CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-127

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER

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)	STRENGTH(S)
Sevelamer Carbonate	800 mg

DOSAGE FORM
Tablet

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.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,496,545	03/05/1996	08/11/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
Genzyme Corporation	500 Kendall St	
	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? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ 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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 Claim Number (*as listed in the patent*) 1-13	Does the patent claim 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
	10/30/2006

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.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

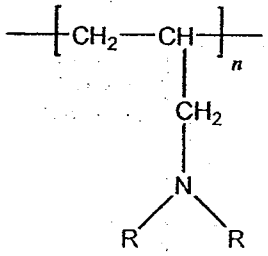
Name Christopher M. Beck	
Address Genzyme Corp. 153 Second Ave	City/State Waltham, MA
ZIP Code 02451	Telephone Number (781) 434-3471
FAX Number *(if available)* (781) 895-4982	E-Mail Address *(if available)* Christopher.Beck@genzyme.com

EXTENDED RESPONSE: SECTION 4.2a

US 5,496,545

Claims 1-5

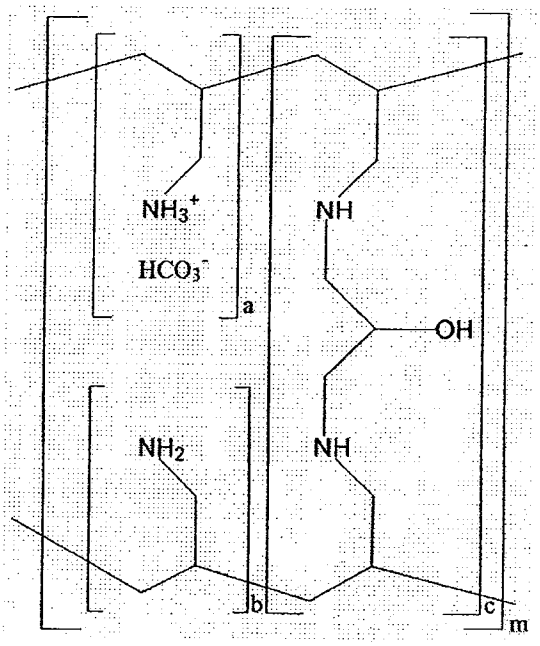
Claims 1-5 recite, *inter alia*, a method for removing phosphate from a patient by ion exchange comprising orally administering to said patient a therapeutically effective amount of a composition comprising at least one polymer characterized by a repeat unit having the formula:



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:



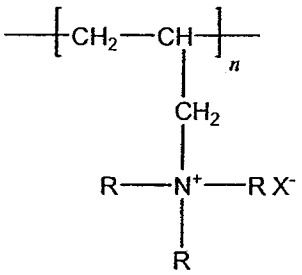
a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
m = large number to indicate extended polymer network

Finally, at Section 12.1, the proposed Renvela labeling states that "[b]y binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum."

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

Claims 6-13

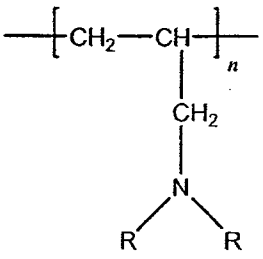
Claims 6-13 recite, *inter alia*, a method for removing phosphate from a patient by ion exchange comprising orally administering to said patient a therapeutically effective amount of a composition comprising at least one polymer characterized by a repeat unit having the formula:



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).

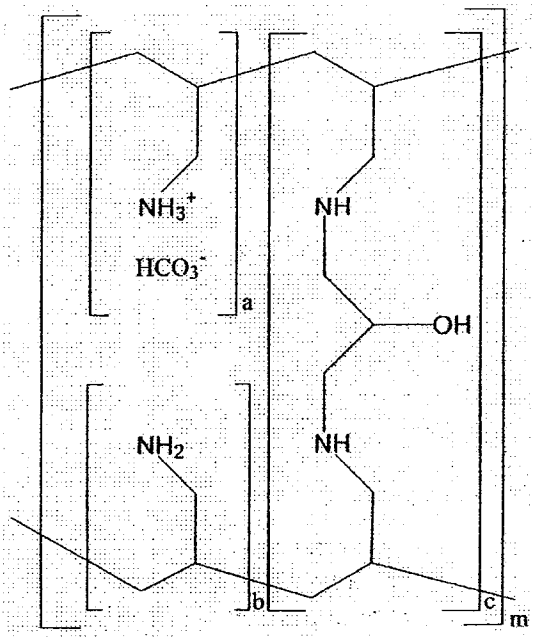
Claims 10-13 also depend upon claim 6 and further define the orally administered polymer as a copolymer further comprising a repeat unit having the formula:



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:



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]y binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum."

Accordingly claims 6-13 of US 5,496,545, read on the methods described in the proposed Renvela labeling.

Department of Health and Human Services
Food and Drug Administration

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NDA NUMBER

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)	STRENGTH(S)
Sevelamer Carbonate	800 mg

DOSAGE FORM
Tablet

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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.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,667,775	09/16/1997	09/16/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Genzyme Corporation	500 Kendall St	
	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? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ 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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 Claim Number (*as listed in the patent*)	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
22		☑ 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.***

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	10/30/2006

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Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Christopher M. Beck	
Address Genzyme Corp 153 Second Ave.	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

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]y binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum."

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

Department of Health and Human Services
Food and Drug Administration

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For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,509,013	01/21/2003	08/11/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
Genzyme Corporation	500 Kendall St	
	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.)*	
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	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? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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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
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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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 Claim Number (*as listed in the patent*)	Does the patent claim 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

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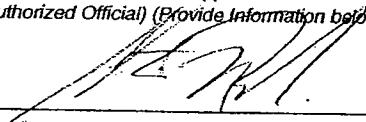
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	10/30/2006

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.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Christopher M. Beck	
Address 153 Second Ave	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

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER

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)	STRENGTH(S)
Sevelamer Carbonate	800 mg

DOSAGE FORM
Tablet

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.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6858203	02/22/2005	08/11/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
Genzyme Corporation	500 Kendall St	
	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? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ 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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 Claim Number (*as listed in the patent*) 1-9	Does the patent claim 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 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.	☐ 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
	12/6/2006

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.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

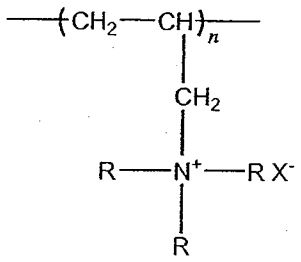
Name Christopher M. Beck	
Address Genzyme Corp. 153 Second Ave.	City/State Waltham, MA
ZIP Code 02451	Telephone Number (781) 434-3471
FAX Number *(if available)* (781) 895-4982	E-Mail Address *(if available)* Christopher.Beck@genzyme.com

EXTENDED RESPONSE: SECTION 4.2a

US 6,858,203

Claims 1-8

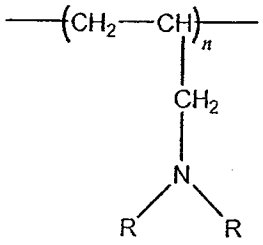
Claims 1-8 recite, *inter alia*, a method for removing phosphate from a patient comprising orally administering to said patient a therapeutically effective amount of a composition comprising at least one polymer characterized by a repeat unit having the formula:



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).

