrochloride tablet treatment. SAEs occurring in ≥ 2% of patients during GD3-163-201 are provided in Table 2.7.4-21.

**Table 2.7.4-21:
Treatment Emergent Serious Adverse Events – ≥2% Patients During the
Randomised Treatment Periods in GD3-163-201 (Safety Set)**

System Organ Class Preferred Term	Sevelamer Carbonate Tablets TID (N=73)		Sevelamer Hydrochloride Tablets TID (N=78)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any SAE	17	8 (11.0)	17	11 (14.1)
Cardiac disorders	5	3 (4.1)	3	2 (2.6)
Coronary artery disease	2	2 (2.7)	2	2 (2.6)
Surgical and medical procedures	0	0	2	2 (2.6)
Renal transplant	0	0	2	2 (2.6)

Data Source: GD3-163-201 CSR Table 14.3.2.2.



The most frequently reported SAE (by preferred term) was coronary artery disease: 2 events in 2 (2.7%) patients during sevelamer carbonate tablet treatment and 2 events in 2 (2.6%) patients during sevelamer hydrochloride tablet treatment. All SAEs during the randomised treatment periods were assessed by the investigator as not related to study treatment.

2.7.4.2.1.3.3 Comparative Assessment of Other Serious Adverse Events in SVCARB00205 and GD3-163-201

A summary of the treatment emergent serious adverse events occurring in ≥ 2 patients during sevelamer carbonate treatment in either SVCARB00205 or in GD3-163-201 is presented in Table 2.7.4-22 by MedDRA preferred term.

The overall frequency of serious adverse events during sevelamer carbonate treatment was lower in SVCARB00205 than in GD3-163-201; there were 17 serious adverse events in 8 (11.0%) patients in GD3-163-201 and 2 serious adverse events in 2 (6.5%) patients in SVCARB00205. The difference in overall frequency of SAEs was likely reflective of the shorter duration of patient exposure in SVCARB00205 than in GD3-163-201.

Overall, the nature of the SAEs were similar.

**Table 2.7.4-22:
Treatment Emergent Serious Adverse Events in ≥ 2 Patients During Sevelamer Carbonate Treatment in SVCARB00205 or GD3-163-201**

System Organ Class Preferred Term	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N=31)		GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N=73)	
	Patients N (%)	Events N	Patients N (%)	Events N
Any SAE	2	2 (6.5)	17	8 (11.0)
Cardiac Disorders	0	0 (0)	5	3 (4.1)
Coronary Artery Disease	0	0 (0)	2	2 (2.7)

Data Source: SVCARB00205 CSR Table 14.3.2.2; GD3-163-201 CSR Table 14.3.2.2.

The serious adverse events reported in both SVCARB00205 and GD3-163-201 were consistent with the known safety profile of sevelamer and with the patients' underlying



renal disease and co-morbidities. All SAEs reported in both studies were assessed by the investigators as not related or remote/unlikely related to sevelamer carbonate treatment.

2.7.4.2.1.3.4 Other Serious Adverse Events in GD3-199-301

In GD3-199-301, a higher percentage of patients in the sevelamer hydrochloride tablet TID group experienced SAEs. There were a total of 85 SAEs in 33 (23.4%) sevelamer carbonate powder QD patients and 72 SAEs in 28 (38.9%) sevelamer hydrochloride tablet TID patients. In general, SAEs coded to similar SOCs during sevelamer carbonate powder QD and sevelamer hydrochloride tablets TID treatment. In both treatment groups, the highest frequency of treatment emergent SAEs occurred in the MedDRA SOCs of Infections and Infestations [19 SAEs in 15 (10.6%) sevelamer carbonate powder QD patients and 12 SAEs in 11 (15.3%) sevelamer hydrochloride tablet TID patients] and Cardiac Disorders [17 SAEs in 9 (6.4%) of sevelamer carbonate powder QD patients and 16 SAEs in 9 (12.5%) sevelamer hydrochloride tablet TID patients]. SAEs occurring in $\geq 2\%$ of patients are provided in Table 2.7.4-23.



**Table 2.7.4-23:
Serious Adverse Events in $\geq 2\%$ Patients in Either Treatment Group
in GD3-199-301 (Safety Set)**

System Organ Class Preferred Term	Sevelamer Carbonate Powder QD (N=141)		Sevelamer Hydrochloride Tablets TID (N=72)	
	Events N	Patients n (%)	Events N	Patients n (%)
Any SAE	85	33 (23.4)	72	28 (38.9)
Cardiac Disorders	17	9 (6.4)	16	9 (12.5)
Cardiac Failure Congestive	7	5 (3.5)	7	4 (5.6)
Coronary Artery Disease	1	1 (0.7)	3	3 (4.2)
Atrial Fibrillation	3	3 (2.1)	1	1 (1.4)
Infections and Infestations	19	15 (10.6)	12	11 (15.3)
Pneumonia	6	6 (4.3)	3	3 (4.2)
Injury, Poisoning and Procedural Complications	5	4 (2.8)	7	6 (8.3)
Arteriovenous Fistula Thrombosis	3	2 (1.4)	5	4 (5.6)
Metabolism and Nutrition Disorders	12	8 (5.7)	5	3 (4.2)
Hyperkalaemia	5	4 (2.8)	2	2 (2.8)
Hypoglycaemia	1	1 (0.7)	2	2 (2.8)
Respiratory, Thoracic and Mediastinal Disorders	8	8 (5.7)	3	3 (4.2)
Pulmonary oedema	3	3 (2.1)	1	1 (1.4)
Surgical and Medical Procedures	2	2 (1.4)	3	3 (4.2)
Arteriovenous Fistula Operation	0	0 (0)	2	2 (2.8)
Vascular Disorders	4	4 (2.8)	11	7 (9.7)
Hypertension	1	1 (0.7)	2	2 (2.8)

Data Source: GD3-199-301 CSR Table 14.3.1.2.1 and Listing 16.2.7.2.

