

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205739Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.1 PATENT INFORMATION

Patent Information Submission Statements

- Statement No. 1: Form FDA 3542a
U.S. Patent No. 7,556,799
- Statement No. 2: Form FDA 3542a
U.S. Patent No. 8,147,873
- Statement No. 3: Form FDA 3542a
U.S. Patent No. 8,216,560
- Statement No. 4: Form FDA 3542a
U.S. Patent No. 8,282,913
- Statement No. 5: Form FDA 3542a
U.S. Patent No. 8,287,847
- Statement No. 6: Form FDA 3542a
U.S. Patent No. 8,337,824
- Statement No. 7: Form FDA 3542a
U.S. Patent No. 8,475,780

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

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

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

NDA NUMBER

205739

NAME OF APPLICANT/NDA HOLDER

Relypsa, Inc.

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)

VELTASSA TM

ACTIVE INGREDIENT(S)

RLY5016S (company code for the calcium-sorbitol counterion
(b)(4) of patiromer)

STRENGTH(S)

(b)(4) 8.4, (b)(4) 16.8, (b)(4) 25.2 grams patiromer

DOSAGE FORM

Powder for Oral Suspension

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

U.S. Patent No. 7,556,799

b. Issue Date of Patent

07/07/2009

c. Expiration Date of Patent

02/27/2025

d. Name of Patent Owner

Relypsa, Inc.

Address (of Patent Owner)

700 Saginaw Drive

City/State

Redwood City/CA

ZIP Code

94063

FAX Number (if available)

Telephone Number

650-421-9500

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

Telephone Number

FAX Number (if available)

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

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

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1-6, 12-14, 17-19	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

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

Sarah McNulty

Date Signed

21 July 2014

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

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Sarah McNulty	
Address 700 Saginaw Drive	City/State Redwood City/CA
ZIP Code 94063	Telephone Number 650-421-9570
FAX Number (if available) 650-421-9770	E-Mail Address (if available) smcnulty@relypsa.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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VELTASSA TM

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RLY5016S (company code for the calcium-sorbitol counterion
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(b)(4) 8.4, (b)(4) 16.8, (b)(4) 25.2 grams patiromer

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1. GENERAL

a. United States Patent Number

U.S. Patent No. 8,147,873

b. Issue Date of Patent

04/03/2012

c. Expiration Date of Patent

03/11/2026

d. Name of Patent Owner

Relypsa, Inc.

Address (of Patent Owner)

700 Saginaw Drive

City/State

Redwood City/CA

ZIP Code

94063

FAX Number (if available)

Telephone Number

650-421-9500

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

Telephone Number

FAX Number (if available)

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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No

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

5. No Relevant Patents

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

6. Declaration Certification

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

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Date Signed

21 July 2014

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<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Sarah McNulty	
Address 700 Saginaw Drive	City/State Redwood City/CA
ZIP Code 94063	Telephone Number 650-421-9570
FAX Number (if available) 650-421-9770	E-Mail Address (if available) smcnulty@relypsa.com

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1. GENERAL

a. United States Patent Number
U.S. Patent No. 8,216,560

b. Issue Date of Patent
07/10/2012

c. Expiration Date of Patent
03/14/2027

d. Name of Patent Owner
Relypsa, Inc.

Address (of Patent Owner)
700 Saginaw Drive

City/State
Redwood City/CA

ZIP Code
94063

FAX Number (if available)

Telephone Number
650-421-9500

E-Mail Address (if available)

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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

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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

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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

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4. Method of Use

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

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

4.2 Patent Claim Number(s) (as listed in the patent) 1-4, 6-14, 17-22 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

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

5. No Relevant Patents

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<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p style="text-align: center;"><i>Sarah McNulty</i></p>	<p>Date Signed</p> <p style="text-align: center;">21 July 2014</p>
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<p><input checked="" type="checkbox"/> NDA Applicant/Holder</p> <p><input type="checkbox"/> Patent Owner</p>	<p><input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</p> <p><input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</p>
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<p>Address 700 Saginaw Drive</p>	<p>City/State Redwood City/CA</p>
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Powder for Oral Suspension

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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

U.S. Patent No. 8,282,913

b. Issue Date of Patent

10/09/2012

c. Expiration Date of Patent

3/11/2026

d. Name of Patent Owner

Relypsa, Inc.