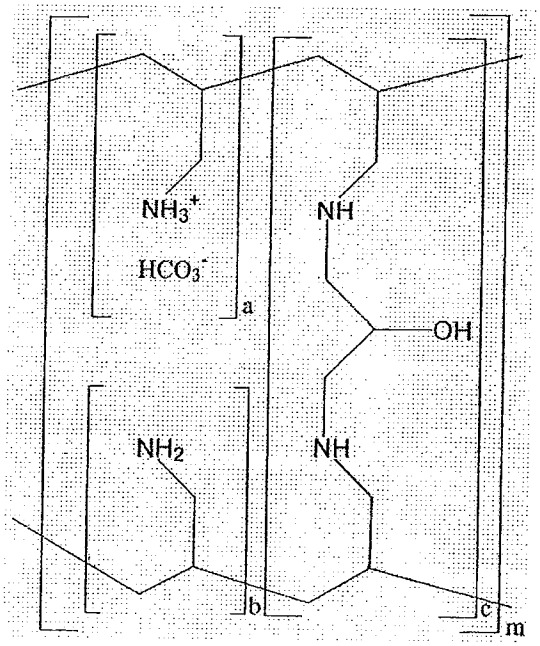
Claims 5-8 also depend upon claim 1 and further define the orally administered polymer as a copolymer further comprising a repeat unit having the formula:



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:



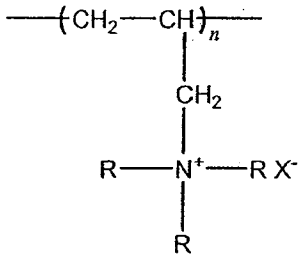
a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
m = large number to indicate extended polymer network

Finally, at Section 12.1, the proposed Renvela labeling states that "[b]y binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum."

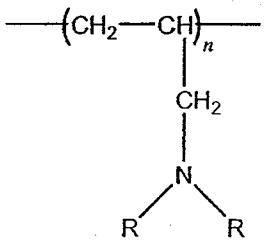
Accordingly claims 1-8 of US 6,858,203 read on the methods described in the proposed Renvela labeling.

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:

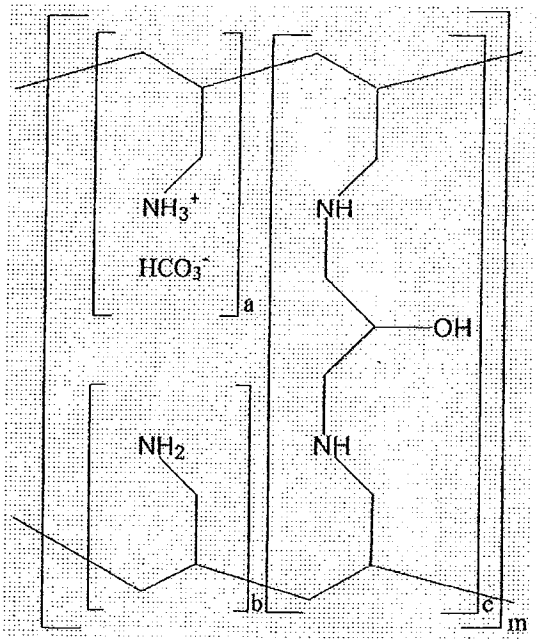


and a second repeat unit having the formula:



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]y binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum."

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

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER

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)	STRENGTH(S)
Sevelamer Carbonate	800 mg

DOSAGE FORM
Tablet

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.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7,014,846	03/21/2006	08/11/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
Genzyme Corporation	500 Kendall St	
	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? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ 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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 Claim Number (*as listed in the patent*)	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
9-12	☑ 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
	10/30/2006

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.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

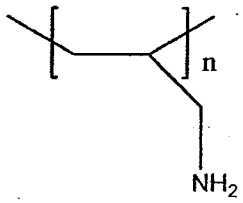
Name Christopher M. Beck	
Address 153 Second Ave	City/State Waltham, MA
ZIP Code 02451	Telephone Number (781) 434-3471
FAX Number *(if available)* (781) 895-4982	E-Mail Address *(if available)* christopher.beck@genzyme.com

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:

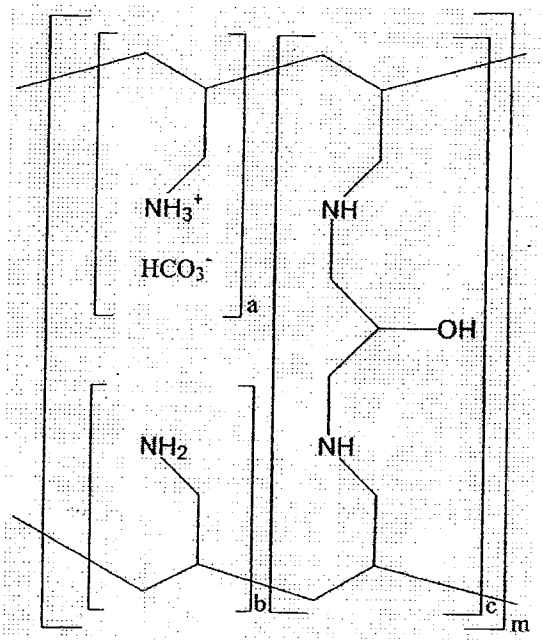


wherein n is an integer, and wherein the homopolymer is fully protonated, partially protonated or unprotonated.

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]y binding phosphate in the dietary tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum."

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

EXCLUSIVITY SUMMARY

NDA # 22-127 SUPPL # N/A HFD # 110

Trade Name Renvela

Generic Name sevelamer carbonate

Applicant Name Genzyme Corporation

Approval Date, If Known October 19, 2007

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# 21-179 Renagel Tablets

NDA# 20-926 Renagel Capsules

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:

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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 ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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 ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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"):

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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 # ——— 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: Alisea Crowley, Pharm.D.
Title: Regulatory Project Manager
Date: October 19, 2007

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

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/

Alisea R. Crowley
10/19/2007 02:29:28 PM

Norman Stockbridge
10/19/2007 02:56:30 PM

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-127 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: December 20, 2006 PDUFA Goal Date: October 20, 2007 (Saturday)
HFD 110 Trade and generic names/dosage form: Renvela (sevelamer carbonate) Tablets, 800 mg tablets

Applicant: Genzyme Corporation Therapeutic Class: Agents for treating hyperphosphatemia

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☒ **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): ONE

Indication #1: for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☒ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☒ **No: Please check all that apply: ____Partial Waiver ☒ Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver: N/A

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below): N/A

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min____ kg____ mo. <1 yr.____ Tanner Stage____
Max____ kg____ mo.____ yr. 16 Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☒ **Formulation needed**

Other: Genzyme intends to submit a powder formulation for sevelamer carbonate in 2007 and has agreed to provide their proposed pediatric plan with their powder formulation. Drug would be ready for approval in adults before studies in children would be completed.