The most frequently reported ($> 4\%$ patients) SAEs (by preferred term) were cardiac failure congestive [7 events in 5 (3.5%) sevelamer carbonate powder QD patients and 7 events in 4 (5.6%) sevelamer hydrochloride tablet TID patients], coronary artery disease [1 event in 1 (0.7) sevelamer carbonate powder QD patient and 3 events in 3 (4.2%) sevelamer hydrochloride tablet TID patients], arteriovenous fistula thrombosis



[3 events in 2 (1.4%) sevelamer carbonate powder QD patients and 5 events in 4 (5.6%) sevelamer hydrochloride tablet TID patients] and pneumonia [6 events in 6 (4.3%) sevelamer carbonate powder QD patients and 3 events in 3 (4.2%) sevelamer hydrochloride tablet TID patients].

The majority of treatment emergent SAEs were assessed by the Investigator as not related to the study treatment. One patient experienced an SAE (probable faecal impaction) considered possibly related to sevelamer hydrochloride. The patient, a 54 year old female with CKD on haemodialysis with a medical history significant for constipation, abdominal surgery including Cesarean-section and tubal ligation, hypertension, coronary atherosclerosis, and type II diabetes mellitus was randomised to sevelamer hydrochloride, two 800 mg tablets TID with meals. Approximately 15 weeks after beginning the study treatment, the patient presented to the Emergency Department with a five day history of abdominal pain and abdominal distension without bowel movements. An abdominal x-ray showed considerable stool in the rectal vault, consistent with probable faecal impaction. No evidence of mass or obstruction was observed. The patient was treated with enemas and ketorolac tromethamine, recovered without sequelae and was discharged. Sevelamer hydrochloride was continued. The relationship between sevelamer hydrochloride and the adverse event of probable faecal impaction was reported as possible, per the investigator.

SAEs that occurred during the randomised treatment periods were also analysed for the following subgroups: males, females, African Americans, Non-African American, < 65 years of age, and ≥ 65 years of age. In general, the SAEs seen within each gender, race and age group were similar and consistent with the analysis of the overall population. Please see GD3-199-301 CSR Table 14.3.1.2.2, Table 14.3.1.2.3, Table 14.3.1.2.4, Table 14.3.1.2.5, Table 14.3.1.2.6 and Table 14.3.1.2.7 for these results.

2.7.4.2.1.4 Other Significant Adverse Events

The adverse events that resulted in discontinuation that occurred during SVCARB00205, GD3-163-201 and GD3-199-301 will be discussed individually. As all three studies compared sevelamer carbonate and sevelamer hydrochloride, the discussion of these studies will include the adverse events during both the sevelamer carbonate and sevelamer hydrochloride treatment periods. A comparative summary of adverse events



that resulted in discontinuation occurring in SVCARB00205 and GD3-163-201 during sevelamer carbonate treatment is also provided.

2.7.4.2.1.4.1 Other Significant Adverse Events in SVCARB00205

Three (9.7%) of the 31 randomised patients experienced a total of 4 AEs leading to discontinuation: all 3 patients discontinued during treatment with sevelamer carbonate powder.

Three of the 4 events leading to discontinuation were coded to the Gastrointestinal Disorders SOC: 1 event each of nausea and vomiting in Patient 0310 and 1 event of nausea in Patient 0907. Both events of nausea were of moderate intensity and considered by the investigator to be either possibly or probably related to study treatment. The investigator considered the event of vomiting to be of mild intensity and possibly related to study treatment.

The other event leading to discontinuation was a SAE of chest pain (General Disorders and Administration Site Conditions SOC) in Patient 0521 that was considered by the investigator to be of severe intensity and unlikely related to study treatment.

2.7.4.2.1.4.2 Other Significant Adverse Events in GD3-163-201

No patients discontinued during the sevelamer carbonate tablet treatment period due to an adverse event. A total of 6 (7.7%) randomised patients discontinued due to adverse events during the sevelamer hydrochloride tablet 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 (by MedDRA preferred term): 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 ischaemia occurring in one individual patient during sevelamer hydrochloride treatment. The events of dermatitis allergic and asthenia were assessed as possibly related to sevelamer hydrochloride by the investigator. All other events were assessed as unrelated.



sevelamer carbonate

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2.7.4.2.1.4.3 Comparative Assessment of Other Significant Adverse Events in SVCARB00205 and GD3-163-201

In SVCARB00205, three of the 4 events leading to discontinuation during sevelamer carbonate treatment were gastrointestinal disorders adverse events. In GD3-163-201, no patients discontinued during sevelamer carbonate treatment. The gastrointestinal adverse events resulting in discontinuation in SVCARB00205 were consistent with the known safety profile of sevelamer and with the patients' underlying renal disease and comorbidities.