Address (of Patent Owner)

700 Saginaw Drive

City/State

Redwood City/CA

ZIP Code

94063

FAX Number (if available)

Telephone Number

650-421-9500

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

Telephone Number

FAX Number (if available)

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

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

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

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

5. No Relevant Patents

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

6. Declaration Certification	
<p>6.1 <i>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.</i></p> <p><i>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</i></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p><i>Sarah McNulty</i></p>	<p>Date Signed</p> <p>21 July 2014</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Sarah McNulty</p>	
<p>Address</p> <p>700 Saginaw Drive</p>	<p>City/State</p> <p>Redwood City/CA</p>
<p>ZIP Code</p> <p>94063</p>	<p>Telephone Number</p> <p>650-421-9570</p>
<p>FAX Number (if available)</p> <p>650-421-9770</p>	<p>E-Mail Address (if available)</p> <p>smcnulty@relypsa.com</p>
<p>This section applies only to requirements of the Paperwork Reduction Act of 1995.</p> <p>*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*</p> <p>The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:</p> <p style="text-align: center;"> Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer Paperwork Reduction Act (PRA) Staff PRASStaff@fda.hhs.gov </p> <p style="text-align: center;"><i>"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."</i></p>	

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

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

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

NDA NUMBER

205739

NAME OF APPLICANT/NDA HOLDER

Relypsa, Inc.

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)

VELTASSA TM

ACTIVE INGREDIENT(S)

RLY5016S (company code for the calcium-sorbitol counterion
(b) (4) of patiromer)

STRENGTH(S)

(b) (4) 8.4, (b) (4) 16.8, (b) (4) 25.2 grams patiromer

DOSAGE FORM

Powder for Oral Suspension

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.

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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

U.S. Patent No. 8,287,847

b. Issue Date of Patent

10/16/2012

c. Expiration Date of Patent

10/11/2025

d. Name of Patent Owner

Relypsa, Inc.

Address (of Patent Owner)

700 Saginaw Drive

City/State

Redwood City/CA

ZIP Code

94063

FAX Number (if available)

Telephone Number

650-421-9500

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

Telephone Number

FAX Number (if available)

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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
4. Method of Use	
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1-4 and 6-25	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) VELTASSA TM (patiromer) is a potassium binder indicated for the treatment of hyperkalemia.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

6. Declaration Certification

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

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

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

Date Signed



21 July 2014

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

Sarah McNulty

Address

700 Saginaw Drive

City/State

Redwood City/CA

ZIP Code

94063

Telephone Number

650-421-9570

FAX Number (if available)

650-421-9770

E-Mail Address (if available)

smcnulty@relypsa.com

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DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

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

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

NDA NUMBER

205739

NAME OF APPLICANT/NDA HOLDER

Relypsa, Inc.

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)

VELTASSA TM

ACTIVE INGREDIENT(S)

RLY5016S (company code for the calcium-sorbitol counterion
(b) (4) of patiromer)

STRENGTH(S)

(b) (4) 8.4, (b) (4) 16.8, (b) (4) 25.2 grams patiromer

DOSAGE FORM

Powder for Oral Suspension

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1. GENERAL

a. United States Patent Number

U.S. Patent No. 8,337,824

b. Issue Date of Patent

12/25/2012

c. Expiration Date of Patent

5/29/2030

d. Name of Patent Owner

Relypsa, Inc.

Address (of Patent Owner)

700 Saginaw Drive

City/State

Redwood City/CA

ZIP Code

94063

FAX Number (if available)

Telephone Number

650-421-9500

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 f.c.)

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

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

4.2 Patent Claim Number(s) (as listed in the patent) 19, 22, 23 and 78 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
VELTASSA TM (patiromer) is a potassium binder indicated for the treatment of hyperkalemia.