Date studies are due (mm/dd/yy): 10/20/09

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered

into DFS.

This page was completed by:

{See appended electronic signature page}

Dianne Paraoan
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Dianne Paraoan
2/21/2007 10:00:11 AM

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DEBARMENT CERTIFICATION

Certification pursuant to 21 USC Section 306(k)(l)

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

Dennis Bucceri, Vice President Regulatory Affairs

10/18/06
Date

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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

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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

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).

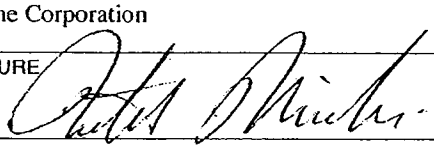
Please mark the applicable checkbox.

☒ (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	TITLE
Richard Moscicki	Chief Medical Officer and Senior Vice President, Biomedical and Regulatory Affairs
FIRM / ORGANIZATION: Genzyme Corporation	
SIGNATURE: 	DATE: 11/6/06

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

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Attachment to Form FDA 3454
Study No. GD3-163-201

Completed financial disclosure forms have been received for the following investigators:

Site Number	Site Name	Name	Responsibility
002	DaVita Dialysis Center Valparaison, IN	Shahabul Arfeen, MD	Principal Investigator
003	DaVita Dialysis Center Denver, CO	Geoffrey Block, MD [redacted]	Principal Investigator Sub-Investigator Sub-Investigator
004	Wake Forest University, Nephrology Section, Winston-Salem, NC	Anthony Bleyer, MD	Principal Investigator
005	Indiana University School of Medicine, Indianapolis, IN	Sharon Moe, MD [redacted]	Principal Investigator Sub-Investigator
006	Chromalloy American Kidney Center St. Louis, MO	James Delmez, MD [redacted]	Principal Investigator Sub-Investigator
007	Nephrology Associates Wynnewood, PA	Robert Benz, MD [redacted]	Principal Investigator Sub-Investigator Sub-Investigator Sub-Investigator
009	Renal Care Group Columbus, MS	John Reed, MD [redacted]	Principal Investigator Sub-Investigator Sub-Investigator
010	Nephrology Associates, P.C. Nashville, TN	Mark Kaplan, MD [redacted]	Principal Investigator Sub-Investigator Sub-Investigator
011	Coastal Clinical Research, Inc. Mobile, AL	Philip Butera, MD [redacted]	Principal Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator

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Site Number	Site Name	Name	Responsibility
014	Apex Research of Riverside Riverside, CA	John Robertson, MD [redacted]	Principal Investigator Sub-Investigator Sub-Investigator Sub-Investigator
015	Renal Care Group Crestwood, IL	Ronald Hamburger, MD	Principal Investigator Sub-Investigator
016	Renal Care Group Berwyn, IL	Laurens Lohmann, MD	Principal Investigator
017	Clinical Research Associates of Tidewater Norfolk, VA	Duane Wombolt, MD [redacted]	Principal Investigator Sub-Investigator Sub-Investigator Sub-Investigator Sub-Investigator

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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 three (3) clinical investigators and thirteen (13) sub-investigators.

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

GENZYME CORPORATION

By: Andrew Blair Date: 11-1-06

Andrew Blair, MD
Vice President, Clinical Research

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Attachment to Genzyme Certification of Due Diligence
Study No. GD3-163-201

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

Site Number	Site Name	Name	Responsibility	Reason
001	DaVita Dialysis Center Easton, PA	Robert Pursell, MD [redacted]	Principal Investigator Sub-investigator Sub-investigator Sub-investigator	Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study.
002	Nephrology Specialists Valparaison, IN	James Hasbargen, MD	Previous Principal Investigator	Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study.
004	Wake Forest University; Nephrology Section Winston-Salem, NC	[redacted]	Sub-investigator	Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study.
005	Indiana University School of Medicine Indianapolis, IN	[redacted] [redacted]	Sub-investigator Sub-investigator Sub-investigator	Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study. Physician came off study prior to study start up.
011	Coastal Clinical Research, Inc Mobile, AL	[redacted] [redacted]	Sub-investigator Sub-investigator Sub-investigator	Initial Financial Disclosure form on file; Follow-up form not returned despite several written and verbal requests. Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study.

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Site Number	Site Name	Name	Responsibility	Reason
012	DaVita Dialysis Center St. Louis, MO	Douglass Domoto, MD [redacted]	Principal Investigator Sub-investigator	Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study.
014	Apex Research Riverside, CA	[redacted],	Sub-investigator	Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study.
017	Clinical Research Associates of Tidewater Norfolk, VA	[redacted]	Sub-investigator	Initial Financial Disclosure form on file. Follow-up form not available due to physician coming off study.

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ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # **22-127**	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: **Renvela** Established Name: **sevelamer carbonate** Dosage Form: **Tablets**		Applicant: **Genzyme Corporation**	
RPM: **Alisea Crowley, PharmD**		Division: **Cardiovascular and Renal Products**	Phone # **301-796-1144**

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: X ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: 505(b)(1) ☐ 505(b)(2) (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.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	**October 20, 2007**
❖ Actions	
• Proposed action	X☐ AP ☐ TA ☐AE ☐ NA ☐CR
• Previous actions *(specify type and date for each action taken)*	X☐ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X☐ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: X☐ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X☐ No
• This application is on the AIP	☐ Yes ☐ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X☐ Yes ☐ No
• Press Office notified of action	X☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	X☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X☐ Included
• Is approval of this application blocked by any type of exclusivity?	X☐ No ☐ Yes
• NDAs/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.*	X☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: 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.)*	X☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: 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.)*	X☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: 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.)*	X☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• 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.	X☐ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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*)).*	☐ N/A (no paragraph IV certification) ☐ 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	☐ Yes ☐ No

notice of certification?