2.7.4.2.1.4.4 Other Significant Adverse Events in GD3-199-301

A total of 17 (12.0%) sevelamer carbonate powder QD patients and 4 (5.6%) sevelamer hydrochloride tablet TID patients discontinued due to AEs. Five patients in the sevelamer carbonate powder QD group discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), eight patients discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea and rectal bleeding), and four patients discontinued for other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident, and central line infection). All of the oral administration complications and 7 of the 8 gastrointestinal disorders that led to discontinuation were classified as related to study treatment by the Investigators. All four patients in the sevelamer hydrochloride group who discontinued due to an AE did so due to a SAE (cardiac arrest, myocardial infarction, septic shock, intracranial bleed), none of which were classified as related to study treatment by the Investigators. Table 2.7.4-24 provides a list of the patient discontinuations due to AEs.



**Table 2.7.4-24:
Patient Discontinuations Due to Adverse Events During the Randomised
Treatment Period in GD3-199-301 (Safety Set)**

Treatment Group	Patient ID	Reason for Discontinuation (Verbatim Term/ Preferred Term)	Intensity	Relationship to Study treatment
sevelamer carbonate powder QD	501102	Bad taste of study drug/ Oral administration complication	Moderate	Definite
	501107	Gagging when taking study drug/ Oral administration complication	Moderate	Definite
	501113	Nausea related to study drug/ Nausea	Moderate	Definite
	501115	Bad taste of study drug/ Oral administration complication	Moderate	Definite
	502113	Nausea/ Nausea	Mild	Possibly
	505110	Nausea/ Nausea	Mild	Definite
	507102	Gagging on study drug/ Oral administration complication	Mild	Definite
	507113	Worsening hyperphosphataemia/ Hyperphosphataemia	Moderate	Probably
	508120	Bloatedness/ Abdominal distension	Moderate	Definite
	514110	Renal transplant due to CRF Renal failure chronic	Mild	Not Related
	516116	Cerebral vascular accident/ Cerebrovascular accident	Severe	Not Related
	516125	Rectal bleeding/ Rectal haemorrhage	Moderate	Unlikely
	517114	Gagging when taking study drug/ Oral administration complication	Moderate	Definite
518102	Vomiting/ Vomiting	Moderate	Probably	



**Table 2.7.4-24:
Patient Discontinuations Due to Adverse Events During the Randomised
Treatment Period in GD3-199-301 (Safety Set)**

Treatment Group	Patient ID	Reason for Discontinuation (Verbatim Term/ Preferred Term)	Intensity	Relationship to Study treatment
	521103	Patient complained of nausea after drinking study medication/ Nausea	Mild	Definite
	522101	Diarrhoea/ Diarrhoea	Severe	Probably
	526107	S. aureus central venous tunnel infection/ Central line infection	Severe	Not Related
sevelamer hydrochloride tablets TID	505121	Cardiac arrest/ Cardiac arrest	Severe	Not Related
	506104	Non-Q Wave MI/ Myocardial infarction	Severe	Unlikely
	508132	Septic shock/ Septic shock	Severe	Not Related
	514108	Intracranial bleed/ Haemorrhage intracranial	Severe	Not Related

Data source: GD3-199-301 CSR Listing 16.2.7.3.

2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome

The analysis of adverse events by body systems is summarised in Section 2.7.4.2.1. The most relevant organ system for a non-absorbed drug is the gastrointestinal system. Gastrointestinal events are discussed in Section 2.7.4.2.1.

2.7.4.2.2 Narratives

Narratives describing deaths, other SAEs and other significant events are located in clinical study reports for SVCARB00205, GD3-163-201 and GD3-199-301.

2.7.4.3 Clinical Laboratory Evaluations

In the Clinical Laboratory Evaluation Section, a comparative assessment of the laboratory results in SVCARB00205 and GD3-163-201 during sevelamer carbonate treatment will



be provided. Laboratory results for the sevelamer hydrochloride treatment regimens in SVCARB00205 and GD3-163-201 as well as the laboratory results from GD3-199-301 will not be discussed, but can be found in the clinical study reports. There were no clinically meaningful findings in laboratory parameters during the sevelamer hydrochloride regimens in either SVCARB00205 or GD3-163-201. There were also no clinically meaningful findings for either sevelamer carbonate powder or sevelamer hydrochloride tablets in GD3-199-301.

2.7.4.3.1 Laboratory Values Over Time

2.7.4.3.1.1 Serum Chemistry

Table 2.7.4-25 presents the change from baseline to the end of treatment for the serum chemistry results during sevelamer carbonate treatment in SVCARB00205 and GD3-163-201.

There were statistically significant increases in mean serum bicarbonate from baseline to end of study in SVCARB00205 (2.7 mEq/L, $p=0.001$) and GD3-163-201 (1.3 mEq/L, $p<0.001$). There was a statistically significant decrease in mean serum chloride in SVCARB00205 (-2.7 mEq/L; $p<0.001$) and GD3-163-201 (-2.6 mEq/L, $p<0.001$). In both SVCARB00205 and GD3-163-201, the baseline laboratory measurement was taken following a sevelamer hydrochloride run-period.

A statistically significant change was also noted in serum albumin (0.07 g/dL, $p=0.021$) from baseline to end of study in GD3-163-201. This change was not considered clinically meaningful.