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

Sarah McNulty

21 July 2014

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Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Sarah McNulty	
Address 700 Saginaw Drive	City/State Redwood City/CA
ZIP Code 94063	Telephone Number 650-421-9570
FAX Number (if available) 650-421-9770	E-Mail Address (if available) smcnulty@relypsa.com

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DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

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Food and Drug Administration
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Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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Department of Health and Human Services Food and Drug Administration	Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2016 See OMB Statement on Page 3.
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	NDA NUMBER 205739
	NAME OF APPLICANT/NDA HOLDER Relypsa, Inc.

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)
 VELTASSA TM

ACTIVE INGREDIENT(S) RLY5016S (company code for the calcium-sorbitol counterion (b) (4) of patiromer)	STRENGTH(S) (b) (4) 8.4, (b) (4) 6.8, (b) (4) 25.2 grams patiromer
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DOSAGE FORM
 Powder for Oral Suspension

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1. GENERAL

a. United States Patent Number U.S. Patent No. 8,475,780	b. Issue Date of Patent 07/02/2013	c. Expiration Date of Patent 3/30/2024
d. Name of Patent Owner Relypsa, Inc.	Address (of Patent Owner) 700 Saginaw Drive	
	City/State Redwood City/CA	
	ZIP Code 94063	FAX Number (if available)
	Telephone Number 650-421-9500	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, Is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 1-6, 9-17	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) VELTASSA TM (patiomer) is a potassium binder indicated for the treatment of hyperkalemia.	

5. No Relevant Patents

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

6. Declaration Certification

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

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

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

Sarah McNulty

Date Signed

21 July 2014

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

Sarah McNulty

Address

700 Saginaw Drive

City/State

Redwood City/CA

ZIP Code

94063

Telephone Number

650-421-9570

FAX Number (if available)

650-421-9770

E-Mail Address (if available)

smcnulty@relypsa.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"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 number."

EXCLUSIVITY SUMMARY

NDA # 205739

SUPPL # n/a

HFD # 110

Trade Name Veltassa

Generic Name Patiromer

Applicant Name Relypsa, Inc.

Approval Date, If Known October 21, 2015

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)

b) 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.

n/a

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:

n/a

c) Did the applicant request exclusivity?

YES NO

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

years

d) 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?

n/a

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# n/a

NDA# n/a

NDA# n/a

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# n/a

NDA# n/a

NDA# n/a

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.

Name of person completing form: Sabry Soukehal
Title: Consumer Safety Officer
Date: October 14, 2015

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

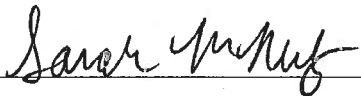
/s/

SABRY SOUKEHAL
10/14/2015

NORMAN L STOCKBRIDGE
10/14/2015

1.3.3 DEBARMENT CERTIFICATION

Relypsa, Inc. 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 (NDA 205739 for RLY5016 for Oral Suspension).

Signature: 

Sarah McNulty
Vice President, Regulatory Affairs

Date: 14 Oct 2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205739	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Veltassa Established/Proper Name: RLY5016 (Patiromer sorbitex calcium) Dosage Form: Oral powder		Applicant: Relypsa, Inc. Agent for Applicant (if applicable): N/A
RPM: Sabry Soukhehal		Division: Cardiovascular and Renal Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action October 21, 2015 User Fee Goal Date is <u>October 21, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1 – New Molecular Entity (NME)
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

- | | |
|---|--|
| NDAs: Subpart H | BLAs: Subpart E |
| <input type="checkbox"/> Accelerated approval (21 CFR 314.510) | <input type="checkbox"/> Accelerated approval (21 CFR 601.41) |
| <input type="checkbox"/> Restricted distribution (21 CFR 314.520) | <input type="checkbox"/> Restricted distribution (21 CFR 601.42) |
| Subpart I | Subpart H |
| <input type="checkbox"/> Approval based on animal studies | <input type="checkbox"/> Approval based on animal studies |

- | | |
|---|---|
| <input type="checkbox"/> Submitted in response to a PMR | REMS: <input type="checkbox"/> MedGuide |
| <input type="checkbox"/> Submitted in response to a PMC | <input type="checkbox"/> Communication Plan |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU |
| | <input checked="" type="checkbox"/> MedGuide w/o REMS |
| | <input type="checkbox"/> REMS not required |