(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 to the next section below (*Summary Reviews*).*

*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).*

(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? ☐ 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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *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*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	**October 19, 2007**
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	**Submitted electronically on 10.19.2007**
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	**Submitted on 10.20.2006**
❖ Patient Package Insert	N/A
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	N/A
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	**Submitted June 9 and August 13, 2007**
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	X☐ DMETS **April 12 &October 18, 2007** N/A☐ DSRCS X☐ DDMAC **5.8.2007** X☐ SEALD **10.11.2007** ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	**February 20, 2007**
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X☐ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	X☐ 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. *(Include certification.)*	X☐ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	X☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	**Acknowledgement Ltr: 1/11/2007; Filing Letter: 2/21/2007; CMC Ltr: 7/13/2007; DMETS: 5/17/2007**
❖ Internal memoranda, telecons, email, etc.	**None**
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg **9.21.2006**
• EOP2 meeting *(indicate date)*	☐ No mtg **1.6.2005**
• Other (e.g., EOP2a, CMC pilot programs)	**Guidance: 6.17.2005**
❖ Advisory Committee Meeting	X☐ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**N/A**
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	**August 28 & October 15, 2007**
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	X☐ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	**August 28, 2007**
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	X☐ Not a parenteral product
❖ Facilities Review/Inspection	N/A
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	X☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**August 16, 2007**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X☐ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	X☐ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**August 24, 2007**
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	**Yes**
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	X☐ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	X☐ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	**October 12, 2007**
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	**N/A**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	N/A☐ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	X☐ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None **September 7, 2007**
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None **August 22, 2007**

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/s/

Alisea R. Crowley
10/19/2007 05:11:44 PM

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NDA 22-127
RHPM Review

RHPM Overview of NDA 22-127
Renvela™ (sevelamer carbonate)
800 mg Tablets
October 17, 2007

Sponsor:	Genzyme Corporation
Receipt Date:	December 20, 2007
User Fee Goal Date:	October 20, 2007
Approval Letter Issued:	October 19, 2007

Primary Reviewers
Medical: Gail Moreshi, M.D.
Secondary Medical: Abraham Karkowsky, M.D.
Statistician: Ququan (Cherry) Liu, Ph.D.
Clinical Pharmacologist: Robert Kumi, Ph.D.
Pharmacologist: Xavier Joseph, Ph.D.
Chemist: Donghao (Robert) Lu, Ph.D.

Background

Genzyme has proposed that sevelamer carbonate, a phosphate binding agent, is a pharmaceutical alternative to their currently approved product, Renagel® (sevelamer hydrochloride). The proposed indication for Renvela™ is for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis. The sponsor believes that Renvela has similar phosphate binding activity, efficacy, and safety characteristics as Renagel (sevelamer HCl).

Medical/Statistical Joint Review

In their review, dated August 24, 2007, Drs. Moreshi and Liu concluded in patients with CKD on hemodialysis, the results of the clinical study demonstrates that sevelamer carbonate and sevelamer hydrochloride were equivalent in controlling serum phosphorus. Sevelamer carbonate and sevelamer hydrochloride have a similar safety and tolerability profile. Drs. Moreshi and Liu recommended an approval regulatory action.

Secondary Medical Review

In his review, dated October 2, 2007, Dr. Karkowsky supports the approval of Renvela for use as a phosphate binder. He stated that his approval recommendation is almost entirely based on the *a priori* mechanistic considerations that in the acid environment of the stomach, the carbonate salt, once disintegrated will completely be transformed to the chloride salt. It is clear that in vitro performance of the two salts differ, particularly in an environment that significantly differs from the pH of the stomach.

Pharmacology Review

In his review, dated August 16, 2007, Dr. Joseph stated that since the non-clinical data indicate that the toxicity profiles for sevelamer carbonate and sevelamer HCl are similar, as sevelamer carbonate is intended to be used in the same patient population t similar dosage levels as Renagel, there are no approvability issues for sevelamer carbonate from the nonclinical toxicity testing program perspective.

Biopharmaceutical Review
In his review dated, August 22, 2007, Dr. Kumi concluded that the clinical pharmacology and biopharmaceutics information was acceptable. However, the following additional information is needed to provide supportive in vitro evidence of the comparability of sevelamer carbonate to sevelamer HCl:

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

Statistical Review
See medical/statistical joint review summary.

Chemistry Review
In his reviews dated, August 28 and October 15, 2007, Dr. Lu stated that Genzyme has submitted sufficient and appropriate information to support approval of Renvela from a CMC perspective. In Dr. Lu's original review, there were several CMC issues which needed to be resolved prior to approval. The CMC issues were sent to the sponsor on July 31, 2007. Dr. Lu concluded that the sponsor has adequately addressed the CMC issues in amendments 006, 007, and 008.

DSI
N/A

Pediatrics
The Division issued a pediatric deferral dated February 21, 2007. The pediatric studies for sevelamer carbonate are deferred until October 20, 2009.

Labeling
The sponsor submitted original electronic labeling dated December 20, 2006. After several email exchanges and conversations with the sponsor, on October 16, 2007, the Division sent electronic draft labeling with revisions to the sponsor's original labeling proposal. The sponsor made minor revisions to the labeling and it was accepted by the Division as final draft labeling on October 19, 2007.

Advisory Committee Meeting
No meeting held.

CSO Summary
Based on the recommendations of each reviewer, there are no issues that might prevent an approval on draft action for this NDA.

NDA 22-127
RHPM Review

Alisea Crowley, Pharm.D.

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/s/

Alisea R. Crowley
10/19/2007 05:10:25 PM
CSO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 22-179 (sevelamer hydrochloride)

Sponsor: Genzyme

Review date: 19 October 2007

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

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

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

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

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

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

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

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

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/s/

Norman Stockbridge
10/19/2007 02:55:58 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 2, 2007

FROM: Abraham Karkowsky, M.D., Ph.D., Acting Deputy Director, Division of Cardiovascular and Renal Products HFD-110

TO: Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products HFD-110

SUBJECT: Approvable recommendation for Renvela® (sevelamer carbonate).

This memo supports the approval of the carbonate salt of sevelamer (named Renvela®) for use as a phosphate binder. The salt should be indicated for the treatment of hyperphosphatemia in patients undergoing dialysis, similar to the indication of the chloride salt (Renagel®). This approval recommendation is almost entirely based on the *a priori* mechanistic considerations that in the acid environment of the stomach, the carbonate salt, once disintegrated, will completely be transformed to the chloride salt. It is clear that the in vitro performance of the two salts differ, particularly in an environment that significantly differs from the pH of the stomach.

Given this strong *a priori* supposition of rapid transformation of the carbonate to the chloride salt, only a minimal supportive data is necessary for approval. There is adequate supportive data derived from one clinical study that is sufficient to recommend approval of Renvela®. The data will be described below. I have to say that this development program was so poor, that it should not be referenced as a prototype for the development of other phosphate binders.

One of the pivotal assessments which support this approval is the speed of disintegration of the carbonate tablet. Currently the release specifications for Renvela® require disintegration at times not more than — minutes. The batches tested so far generally disintegrated within ——— at pH 1. The specifications should be tightened to disintegration at NMT than ——— In addition, the sponsor should assess the disintegration times at less acidic pH values (e.g., pH 4). This information can be supplied post approval. Should the sponsor not agree to tighter specifications for disintegration, I have no guarantee that the two salts will perform equivalently and would recommend a not approval letter be sent.