**Table 2.7.4-25:
Serum Chemistry Measures During Sevelamer Carbonate Treatment in
SVCARB00205 and GD3-163-201**

Laboratory Parameter Timepoint/Statistics	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N = 31) [Mean ± SD]	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N = 73) [Mean ± SD]
Bicarbonate[†] (mEq/L)		
Baseline	18.0 ± 3.1	21.1 ± 3.8
Final	20.2 ± 2.8	22.4 ± 3.7
Change	2.7 ± 3.7	1.3 ± 4.1
P-value*	0.001	< 0.001
Chloride (mEq/L)		
Baseline	101.9 ± 4.0	102.0 ± 4.4
Final	99.6 ± 3.5	99.4 ± 4.3
Change	-2.7 ± 2.7	-2.6 ± 3.6
P-value*	<0.001	<0.001
Calcium (mg/dL)		
Baseline	9.12 ± 0.92	9.30 ± 0.67
Final	9.09 ± 0.79	9.29 ± 0.53
Change	-0.11 ± 0.49	0.00 ± 0.64
P-value*	0.173	0.402
Albumin (g/dL)		
Baseline	4.09 ± 0.42	3.82 ± 0.31
Final	4.18 ± 0.38	3.89 ± 0.27
Change	0.09 ± 0.24	0.07 ± 0.23
P-value*	0.054	0.021
Glucose (mg/dL)		
Baseline	116.9 ± 108.5	121.8 ± 65.3
Final	118.2 ± 58.2	139.4 ± 83.7
Change	-4.2 ± 90.9	16.2 ± 65.0
P-value*	0.547	0.104
SGOT (AST) (U/L)		
Baseline	17.8 ± 9.2	18.5 ± 10.3
Final	17.9 ± 8.8	19.3 ± 13.6
Change	1.1 ± 4.4	0.6 ± 12.5
P-value*	0.186	0.935



Table 2.7.4-25:
Serum Chemistry Measures During Sevelamer Carbonate Treatment in
SVCARB00205 and GD3-163-201

Laboratory Parameter Timepoint/Statistics	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N = 31) [Mean ± SD]	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N = 73) [Mean ± SD]
SGPT (ALT) (U/L)		
Baseline	14.3 ± 7.7	15.6 ± 10.8
Final	13.9 ± 8.1	16.4 ± 12.6
Change	-0.2 ± 5.4	0.9 ± 10.3
P-value*	0.906	0.846
Alkaline Phosphatase (U/L)		
Baseline	92.5 ± 53.1	118.6 ± 57.0
Final	96.0 ± 45.9	126.3 ± 81.6
Change	0.1 ± 23.8	7.6 ± 45.3
P-value*	0.357	0.165
Sodium (mEq/L)		
Baseline	138.5 ± 2.8	139.5 ± 2.8
Final	138.9 ± 3.0	139.5 ± 2.5
Change	0.7 ± 3.1	0.0 ± 2.5
P-value*	0.383	0.778
Potassium (mEq/L)		
Baseline	4.91 ± 0.62	4.83 ± 0.55
Final	4.93 ± 0.74	4.82 ± 0.61
Change	-0.12 ± 0.94	-0.01 ± 0.57
P-value*	0.486	0.932

Data source: SVCARB00205 CSR: Table 14.3.4.1.2.1, Table 14.3.4.2.1, Table 14.3.4.4.1, Table 14.3.4.5.1, Table 14.3.4.6.1, Table 14.3.4.7, Table 14.3.4.8, Table 14.3.4.9, Table 14.3.4.10.1, and Table 14.3.4.11.1; GD3-163-201 CSR: Table 14.3.4.2.1, Table 14.3.4.4, Table 14.3.4.6.1, Table 14.3.4.7.1, Table 14.3.4.8, Table 14.3.4.9, Table 14.3.4.10, Table 14.3.4.11, Table 14.3.4.12, and Table 14.3.4.13.

* P-values are from Wilcoxon signed rank test.

† Serum carbon dioxide was measured in GD3-163-201. This will be represented as bicarbonate in this report to represent the similar medical concept of serum bicarbonate and serum carbon dioxide.

Note: The number of observations varies in the statistics shown. Please refer to the CSR tables for details.
 ND: not done



2.7.4.3.1.2 Haematology Measures

Table 2.7.4-26 presents the change from baseline to the end of treatment for the haematology measures during sevelamer carbonate treatment in SVCARB00205 and GD3-163-201. The differential results are included in the individual study reports.

There were statistically significant changes in haemoglobin in both SVCARB00205 (mean change = -0.66 g/dL; $p=0.037$) and GD3-163-201 (mean change = 0.33 g/dL; $p=0.050$). In SVCARB00205, statistically significant decreases were also observed in the levels of white blood cells (mean change = -0.80 thou/mcL, $p=0.037$), red blood cells (mean change = -0.22 mill/mcL, $p=0.027$), and haematocrit (mean change = -2.22% , $p=0.018$).

The changes in the haematology measures were not considered clinically meaningful. There were no statistically significant changes in the other haematology measures in either SVCARB00205 or GD3-163-201.