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval October 21, 2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Note: Applicant originally submitted a PPI.
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	11/25/14 11/18/14
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: DMEPA: 02/13/15, 06/01/15, 08/27/15 DMPP/PLT (DRISK): 10/08/15 OPDP: 10/08/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	12/30/14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC 09/23/15 If PeRC review not necessary, explain: <u>N/A</u> 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA meeting (<i>indicate date of mtg</i>) 	03/27/13
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	11/22/11
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	05/01/15
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	07/27/15
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>): CMC End of Phase 2 meeting 	12/15/10
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	10/21/15
Division Director Summary Review (<i>indicate date for each review</i>)	10/17/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	10/09/15
PMR/PMC Development Templates (<i>indicate total number</i>)	2
Clinical	
❖ Clinical Reviews	

<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	12/03/14, 06/19/15
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	In review dated 06/19/15
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) 	06/22/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Microbiology Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Review(s) (<i>indicate date for each review</i>) 	12/12/14, 06/11/15
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) 	10/12/15
<ul style="list-style-type: none"> Clinical Pharmacology review(s) (<i>indicate date for each review</i>) 	12/18/14, 7/23/15, 10/16/15
<ul style="list-style-type: none"> ❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>) 	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Pharmacology/Toxicology Discipline Reviews 	
<ul style="list-style-type: none"> <ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	10/20/15
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	12/03/14, 06/19/15
<ul style="list-style-type: none"> ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No carc
<ul style="list-style-type: none"> ❖ ECAC/CAC report/memo of meeting 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>) 	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	7/28/15, 10/15/15 (addendum memorandum)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Not applicable
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	Included in the 7/28/15 Integrated Quality Assessment. FONSI recommended on 7/6/15
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	No significant environmental impact expected, 7/6/15
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Overall Manufacturing Inspection Recommendation: Approve (8/10/15) No Active OAI/POAI Alerts for any facilities confirmed 10/19/15

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

SABRY SOUKEHAL
10/23/2015

From: [Sarah McNulty](#)
To: [Soukehal, Sabry](#)
Subject: RE: NDA 205739 Teleconference on October 20, 2015
Date: Tuesday, October 20, 2015 7:53:45 PM

Hi Sabry,

With this email I am confirming receipt of your email below and the OPQ memo dated October 20, 2015. We agree to the four conditions listed in the memo.

As discussed with the review team in the teleconference earlier today, we would like to clarify that conditions # 1-3 apply to the packet labels only and that the carton labels as well as all other labeling materials will contain the final approved label language.

Thanks,
Sarah

From: Soukehal, Sabry [mailto:Sabry.Soukehal@fda.hhs.gov]
Sent: Tuesday, October 20, 2015 4:23 PM
To: Sarah McNulty
Subject: NDA 205739 Teleconference on October 20, 2015

Dear Sarah,

During our teleconference today we discussed the attached OPQ memo dated October 20, 2015 documenting our recommended corrective action for your printed carton and container labels. The memo required compliance with four conditions. It is our understanding that you agreed to the four conditions mentioned in the memo.

Kindly confirm receipt of this email and your agreement to the conditions mentioned in the memo.

If you have any questions, please do not hesitate to contact me.

Best regards,

Sabry Soukehal

Consumer Safety Officer

Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
sabry.soukehal@fda.hhs.gov

p: (240) 402 6187

f:(301) 796-9838

Address for desk and courtesy copies:

Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4170

Silver Spring, MD 20993

Address for official submissions to your administrative file:

Division of Cardiovascular and Renal Products

FDA, CDER, HFD-110

5901-B Ammendale Rd.