The labeling of the Renvela® (the carbonate salt) should, in general, mirror that of Renagel® (the chloride salt). The initial dose of the carbonate salt should be the same as that of the hydrochloride, although the label should indicate that further titration may be necessary. I saw no data that indicates a benefit of the carbonate relative to the hydrochloride salt.

Although a pediatric waiver was issued for Renvela®, renal failure does occur in children. A development program to address the need of this under supported population, with this or a related formulation should be submitted.

The following reviews were consulted in the construction of this memo:

- Joint medical/statistical review by Gail Moreschi, M.D., M.P. H. and Ququan Liu, M.D., M.S. Completed August 24, 2007.
- Clinical pharmacology and biopharmaceutics review by Robert O. Kumi, Ph.D. dated August 22, 2007
- Pharmacology and Toxicology review by Xavier Joseph, D.V.M. dated August 8, 2007
- Chemistry review by Donghao (Robert) Lu, Ph.D. dated August 27, 2007.
- Division of medication errors and technical support review by Linda M. Wisniewski, RN dated January 25, 2007.
- DDMAC consult by Lisa Hubbard, R.Ph, Regulatory Review Officer dated May 8, 2007

Housekeeping issues:

- DMETS considered the name Renvela® as acceptable from the medication errors perspective, although they suggested that the base-name of the new salt should be the same as that of the currently marketed chloride salt (Renagel®). The concern expressed by DMETS was that the Sevelamer requires electrolyte monitoring because of potential for metabolic acidosis. Since, however, a dialysis population is frequently monitored for their electrolyte status and there is no reason to diminish electrolyte follow-up with Renvela® the concern does not appear to be an impediment to the use of the proposed trade name.
- DDMAC has reviewed the PI for Renvela® and their comments will be incorporated in the PI.
- A pediatric deferral was granted on December 20, 2006. Since, however, renal failure requiring phosphate control does occur in a pediatric population, I see no reason that pediatric studies should not be requested.
- The financial disclosure statement appears acceptable.
- The establishment evaluation report was acceptable.
- The environmental assessment impact was considered as acceptable.

Chemistry:

From a chemistry perspective the original application of Renvela® is acceptable. The deficiencies that were noted by the chemist were related to the need of additional specifications of the product and clarification of the results from already performed studies.

Since the time of the chemist's review, the sponsor submitted additional information that according to Dr. Lu addresses these unresolved issues.

As noted above, the sponsor needs to tighten the disintegration specification. Since once the carbonate has disintegrated it would likely immediately become the chloride salt and the identical effects of the two salts would be expected. The disintegration of the carbonate salt should also be assessed at less acidic conditions (e.g., pH 4).

Pharmacology:

The only studies performed with sevelamer carbonate included *in vitro* phosphate binding studies, a 28-day mass balance and pharmacokinetic study in dogs with radio-labeled carbonate and 4-week oral toxicity studies in dogs and rats.

The phosphate binding studies were more fully described in the biopharmaceutic review and I will address these studies there.

The tracer-labeled studies in dogs that were dosed with labeled sevelamer carbonate on days 1 and 28 showed that 94% of the radioactivity was excreted in the feces within 24 hours. Only 0.04-0.07% of the label was excreted in the urine.

Four week toxicity studies in both rats and dogs showed no differences in toxicity comparing the two salt forms. There were decreases in fat-soluble vitamins (Vitamin E and D) in dogs for both salts. In summary, no additional concerns (or benefits) were observed in short term studies with the chloride or carbonate salts.

None of these results are surprising.

Biopharmaceutics:

The key portion in this submission is an assessment of the binding of phosphate to the two salts of sevelamer. Three types of studies were performed.

- Equilibrium studies that required a 24-hour pretreatment of Renvela® with 1 N HCl
- A binding study for which the incubation time for Renvela® was 4 hours without HCl and
- Kinetic studies of binding of Renvela® at two phosphate concentrations 2.5 and 38.7 mM phosphate.

With respect to the binding studies the data was modeled to a Lagmuir-type equation.

Equation 1

$$\frac{x}{m} = \frac{k_1 k_2 C_{eq}}{1 + k_1 C_{eq}}$$

Rearranging

Equation 2

$$\frac{C_{eq}}{x/m} = \frac{1}{k_1 k_2} + \frac{C_{eq}}{k_2}$$

Where:

Ceq= The amount of free phosphate remaining in the supernatant at the time of assay

x= The amount of phosphate bound to the resin (derived from total incubated –free)

m= The amount of resin

The constant k_1 is an affinity constant of the binding of phosphate (units are $mmol^{-1}$),

k_2 corresponds to the maximum capacity of binding at equilibrium (units are mmol phosphate/g resin

The values for k_1 and k_2 are derived a plot of equation 2.

The affinity for the two salts differed when they were not pre-incubated with HCl but were similar when they were pre-incubated with 1 N HCl. The capacity constants were not that dissimilar comparing the two salts either when or when not pre-incubated with HCl.