**Table 2.7.4-26:
Haematology Measures During Sevelamer Carbonate Treatment in SVCARB00205
and GD3-163-201**

Laboratory Parameter Timepoint/Statistics	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder QD (N = 31) [Mean \pm SD]	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N = 73) [Mean \pm SD]
White Blood Cells (thou/mcL)		
Baseline	7.30 \pm 1.76	6.73 \pm 2.07
Final	6.32 \pm 1.66	6.46 \pm 1.86
Change	-0.80 ± 1.52	0.02 ± 1.38
P-value*	0.037	0.941
Red Blood Cells (mill/mcL)		
Baseline	3.78 \pm 0.51	3.80 \pm 0.51
Final	3.45 \pm 0.47	3.89 \pm 0.51
Change	-0.22 ± 0.41	0.09 ± 0.52
P-value*	0.027	0.136



**Table 2.7.4-26:
Haematology Measures During Sevelamer Carbonate Treatment in SVCARB00205
and GD3-163-201**

Laboratory Parameter Timepoint/Statistics	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder QD (N = 31) [Mean ± SD]	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N = 73) [Mean ± SD]
Haemoglobin (g/dL)		
Baseline	11.78 ± 1.22	11.92 ± 1.23
Final	10.87 ± 1.44	12.21 ± 1.36
Change	-0.66 ± 1.33	0.33 ± 1.46
P-value*	0.037	0.050
Haematocrit (%)		
Baseline	35.68 ± 3.58	36.57 ± 4.17
Final	32.69 ± 4.37	37.01 ± 4.22
Change	-2.22 ± 4.23	0.59 ± 4.84
P-value*	0.018	0.274
Platelet Count (/cu mm)		
Baseline	229241 ± 67629	231672 ± 63702
Final	228391 ± 91556	226338 ± 67245
Change	773 ± 33868	3965 ± 48426
P-value*	0.875	0.155

Data source: SVCARB00205 CSR: Table 14.3.4.14.1, Table 14.3.4.15.1, Table 14.3.4.16.1, Table 14.3.4.17.1, and Table 14.3.4.18.1; GD3-163-201 CSR: Table 14.3.4.16, Table 14.3.4.17, Table 14.3.4.18, Table 14.3.4.19 and Table 14.3.4.20.

* P-values are from Wilcoxon signed rank test.

Note: The number of observations varies in the statistics shown. Please refer to the CSR tables for details.

2.7.4.3.1.3 Renal Function Measures

Table 2.7.4-27 presents the change from baseline to the end of treatment for the renal function measures during sevelamer carbonate treatment in SVCARB00205 and GD3-163-201.

There were statistically significant changes in mean serum BUN in both SVCARB00205 (mean change = -7.3 mg/dL; p=0.005) and GD3-163-201 (mean change = 4.6 mg/dL; p<0.001). There were statistically significant changes in mean serum creatinine in both



SVCARB00205 (mean change = -0.86 mg/dL; p=0.002) and GD3-163-201 (mean change = 0.33 mg/dL; p=0.001). The changes in renal function measures were not considered clinically meaningful.

Table 2.7.4-27:
Renal Function Measures During Sevelamer Carbonate Treatment in
SVCARB00205 and GD3-163-201

Laboratory Parameter Timepoint/Statistics	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder QD (N = 31) [Mean ± SD]	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N = 73) [Mean ± SD]
BUN (mg/dL)		
Baseline	58.9 ± 16.5	48.1 ± 13.2
Final	53.6 ± 16.3	52.1 ± 14.9
Change	-7.3 ± 20.0	4.6 ± 11.3
P-value*	0.005	<0.001
Creatinine (mg/dL)		
Baseline	11.38 ± 3.31	9.06 ± 2.73
Final	10.67 ± 3.13	9.43 ± 2.72
Change	-0.86 ± 1.47	0.33 ± 1.09
P-value*	0.002	0.001

Data source: SVCARB00205 CSR: Table 14.3.4.12.1 and Table 14.3.4.13.1; GD3-163-201 CSR: Table 14.3.4.14 and Table 14.3.4.15.

* P-values are from Wilcoxon signed rank test.

Note: The number of observations varies in the statistics shown. Please refer to the CSR tables for details.

2.7.4.3.1.4 Vitamin D and iPTH

Table 2.7.4-28 presents the change from baseline to the end of treatment for the vitamin D and iPTH during sevelamer carbonate treatment in SVCARB00205 and GD3-163-201.

There was a statistically significant increase in iPTH (38 pg/mL, p<0.001) in GD3-163-201. This change was not considered clinically meaningful. There were no statistically significant changes in the vitamin D measures in either SVCARB00205 or GD3-163-201.



**Table 2.7.4-28:
Vitamin D and iPTH During Sevelamer Carbonate Treatment in SVCARB00205
and GD3-163-201**

Laboratory Parameter Timepoint/Statistics	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder QD (N = 31) [Mean ± SD]	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N = 73) [Mean ± SD]
iPTH(pg/mL)[†]		
Baseline	291	245
Final	390	297
Change	30	38
P-value*	0.272	<0.001
25 Hydroxyvitamin D (ng/mL)		
Baseline	21.6 ± 13.1	30.3 ± 19.4
Final	19.1 ± 11.6	32.1 ± 21.0
Change	-2.0 ± 6.3	-1.0 ± 13.5
P-value*	0.170	0.514
1,25 Dihydroxyvitamin D (pg/mL)		
Baseline	24.4 ± 11.5	29.4 ± 11.0
Final	28.9 ± 19.0	28.4 ± 12.0
Change	4.2 ± 13.7	-1.5 ± 12.5
P-value*	0.156	0.536

Data source: SVCARB00205 CSR: Table 14.3.4.3.1, Table 14.3.4.24.1 and Table 14.3.4.25.1;
GD3-163-201 CSR: Table 14.3.4.5.1, Table 14.3.4.30.2 and Table 14.3.4.31.

* P-values are from Wilcoxon signed rank test.

† iPTH is presented as median

Note: The number of observations varies in the statistics shown. Please refer to the CSR tables for details.