Beltsville, MD 20705-1266

Sarah McNulty

Vice President, Regulatory Affairs

Relypsa, Inc | 100 Cardinal Way | Redwood City | CA 94063

T 650.421.9570 | F 650.421.9770 | smcnulty@relypsa.com | www.relypsa.com

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 20, 2015

FROM: Wendy I. Wilson-Lee, Ph.D., OPQ/ONDP/ DNDPI/Branch I

SUBJECT: NDA 205739 – Recommended Corrective Action for Printed Carton and Container Labels

This memorandum documents the OPQ recommended corrective action to address the issue of incorrect storage condition printed on the carton and container labels for Patriomer powder, for oral suspension. Relypsa Inc. contacted the clinical division during the week of October 12, 2015 and indicated that the drug product intended for launch was labeled prior to receiving the Agency's final edits to the carton and container labels. Thus, the incorrect storage condition statement is listed on the to-be-marketed product. The applicant inquired if potential solutions exist to allow for distribution of the mislabeled product.

The ONDP review team members discussed this issue. Several concerns exist with allowing distribution of the mislabeled product – 1) the product would be mislabeled; 2) the current storage condition statement is vague and does not adequately described the recommended storage condition; and 3) the application does not contain data to support potential storage at (b)(4) conditions.

The recommended corrective action is to include a (b)(4) sticker on all carton and container labels for the launch product. We conferred with DMEPA regarding this recommended corrective action. DMEPA indicated that this approach was acceptable as an interim solution as long as all edits will be incorporated at the next printing. The applicant will need to commit to correct the storage condition statement at the next reprint and report the change to the Agency using the appropriate post-approval change mechanism. The following comment should be communicated to the applicant as soon as possible:

We acknowledge Relypsa's communication to the Agency regarding premature printing and labeling operations for Patriomer powder for oral suspension prior to final Agency approval of the proposed labels, resulting in inclusion of the incorrect storage condition statement. The current labels include the statement (b)(4). This language is considered vague and does not provide clear guidance to the patient regarding proper storage conditions. In addition, the submission did not include sufficient evidence of product quality at (b)(4) storage conditions. In order to allow distribution of the drug product labeled with the incorrect storage condition statement, we require compliance with four conditions:

- 1. Addition of a (b)(4) to all drug product carton and container labels currently mislabeled with the incorrect storage statement. Evidence of implementation should be provided to the Agency as soon as available.*
- 2. Commitment to implement the revised carton and container labels that incorporate the agreed upon storage condition statement and all other revisions at the next labeling printing.*
- 3. Communication to the Agency when the revised labels are implemented via the appropriate post-approval reporting mechanism.*
- 4. Commitment to not print and affix carton and container labels on any future drug product(s) intended for commercialization until final agreement is reached with the Agency on all aspects of the carton and container labels under this application or any future applications.*

We are available to discuss these requirements via teleconference if additional clarification is needed.

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/s/

SABRY SOUKEHAL
10/21/2015



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Application: NDA 205739

Drug Name: Veltassa (Patiromer Sorbitex Calcium)

Applicant: Relypsa Inc.

Meeting Type: Regulatory Briefing

Meeting Date and Time: September 18, 2015; 11:00 a.m. – 1:00 p.m.

Meeting Topic: Patiromer's Drug-Drug Interaction Liability

Meeting Chair: Sandra L. Kweder, MD

PRESENTERS

Aliza Thompson, MD
Clinical Team Leader, Division of Cardiovascular and Renal Products

Rajanikanth Madabushi, PhD
Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 1

MEETING RECORDER

Sabry Soukehal
Consumer Safety Officer, Division of Cardiovascular and Renal Products

SUMMARY OF THE ISSUE

Patiromer is a non-absorbed cation-exchange polymer that binds potassium in the lumen of the colon. On October 21, 2014, Relypsa submitted a new drug application for patiromer for the treatment of hyperkalemia. While the applicant's clinical development program demonstrated that patiromer is effective in lowering serum potassium concentrations in patients with

hyperkalemia (an accepted surrogate endpoint in this population), the results of *in vitro* drug-drug interaction studies raise concern about the drug's potential to bind other oral medications, thus limiting their absorption. How best to address and mitigate this risk remains an outstanding issue. The goal of the regulatory briefing is to get input from the panel on the strategy used to evaluate patiromer's drug-drug interaction potential and the proposed measures to mitigate risk.

BACKGROUND

Disease Background: Hyperkalemia is typically seen in patients with acute or chronic kidney disease or heart failure, particularly in those who are on renin-angiotensin-aldosterone system inhibitors (RAAS inhibitors). The population that develops hyperkalemia is often on multiple medications, and some of which provide important morbidity and mortality benefits.