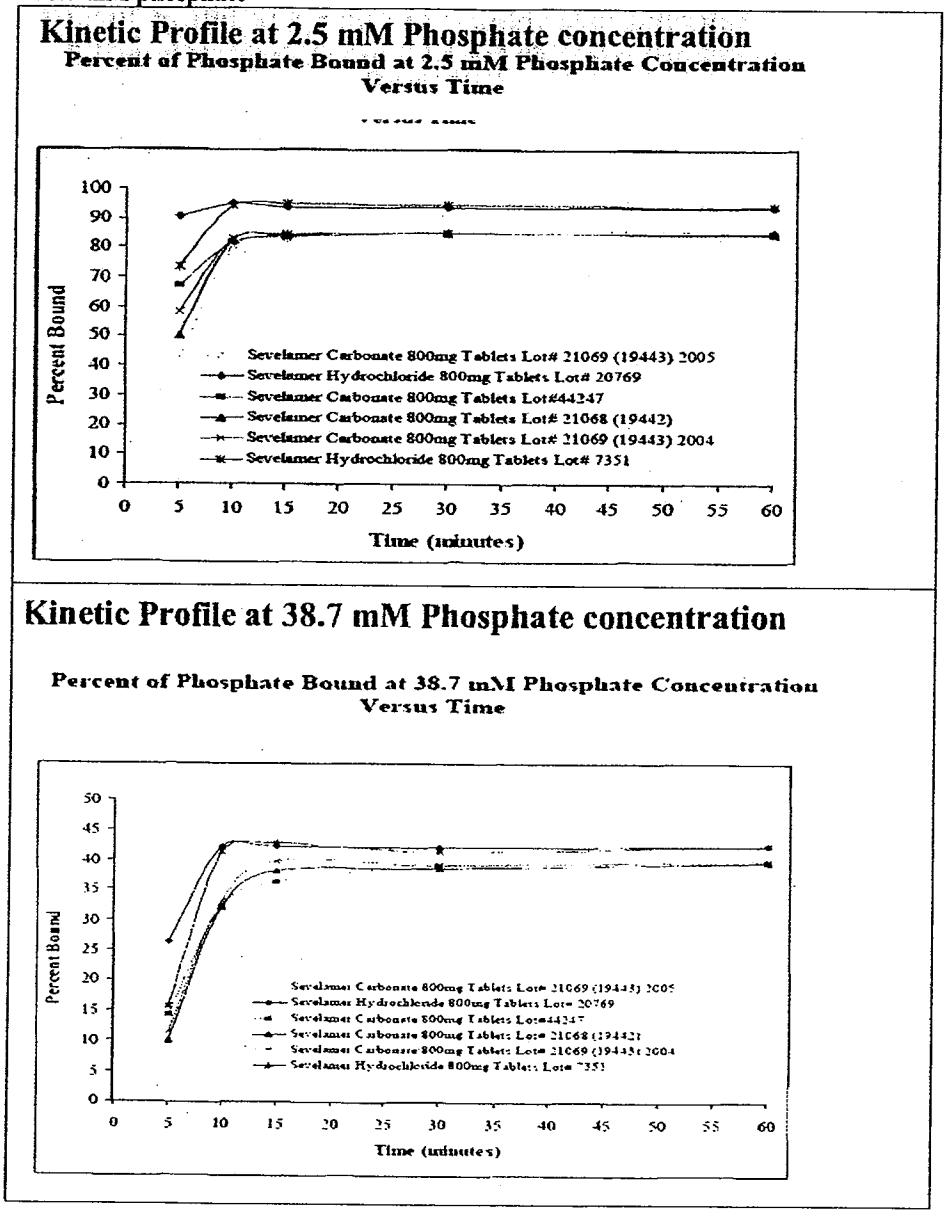
Table 1: In vitro binding constants for the chloride and carbonate salts of sevelamer with and without acid pretreatment

	No pre-incubation			Pre-incubated with HCl	
	Carbonate	Chloride		Carbonate	Chloride
# of batches	4	2		4	2
Affinity (k_1, $mmol^{-1}$)	0.36 + 0.05	0.85 + 0.04		0.61 + 0.09	0.71 + 0.11
Capacity (k_2, mmol phosphate/g resin)	6.24 + 0.35	6.04 + 0.27		6.77 + 0.40	6.47 + 0.33

With respect to the kinetic characteristics of the binding comparing the carbonate to chloride salt, there were substantial differences early on that converged within 10-15 minutes after the start of the incubation. Although, in addition, there are clear but small differences in total amount of phosphate bound (capacity) comparing the carbonate to chloride salt, the difference is less than 10%.

The kinetic profiles at two different phosphate concentrations are shown below.

Figure 1: Time course of two batches of hydrochloride and four batches of carbonate at 2.5 and 38.7 mM phosphate



In summary, the binding affinity and binding capacity of the two different salts of sevelamer differ. The assertion of that the salts are interchangeable, therefore, rests on the assumption that once exposed to HCl in the gut, with rapid disintegration, the two salts act equivalently. In the absence of rapid disintegration there is insufficient information to assert reasonable phosphate binder behavior of the carbonate salt of sevelamer.

Clinical:

Only a single clinical study was submitted. This study as a randomized cross-over study in which 79 subjects requiring dialysis were randomized in a 1:1 ratio to one of two

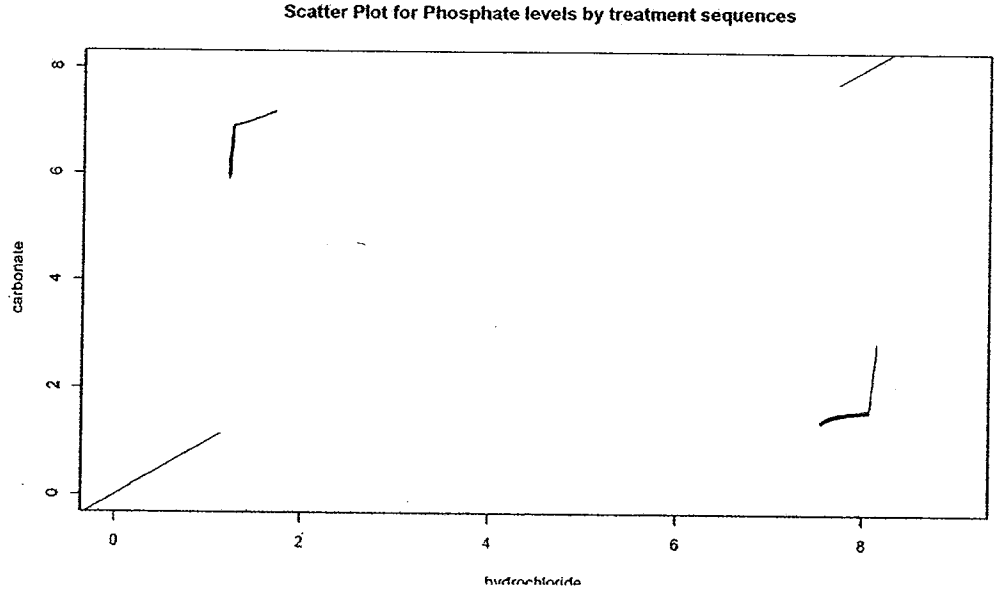
treatment sequences. The two sequences differed as to which salt (carbonate or hydrochloride) was administered first with the second salt following. Each of the treatment sequences lasted eight weeks. Prior to entering the study, each subject was on 5 weeks of stable sevelamer hydrochloride doses. After the study was initiated, at the request of this Division, a subgroup (not pre-specified at the time of randomization) were randomly withdrawn from treatment. The daily dose of either phosphate binder is shown below.

Table 2: Doses used during cross-over study

	Total daily dose		
	≤ 4.8	>4.8 to <9.9	≥ 9.6
N	22	14	20

There did not appear to a difference between the effects of the two salts on mean phosphate levels. The mean $\pm$ SD for the carbonate treated patients was 4.8 ± 0.9 and for the hydrochloride-treated subjects was. 4.8 ± 0.9. However, there was considerable variability in the effect of the two treatments. Given the large variability it is difficult to assert that the two formulations are bioequivalent (plot supplied by Dr. Q Liu).