2.7.4.3.2 Laboratory Values Over Time Summary and Discussion

In both SVCARB00205 and GD3-163-201, fluctuations in laboratory parameters were representative of co-morbidities in patients with CKD. There were no clinically significant changes in safety laboratory measures during sevelamer carbonate treatment in either SVCARB00205 or GD3-163-201. Statistically significant increases in serum bicarbonate and decreases in serum chloride levels were observed during treatment with sevelamer carbonate in both SVCARB00205 and GD3-163-201. Sevelamer carbonate is an anion exchange resin in which carbonate serves as the anion. The carbonate provides



alkali that may mitigate the potential risk of metabolic acidosis, a common clinical complication observed in the CKD population who are predisposed to fluctuations in acid-base status.

2.7.4.3.3 Clinically Significant Laboratory Changes in Individual Patients

Clinically significant laboratory changes in individual patients that occurred during SVCARB00205, GD3-163-201 and GD3-199-301 will be discussed individually. As all three studies compared sevelamer carbonate and sevelamer hydrochloride, the discussion of these studies will include the clinically significant laboratory changes in individual patients that occurred during both the sevelamer carbonate and sevelamer hydrochloride treatment periods. A comparative summary of clinically significant laboratory changes in individual patients occurring in SVCARB00205 and GD3-163-201 during sevelamer carbonate treatment is also provided.

2.7.4.3.3.1 Clinically Significant Laboratory Changes in Individual Patients in SVCARB00205

Individual patient changes that were assessed as clinically significant by the investigator were to be captured as AEs. The frequency of clinically significant laboratory changes recorded as AEs during the randomised treatment periods was low with a total of 4 events reported in 4 patients in the Safety Set: 1 event of haemoglobin decreased in 1 (3.2%) patient during treatment with sevelamer carbonate powder; and 1 event of anaemia (verbatim term: symptomatic anaemia, tired [Hb 8.6]) in 1 (3.6%) patient, 1 event of blood calcium decreased in 1 (3.6%) patient, and 1 event of hypocalcaemia in 1 (3.6%) patient during treatment with sevelamer hydrochloride tablets.

These events were of mild or moderate intensity and considered by the investigator to be either not related or remote/unlikely related to study treatment. No consistent pattern or trends were observed and the AEs appear to represent isolated fluctuations in laboratory values.



2.7.4.3.3.2 Clinically Significant Laboratory Changes in Individual Patients in GD3-163-201

During the randomised treatment periods, the frequency of patients experiencing adverse events in the SOC Investigations was similar between treatment regimens: 19 events in 14 (19.2%) patients during sevelamer carbonate treatment and 17 events in 13 (16.7%) patients during sevelamer hydrochloride treatment.

Adverse events in the SOC Investigations that were assessed as treatment related by the investigators included (by MedDRA preferred term): Carbon dioxide decreased (4 events in 4 [5.5%] patients during sevelamer carbonate treatment and 5 events in 4 [5.1%] patients during sevelamer hydrochloride treatment); Blood triglycerides increased (2 events in 2 [2.7%] patients during sevelamer carbonate treatment and 1 event in 1 [1.3%] patient during sevelamer hydrochloride treatment); Blood bicarbonate decreased (1 event in 1 [1.4%] patient during sevelamer carbonate treatment and 2 events in 2 [2.6%] patients during sevelamer hydrochloride treatment); Blood parathyroid hormone increased (1 event in 1 [1.4%] patient during sevelamer carbonate treatment and 2 events in 2 [2.6%] patients during sevelamer hydrochloride treatment).

A review of the reported treatment related adverse events coding to the MedDRA SOC Investigations revealed that all but two of the events were reported by a single investigative site and that several of the events were reported for two unique patients at one investigative site (patient 3004 and patient 3010). For all patients, medical history and/or co-morbidities may have contributed to the fluctuations in laboratory results. Per protocol, adverse events included changes in laboratory abnormalities that were clinically significant as assessed by the investigator and for which a medical intervention was initiated. For all the treatment related adverse events coding to the SOC Investigations, no medical intervention was initiated, no action was taken with regards to study treatment; and all but two adverse events (increased iPTH) resolved spontaneously. Thus, the isolated fluctuations in laboratory abnormalities that were reported as adverse events by the investigator do not accurately represent the trends in laboratory results.



2.7.4.3.3.3 Comparative Assessment of Clinically Significant Laboratory Changes in Individual Patients in SVCARB00205 and GD3-163-201

The clinically significant laboratory changes in individual patients reported in both SVCARB00205 and GD3-163-201 were consistent with the known safety profile of sevelamer and with the patients' underlying renal disease and co-morbidities.

2.7.4.3.3.4 Clinically Significant Laboratory Changes in Individual Patients in GD3-199-301

Individual patient changes that were assessed as clinically significant by the Investigator were captured as AEs (coded to the SOC Investigations). The percent of patients experiencing AEs in the SOC Investigations was greater in the sevelamer hydrochloride tablet TID group. A total of 11 (7.8%) sevelamer carbonate powder QD patients and 12 (16.7%) sevelamer hydrochloride tablet TID patients experienced a treatment emergent AE coded to the SOC Investigations. Adverse events coded to the MedDRA SOC Investigations occurring in more than one patient in either treatment group included: blood parathyroid hormone abnormal [3 events in 2 (1.4%) sevelamer carbonate powder QD patients and 1 event in 1 (1.4%) sevelamer hydrochloride tablet TID patient], carbon dioxide decreased [3 events in 3 (2.1%) sevelamer carbonate powder QD patients and 3 events in 2 (2.8%) sevelamer hydrochloride tablet TID patients], heart rate increased [2 events in 2 (1.4%) sevelamer carbonate powder QD patients and 1 event in 1 (1.4%) sevelamer hydrochloride tablet TID patient], and heart rate irregular [5 events in 2 (1.4%) sevelamer carbonate powder QD patients and 4 events in 4 (5.6%) sevelamer hydrochloride tablet TID patients].