Marked elevations in serum potassium levels can cause fatal cardiac arrhythmias, conduction abnormalities, muscle weakness and paralysis. Unfortunately, treatment options for removing excess potassium from the body are limited. Sodium polystyrene sulfonate (SPS, Kayexalate), approved in 1958, is the only cation-exchange resin approved in the U.S. for the treatment of hyperkalemia. To date, use of SPS has been limited by tolerability and safety concerns (i.e., colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy. Of note, SPS's potential to bind other co-administered medication has not been evaluated; hence, drug-drug interactions may also be an issue for this product.

Patiromer's Drug-Drug Interaction (DDI) Potential: Patiromer is not absorbed and interactions involving intestinal and hepatic enzymes and transporters are not a concern. Accordingly, patiromer's DDI evaluation focused on the product's potential to bind other medications in the gastrointestinal tract.

An *in vitro* screening test was used to evaluate patiromer's potential to bind co-administered medications; drugs from classes of medications commonly administered in the target population were screened. The results of this evaluation are shown in the table below. Of the 28 drugs that were tested, approximately half showed a positive interaction.

Table 1: Patiromer's Drug-Drug Interaction Potential-- Medications that were tested *in vitro* and results of testing

Allopurinol	Cinacalcet	Lisinopril	Rivaroxaban
Amlodipine	Ciprofloxacin	Lithium	Spirolactone
Amoxicillin	Clopidogrel	Metformin	Thiamine
Apixaban	Digoxin	Metoprolol	Trimethoprim
Aspirin	Furosemide	Phenytoin	Valsartan
Atorvastatin	Glipizide	Quinidine	Verapamil
Cephalexin	Levothyroxine	Riboflavin	Warfarin

Green: > 50% binding; Blue: 30% – 50% binding; Red: 28% binding

DISCUSSION

Question 1: Is our strategy for evaluating patiromer's drug-drug interaction potential rational?

In general the panel felt the approach for evaluating the interaction potential was reasonable. The Division confirmed that the *in vitro* data that were presented represent a worst-case scenario, and that the strategy for mitigating the interaction potential is mostly based on GI transit times. Some panel members felt that the clinical/practical implications of the *in-vitro* model were unclear and recommended clarifying that the findings represent *potential* drug-drug-interactions, as in practice, they may or they may not translate into clinically significant drug-drug interactions.

Question 2: Have we identified a reasonable strategy to mitigate the risk of drug-drug interactions with patiromer?

There were a range of opinions on what represented a reasonable strategy to mitigate risk. One panel member thought the interaction potential deserved to be clearly mentioned in the label and supported utilizing a Boxed Warning. Another panel member voiced concern that if the Division placed too many conditions on the use of Veltassa, it would drive prescribers to use sodium polystyrene sulfonate, a product with a less well characterized safety and efficacy profile. Another panel member thought that the conservative strategy adopted by the Division was appropriate. Some members voiced concern about restricting the duration of use as a means to mitigate the risk of drug-drug interactions. The panel emphasized that it was important that the label specify that the interaction occurs with medications that are orally administered.

Question 3: Should further studies be done prior to or after approval to address patiromer's drug-drug interaction potential?

Opinions varied on whether further studies are needed. Because of uncertainty regarding the practical application of the *in vitro* finding, some felt that clinical data would be useful.

Question 4: Should patiromer be approved?

The panel was in agreement that Veltassa provides net benefit and should be approved

Regulatory Briefing Meeting:

NDA 205739 – Treatment of Hyperkalemia

September 18, 2015

Sign In Sheet

Name	Sign-in	Office
Francis A Becker	<i>[Signature]</i>	DNDP
Leah Hart	<i>[Signature]</i>	DRISK
Alize Thompson	<i>[Signature]</i>	DCRP
Kim De Franco	<i>[Signature]</i>	DDF
Adeola Adekunle	<i>[Signature]</i>	DCI
Mona Khumava	<i>[Signature]</i>	DNDP/ONEIU
Rainer Paine	<i>[Signature]</i>	OND/ONP
Ju-Ping Lui	<i>[Signature]</i>	OND/OCP
Deepak Aggarwal	<i>[Signature]</i>	DAIP
Rama Duvach	<i>[Signature]</i>	DCRP
Fred Sewatore	<i>[Signature]</i>	DCRP
MARTIN ROSE	<i>[Signature]</i>	DCRP
Tzu-Yun McDonald	<i>[Signature]</i>	DCRP
Bridget Kane	<i>[Signature]</i>	DCRP
Brian Proesse	<i>[Signature]</i>	DCRP
Janine Stewart	<i>[Signature]</i>	DMPPA
Rachel Williamson	<i>[Signature]</i>	DMPPA
Amy Chen	<i>[Signature]</i>	DPV OSE
CYNTHIA LACIVITA	<i>[Signature]</i>	OSE
Kim LHERFELD	<i>[Signature]</i>	OSE
Shari Targum	<i>[Signature]</i>	OND/DCRP
Xuan Chi	<i>[Signature]</i>	OND/DCRP
Susan Lu	<i>[Signature]</i>	OSE/DPV

Name	Sign-in	Office
Fanki Kay	[Signature]	OB
Elaine Ferguson	[Signature]	OSE
Shewit Bezder	[Signature]	OGD
Prakash Bhagav	[Signature]	OGD/OB
Kellie Taylor	[Signature]	OSE
Vishali Papar	[Signature]	OND
Christa Mastromarino	[Signature]	JND
John Sharrett	[Signature]	OND
Charles Gamby	[Signature]	OND
JONATHAN GOLDSMITH	[Signature]	OND
Lynne Yao	[Signature]	OND
HONGLIU DING	[Signature]	OSE
Kachi Iloh	[Signature]	OND
KAREN MAHER	[Signature]	OND/NDP
Theresa Michele	[Signature]	OND/NDP
Danella Fitzgerald	[Signature]	OSE
Benata Albrecht	[Signature]	DTOP
Ramya Gopinath	[Signature]	DAIP
John Frutani	[Signature]	CDER/OS
Steve Grant	[Signature]	CDER/OND
Yu-Mee Kim	[Signature]	CDER/DPARP
Wiley Chambers	[Signature]	OAP/DTOP

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/s/

SABRY SOUKEHAL
10/21/2015



NDA 205739

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

Relypsa, Inc.
Attention: Ms. Sarah McNulty
Vice President, Regulatory Affairs
100 Cardinal Way
Redwood City, CA 94063

Dear Ms. McNulty:

We acknowledge your February 2, 2015 correspondence notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

Relypsa, Inc.
700 Saginaw Drive
Redwood City, CA 94063

to

Relypsa, Inc.
100 Cardinal Way
Redwood City, CA 94063

for NDA 205739 for RLY5016 for Oral Suspension, (b) (4) 8.4, (b) (4) 16.8, (b) (4) 25.2 grams patiromer.

We have revised our records to reflect this change.

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

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

If you have any questions, please contact:

Mr. Sabry Soukehal
Consumer Safety Officer
(240) 402-6187

Sincerely,

{See appended electronic signature page}

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

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/s/

EDWARD J FROMM
03/03/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 20, 2015

FROM: Wendy I. Wilson-Lee, Ph.D., OPQ/ONDP/ DNDPI/Branch I

SUBJECT: NDA 205739 – Recommended Corrective Action for Printed Carton and Container Labels

This memorandum documents the OPQ recommended corrective action to address the issue of incorrect storage condition printed on the carton and container labels for Patriomer powder, for oral suspension. Relypsa Inc. contacted the clinical division during the week of October 12, 2015 and indicated that the drug product intended for launch was labeled prior to receiving the Agency's final edits to the carton and container labels. Thus, the incorrect storage condition statement is listed on the to-be-marketed product. The applicant inquired if potential solutions exist to allow for distribution of the mislabeled product.

The ONDP review team members discussed this issue. Several concerns exist with allowing distribution of the mislabeled product – 1) the product would be mislabeled; 2) the current storage condition statement is vague and does not adequately describe the recommended storage condition; and 3) the application does not contain data to support potential storage at (b) (4).