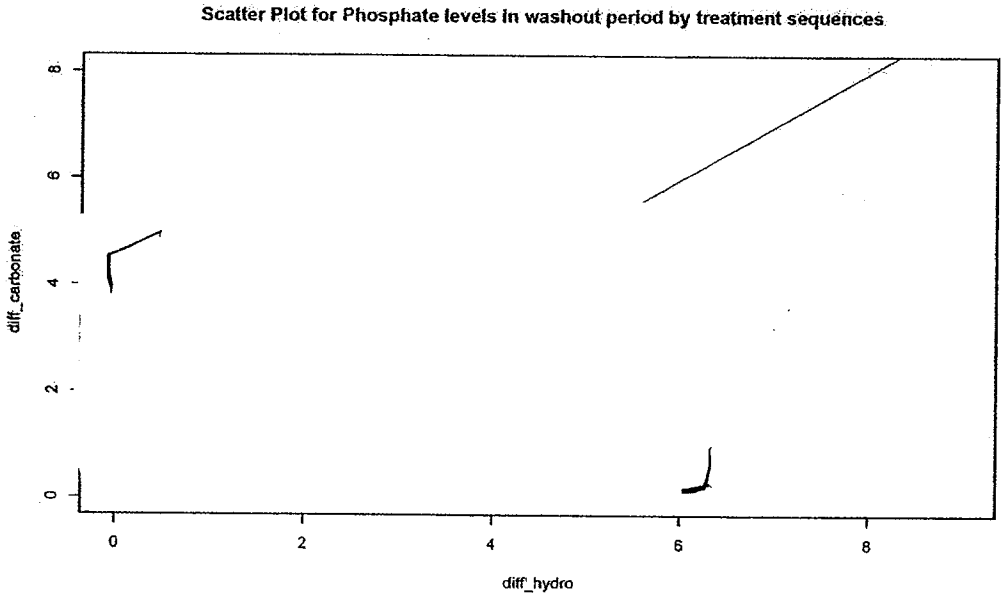
Figure 2: Scatter plat of phosphate levels on the hydrochloride salt (X-axis) and the carbonate salt (Y-axis).



With respect to the magnitude of effect, the plot below consists of a scatter plot comparing the effect in the cohort of patients who had phosphate levels at the end of the two-week withdrawal with their response at the end of the cross-over period. The key effect that I was looking for was whether the population that was enrolled actually had some effect on phosphate binders. The scatter plot indicates that some subjects did not really respond to either phosphate binder with some subjects having a robust response. Consequently, the data

do support that the phosphate binders both alter phosphate levels. It is, however, impossible to assert that the formulations are bioequivalent (plot supplied by Dr. Q Liu)..

Figure 3: Scatter plot comparing the difference of phosphate levels at withdrawal compared to the end of treatment for the hydrochloride salt (X-axis) and carbonate salt (Y-axis).



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/s/

Abraham Karkowsky
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MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-127

DISCIPLINE REVIEW LETTER

Genzyme Corporation
Attention: Mary Beth Clarke
Director, Regulatory Affairs
153 Second Avenue
Waltham, MA 02451

Dear Ms. Clarke:

Please refer to your December 20, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renvela (sevelamer carbonate) 800 mg Tablets.

A review of the Division of Medication Errors and Technical Support (DMETS) is complete and we have the following recommendations.

1. CONTAINER LABEL

a. Ensure the proprietary, established name, and strength are the most prominent information on the label. The established name should be at least ½ the size of the proprietary name. For further guidance we refer you to 21 CFR 201.10(g)(2).

b. It appears that the net quantity, 270 tablets, is more prominent than the strength, both in font size and because it appears in all capital letters. Decrease the font size of the net quantity and relocate it so that it is not in close proximity to the strength.

c. Relocate the 'RX ONLY' statement to the bottom 1/3 of the principal display panel so that it does not interfere with the readability of the proprietary name, established name, dosage form, and strength.

d. In the current presentation, the strength immediately follows the established name and the dosage form immediately follows the net quantity. Relocate the dosage form to appear in conjunction with the established name. For example, 'Sevelamer Carbonate Tablets' 800 mg.

e. [redacted] added to the label as a reminder to pharmacists to counsel patients prior to dispensing on this important information. Additionally, this packaging configuration could represent a unit-of-use 3-month supply. Thus, this warning could benefit patients if the bottle is dispensed directly to patients.

f. If you are proposing this packaging configuration as a unit-of-use (i.e. 3-month supply), then the container should have a child-resistant-closure in compliance with the Poison Prevention Act.

2. We request that you submit colored carton and container labels as soon as possible to allow for DMETS to review. You should also submit colored carton and container labels for Renagel.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and

in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Dr. Alisea Crowley
Regulatory Health Project Manager
(301) 796-1144

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
5/17/2007 07:41:03 AM

MEMORANDUM

To: Dianne Paraoan, RPM
Division of Cardiovascular and Renal Products, HFD-110

From: Lisa Hubbard, R.Ph., Regulatory Review Officer
DDMAC, HFD-42

Date: May 8, 2007

Re: Comments on draft labeling:
NDA 22-127
Renvela (sevelamer carbonate)

DDMAC has reviewed the annotated version of the proposed label (PI) for NDA 22-127 Renvela (sevelamer carbonate) and offers the following comments with regard to promotional considerations. Proposed wording from the insert is presented in *Italics,* followed by DDMAC comment.

HIGHLIGHTS: Indication and Usage
The proposed PI presents the phrase, " [redacted] " The phrase appears promotional in tone in this section of the label. DDMAC recommends eliminating the phrase from this section of the label.

Section 6.1: ADVERSE REACTIONS: Clinical studies experience
This section of the proposed PI presents the phrase, "possibly or probably" throughout and with an increased frequency then used in the Renagel label. For example, the title of Table 1 includes the phrase, "Possibly or Probably." The phrase does not appear in similar tables and text in the Renagel label. DDMAC recommends limiting the use of the phrase in order to prevent minimization of risks in promotional materials.

Section 9: DRUG ABUSE AND DEPENDENCE
This section of the PI does not appear in the Renagel PI. DDMAC recommends deleting the section unless the language is essential.

Section 12.2: Pharmacodynamics
This section of the PI makes claims such as, " [redacted] " The proposed section appears promotional in tone. Further, it is unclear from the language whether sevelamer carbonate has the same effect. Please consider eliminating the section or revising the section.

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/s/

Lisa Hubbard
5/8/2007 04:27:10 PM
DDMAC REVIEWER

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; WO 22, Mailstop 4447 Center for Drug Evaluation and Research

To: Norman Stockbridge, M.D.
Director, Division of Cardiovascular and Renal Products
HFD-110

Through: Nora Roselle, Pharm.D., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

From: Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: January 25, 2007

Re: ODS Consult 2007-71, Renvela (Sevelamer Carbonate Tablets), 800 mg
NDA# 22-127

This memorandum is in response to a January 10, 2007 request from your Division for a re-assessment of the proprietary name, Renvela, and evaluation of the container label and insert labeling. Renvela was previously evaluated in OSE Consult # 05-0243, dated August 18, 2006, and the name was found acceptable from a sound and look-alike perspective. However, we recommended the sponsor use a single proprietary name for this product rather than ———————. We have reiterated those concerns in Section A below.