Treatment emergent AEs in the SOC Investigations that were assessed as treatment related by the Investigators included (by MedDRA preferred term): blood parathyroid hormone increased (sevelamer carbonate powder QD: 1 (0.7%) patient and sevelamer hydrochloride tablet TID: 0 (0%) patients) and carbon dioxide decreased (sevelamer carbonate powder QD: 1 (0.7%) patient; sevelamer hydrochloride tablet TID: 2 (2.8%) patients).



2.7.4.4 Vital Signs, Physical Findings, and Other Observations

In the Vital Signs, Physical Finding and Other Observations Section, a comparative assessment of the vital signs results in SVCARB00205 and GD3-163-201 during sevelamer carbonate powder treatment will be provided. Vital signs results for the sevelamer hydrochloride treatment regimens in SVCARB00205 and GD3-163-201 as well as the vital signs results from GD3-199-301 will not be discussed, but can found in the clinical study reports. There were no clinically meaningful findings for vital signs during the sevelamer hydrochloride regimens in either SVCARB00205 or GD3-163-201 and no clinically meaningful findings in GD3-199-301.

2.7.4.4.1 Vital Signs

Table 2.7.4-29 presents the change from baseline to the end of treatment for vital signs during sevelamer carbonate treatment in SVCARB00205 and GD3-163-201. There were no statistically significant changes in vital signs during either clinical trial.



**Table 2.7.4-29:
Vital Signs Over Time During Sevelamer Carbonate Treatment in SVCARB00205
and GD3-163-201**

Vital Sign Timepoint/Statistics	SVCARB00205 4 Week Treatment Period Sevelamer Carbonate Powder TID (N = 31)	GD3-163-201 8 Week Treatment Period Sevelamer Carbonate Tablets TID (N = 73)
Pulse (beats/min)		
Baseline	73.8 ± 8.9	77.8 ± 11.7
Final	77.9 ± 14.3	78.8 ± 14.1
Change	3.0 ± 12.2	1.4 ± 11.9
P-value	0.369	0.634
Systolic Blood Pressure (mmHg)		
Baseline	144.3 ± 29.5	132.9 ± 21.2
Final	140.6 ± 23.5	129.7 ± 20.5
Change	-1.0 ± 23.6	-2.7 ± 22.6
P-value	0.835	0.496
Diastolic Blood Pressure (mmHg)		
Baseline	81.1 ± 17.7	69.3 ± 13.2
Final	79.1 ± 16.3	69.1 ± 13.9
Change	0.0 ± 18.7	0.1 ± 14.8
P-value	0.923	0.821

Data source: SVCARB00205 CSR: Table 14.3.6.2, Table 14.3.6.4, and Table 14.3.6.5; GD3-163-201 CSR: Table 14.3.5.2, Table 14.3.5.3 and Table 14.3.5.4.

* P-values are from Wilcoxon signed rank test.

ND: Not done

Note: The number of observations varies in the statistics shown. Please refer to the CSR tables for details.

2.7.4.4.2 Physical Examination

Clinically significant changes noted on physical exam for each individual patient were captured and assessed as adverse events in SVCARB00205, GD3-163-201 and GD3-199-301 (refer to Section 2.7.4.2).



2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Intrinsic Factors

Clinical studies of sevelamer carbonate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Drug-demographic interactions with sevelamer carbonate were investigated in SVCARB00205, GD3-163-201 and GD3-199-301 and are discussed in Section 2.7.4.2.1. In general, there was no evidence of increased frequency of adverse events or SAEs in the major demographic subgroups (gender, age or race) during sevelamer carbonate treatment (powder or tablets).

2.7.4.5.2 Extrinsic Factors

No adverse events or laboratory abnormalities were reported in patients that indicated that extrinsic factors, such as the use of tobacco and alcohol, affected the safety of sevelamer carbonate powder or tablets.

2.7.4.5.3 Drug Interactions

As an oral anion exchange resin, the major potential mechanism by which sevelamer (carbonate or hydrochloride) can interact with other drugs is by affecting their absorption, or in the case of drugs undergoing enterohepatic circulation, by affecting excretion. Both types of interactions are limited to the gastrointestinal tract and therefore the range of possible drug interactions is reduced.

A series of pharmacokinetic studies was performed to assess the effects of sevelamer hydrochloride on the absorption of drugs. Six drugs were evaluated with sevelamer hydrochloride: digoxin, warfarin, enalapril, metoprolol, ciprofloxacin, and iron. Refer to NDA 022127, Sequence 000, 2006-12-20, summary-clin-pharm.pdf pages 1 to 34, for the discussion of these studies. In these studies, sevelamer hydrochloride was found to have no effect on the bioavailability of digoxin, warfarin, metoprolol, enalapril or iron. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride. In addition, during post-marketing experience, very rare cases of increased TSH levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine.



Sevelamer carbonate is an anion exchange resin with the same polymeric structure as sevelamer hydrochloride in which carbonate replaces the chloride counterion. After exposure to stomach fluids, both sevelamer carbonate and sevelamer hydrochloride are similarly protonated salts of cross-linked poly(allylamine hydrochloride) and are expected to have similar drug-drug interactions. The current sevelamer hydrochloride and sevelamer carbonate tablet labels recommend that when administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, the medication should be administered at least one hour before or three hours after sevelamer (carbonate or hydrochloride), or the physician should consider monitoring blood levels of the drug. The current labels also recommend closer monitoring of TSH levels in patients receiving both medications.

2.7.4.5.4 Use in Pregnancy and Lactation

The safety of sevelamer carbonate (powder or tablets) has not been established in pregnant or lactating women.

In pregnant rats given dietary doses of 0.5, 1.5, 4.5 g/kg/day of sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, during organogenesis, reduced or irregular ossification of foetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred in the mid and high dose groups (exposures less than the maximum human dose of 13 grams, based on a comparison of relative body surface).

In pregnant rabbits given oral doses of 100, 500, and 1000 mg/kg/day of sevelamer hydrochloride by gavage during organogenesis, an increase in early resorption occurred at exposure 2 times the maximum human dose of 13 grams, based on a comparison of relative body surface area.

Requirements for vitamins and other nutrients are increased in pregnancy. The effect of sevelamer on the absorption of vitamins and other nutrients has not been studied in pregnant women.

2.7.4.5.5 Overdose

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight



days with no adverse effects. In CKD patients, the maximum average actual daily dose of sevelamer carbonate studied was 14 grams/day (both TID and QD). There are no reports of overdosage with sevelamer carbonate (powder or tablets) or sevelamer hydrochloride in patients. Since sevelamer carbonate is not absorbed, the risk of systemic toxicity is low.

2.7.4.5.6 Drug Abuse

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

2.7.4.5.7 Withdrawal and Rebound

Since sevelamer carbonate is not absorbed, withdrawal of therapy should not lead to central nervous system, cardiovascular, pulmonary, or other organ system withdrawal or rebound effects. In previous studies, the discontinuation of sevelamer (carbonate or hydrochloride) during a post-treatment washout period was associated with a return of serum phosphorus concentrations back to unacceptably high levels.

2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the ability to drive and use machines have been conducted. On the basis of the reported adverse drug reactions, sevelamer carbonate (powder or tablets) has no or negligible influence on the ability to drive or use machines.

2.7.4.6 Post-marketing Data

Renvela[®] (sevelamer carbonate) Tablets were approved for marketing on October 19, 2007. No post-marketing data on sevelamer carbonate tablets is currently available, but will be provided at the time of the 120-day safety update.

Renagel[®] (sevelamer hydrochloride), which contains the same active moiety as sevelamer carbonate, was approved in the United States on October 30, 1998 for capsules (NDA 20-926) and July 12, 2000 for tablets (NDA 21-179). The estimated US patient exposure to Renagel is greater than _____ patient-years. Renagel is currently approved for

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marketing in over 55 countries. Post marketing safety surveillance of sevelamer hydrochloride (Renagel) has been ongoing since initial approval of sevelamer hydrochloride in 1998. The most recent Periodic Safety Update Report (PSUR), covering the period between 31 October 2006 and 30 October 2007, was submitted on 21 December 2007 and is provided in Section 5.3.6.

The most frequent post-marketing adverse event for sevelamer hydrochloride is hyperphosphataemia. Successful control of serum phosphorus in this patient population is multifactorial, including reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis. An ongoing evaluation of all reported cases of hyperphosphataemia received spontaneously for Renagel, including the patient's prior phosphate binder and phosphorus levels, the patient's Renagel dosage regimen and phosphorus levels, and patient compliance with diet and medication, has not revealed any new product or safety related issues.

Other commonly reported spontaneous adverse events for patients on Renagel included nausea, diarrhoea, vomiting, constipation, flatulence, dyspepsia, headache, dyspnoea and hypertension. These events were observed in clinical trials with Renagel, are described in the product labelling and are considered expected (labelled) adverse events. Events of nausea, vomiting, flatulence, and dyspepsia were seen in patients during sevelamer carbonate treatment.

Pruritus, abdominal pain and rash are other adverse events that were seen during clinical trials with Renagel and were frequently reported during post-marketing experience with Renagel. These three terms are described as post-marketing experience in the current Renagel and Renvela labels.

Reports of intestinal obstruction, intestinal perforation and ileus for patients on Renagel have been rare. An in depth review of these gastrointestinal event reports received for patients on Renagel revealed there was no dose relationship, and that age and treatment duration varied. Patient medical histories were complicated and may have contributed to the events. Due to the nature of post-marketing reporting, details regarding Renagel therapy, clinical diagnosis and medical history were limited, which complicated the review of these reports. A comprehensive review of post-marketing reports of ileus,



intestinal obstruction and intestinal perforation revealed that complex co-morbidities and concomitant medications often contributed to the event. The current Renagel and Renvela labels describe the risk of intestinal obstruction, intestinal perforation, and ileus during sevelamer therapy.

Deaths and serious adverse events reported for patients on sevelamer hydrochloride were rare, were reported across system organ classes, and were consistent with patients' underlying renal disease.

There are limited data on the safety of sevelamer carbonate. However, based on the fact that it contains the same active ingredient as the hydrochloride salt, the adverse event profiles of the two salts should be similar. Overall, adverse events seen during treatment with sevelamer carbonate powder and tablets in clinical trials were similar in nature to adverse events spontaneously received by Genzyme during sevelamer hydrochloride post-marketing surveillance.

2.7.4.7 Appendix

Not applicable.