The sponsor has revised the dosing of Renvela from ———————— to 1-2 tablets (800 mg to 1600 mg) three times a day with meals. Because of this revision, DMETS re-reviewed the names from our previous consult to determine if the new dosing poses any new safety concerns that were not considered at the time of the initial review. Following consideration of the new product characteristics, we have concluded that the dosing regimen does not pose any concerns with the names previously reviewed. However, DMETS has found two additional names, *** (NDA#) and Revatio, that have the potential to look similar to Renvela. *** is a pending application in which DMETS found the name acceptable. The two names are discussed in detail in Section B below followed by our comments on the revised labels and labeling.

A. SAFETY CONCERNS WITH CO-MARKETING OF RENAGEL AND RENVELA

The sponsor currently markets the product Renagel with an approved indication for the reduction of serum phosphorus in patients with end-stage renal disease on hemodialysis. The sponsor submitted a supplement for a new indication of use for Renagel, for use in patients receiving peritoneal dialysis. The Renvela indication of use is for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis. Although this does not specify hemodialysis or peritoneal dialysis, the indication of use for both products appears to be the same, or similar. Therefore, DMETS questions the need for two different names for the same active ingredient, overlapping indication of use, and manufactured by the same sponsor. Our experience with

*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

companies using dual trade names has led to concomitant use of both products resulting in medication errors with adverse outcomes (e.g. Wellbutrin and Zyban). DMETS notes that these products have similar drug profiles, except that the hydrochloride salt (Renagel) requires monitoring for ionic imbalance while Renvela does not. If a patient received the wrong drug (e.g., Renagel) and was not appropriately monitored, then the result could be an adverse outcome. Therefore, DMETS questions if both sevelamer products should be marketed concurrently, as there appears to be no clinical advantage to Renagel over Renvela.

B. NAME EVALUATION

——— *** and Revatio were evaluated for their likelihood for confusion with Renvela.

1. ——— *** is indicated in the treatment of a variety of bacterial infections. Both names begin with letters that may look similar when scripted (Ren vs.) and end in the same three letters (vel). However, each name contains additional letters in different placements that may help to differentiate the two names ('a' at the end of Renvela and in the middle of ***). Both products are supplied in one strength (800 mg vs. mg), dosage form (tablet), route of administration ( ), and overlap with respect to dose as they can be dosed as 'one tablet'. However, they do differ with respect to duration of therapy (continuous and chronic vs.). Therefore, prescriptions for *** will likely be prescribed for less than 10 tablets. Since Renvela is given three times a day, 10 tablets would only be for a 3 day supply. It is likely that this would cue the pharmacist to double check the prescription. Thus, the lack of convincing look-alike similarities, along with the duration of therapy of ——— *** will help to differentiate these two products when ordered.

2. Revatio was identified as a name that may look similar to Renvela when written. Revatio is used to treat pulmonary hypertension.

   Both names contain seven letters, begin with letters that may look similar when scripted (Ren vs. Rev), and contain upstrokes in similar placements (l vs. t). However, the endings of each name look different when scripted (vela vs. atio). Although there are some overlapping product characteristics such as strength (i.e., only one strength which can be omitted) and dose (800 mg and one or two tablets vs. 20 mg or one tablet), frequency of administration (TID), route of administration (oral), and dosage form (tablet), DMETS believes that the orthographic differences will help to differentiate these two names when written.

Renvela
Revatio

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C. LABELING AND LABELING EVALUATION

In the review of the container labels and insert labeling of Renvela, DMETS focused on safety issues relating to possible medication errors. However, draft copies of the labels were provided in black and white, and may not represent the true color of the labels and labeling. It is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used in the marketplace (i.e. color, design, etc.). Therefore, DMETS was unable to evaluate the effect that color, logos, design, etc may have on the readability of the labels. Despite this, we have identified the following areas of improvement, which may minimize potential user error.

1. CONTAINER LABEL

   a. Ensure the proprietary, established name, and strength are the most prominent information on the label. The established name should be at least ½ the size of the proprietary name. For further guidance we refer you to 21 CFR 201.10(g)(2).

   b. It appears that the net quantity, 270 tablets, is more prominent than the strength, both in font size and because it appears in all capital letters. Decrease the font size of the net quantity and relocate it so that it is not in close proximity to the strength.

   c. Relocate the 'RX ONLY' statement to the bottom 1/3 of the principal display panel so that it does not interfere with the readability of the proprietary name, established name, dosage form, and strength.

   d. In the current presentation, the strength immediately follows the established name and the dosage form immediately follows the net quantity. Relocate the dosage form to appear in conjunction with the established name. For example, '*Sevelamer Carbonate Tablets*' 800 mg.

   e. DMETS recommends that [redacted] to the label as a reminder to pharmacists to counsel patients prior to dispensing on this important information. Additionally, this packaging configuration could represent a unit-of-use 3-month supply. Thus, this warning could benefit patients if the bottle is dispensed directly to patients.

   f. If the sponsor is proposing this packaging configuration as a unit-of-use (i.e. 3-month supply), then the container should have a child-resistant-closure in compliance with the Poison Prevention Act.

2. INSERT LABELING

   No comments.

We would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have any other questions or need clarification, please contact Diane Smith, project manager, at 301-796-0538.

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/s/

Linda Wisniewski
4/12/2007 02:12:34 PM
DRUG SAFETY OFFICE REVIEWER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION
PREA DEFERRAL GRANTED

NDA 22-127

Genzyme Corporation
Attention: Mary Beth Clarke
Director, Regulatory Affairs
153 Second Avenue
Waltham, MA 02451

Dear Ms. Clarke:

Please refer to your December 20, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renvela (sevelamer carbonate) 800 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 18, 2007 in accordance with 21 CFR 314.101(a).

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

Reference is also made to your request for a deferral of pediatric studies and to our March 9, 2006 letter, in which we encouraged you to discuss obtaining a Written Request at the time of submitting this NDA for sevelamer carbonate.

We agree that a deferral of pediatric studies in patients < 1 month to 16 years of age is justified for sevelamer carbonate for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis because the drug would be ready for approval in adults before studies in children would be completed and of your intent to submit a NDA for the powder formulation of sevelamer carbonate.

In your submission, you agreed to provide your pediatric plan with your NDA for the powder formulation of sevelamer carbonate in which you intend to submit this year.

Accordingly, pediatric studies are deferred for your application under 505B(a) of the Federal Food, Drug, and Cosmetic Act until October 20, 2009.

We will fully address the requirements for your deferred pediatric studies upon our approval of this application. Deferred studies are considered required postmarketing study commitments.

If you have any questions, please call:

Dianne Paraoan
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
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