The recommended corrective action is to include a (b) (4) on all carton and container labels for the launch product. We conferred with DMEPA regarding this recommended corrective action. DMEPA indicated that this approach was acceptable as an interim solution as long as all edits will be incorporated at the next printing. The applicant will need to commit to correct the storage condition statement at the next reprint and report the change to the Agency using the appropriate post-approval change mechanism. The following comment should be communicated to the applicant as soon as possible:

We acknowledge Relypsa's communication to the Agency regarding premature printing and labeling operations for Patriomer powder for oral suspension prior to final Agency approval of the proposed labels, resulting in inclusion of the incorrect storage condition statement. The current labels include the statement (b) (4). This language is considered vague and does not provide clear guidance to the patient regarding proper storage conditions. In addition, the submission did not include sufficient evidence of product quality at (b) (4) storage conditions. In order to allow distribution of the drug product labeled with the incorrect storage condition statement, we require compliance with four conditions:

1. *Addition of a (b) (4) to all drug product carton and container labels currently mislabeled with the incorrect storage statement. Evidence of implementation should be provided to the Agency as soon as available.*
2. *Commitment to implement the revised carton and container labels that incorporate the agreed upon storage condition statement and all other revisions at the next labeling printing.*
3. *Communication to the Agency when the revised labels are implemented via the appropriate post-approval reporting mechanism.*
4. *Commitment to not print and affix carton and container labels on any future drug product(s) intended for commercialization until final agreement is reached with the Agency on all aspects of the carton and container labels under this application or any future applications.*

We are available to discuss these requirements via teleconference if additional clarification is needed.

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/s/

SABRY SOUKEHAL
10/21/2015



NDA 205739

GENERAL ADVICE

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) dated October 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We also refer to the information you provided during the teleconference on July 21, 2015, and to your July 29, 2015 submission.

We have reviewed your submission as well as the published literature on gastric emptying of liquids and small particles. Based on our review of this information, we do not believe that a (b) (4) hour window of separation is sufficient to mitigate the risk of a clinically significant interaction between patiromer and concomitant medications. Instead, we conclude that a 6-hour window of separation should be used to mitigate this risk. The basis for our conclusion is as follows:

1. You state that there is strong evidence that liquids and small particles (less than 2 – 3 mm) are emptied rapidly from the stomach, whereas, larger particles are retained in the stomach for longer periods of time (Christensen, 1985). You also cite literature that indicates that pellet dosage forms ≤ 1 mm pass through the closed pylorus and behave more like a solution than a solid (Christensen, 1985, Kelly, 1980). Therefore, you expect patiromer, which is administered as a suspension of polymer beads that are approximately (b) (4) in diameter, to leave the stomach in the first “liquid phase” of gastric emptying.

We question your assumption that small particles behave like liquids for the purpose of determining gastric emptying [Davis (Gut, 1986, 27, 886-892) and Newton [Int. J. Pharmaceutics 395(2010) 2-8]. The publication by Davis provides a comparison of the transit time of various pharmaceutical dosage forms through the gastrointestinal tract. As shown in the figure below, pellets ranging from 0.3 – 1.2 mm displayed a wide range of transit times for gastric emptying. We also note that transit times sometimes exceeded (b) (4) hours, especially when the pellets were administered with a heavy breakfast (see P13 and P14 in the figure below). Based on the submitted information and our review of the published literature, we believe that a 6-hour window of separation is more appropriate for mitigating the risk of a drug interaction.

Figure: Comparison of gastric emptying of pharmaceutical dosage forms [Davis (Gut, 1986, 27, 886-892)].

COPYRIGHT MATERIAL WITHHELD



Table *Details of pharmaceutical formulations, subjects, and fed states*

COPYRIGHT MATERIAL WITHHELD

M—male, F—female, D—diarrhoea, C—constipation, FA—fasted, LB—light breakfast (~1500 kJ), HB—heavy breakfast (~3600 kJ), VA—variable meal, SM—standard meal (800 kJ).

2. To address the potential effect of food on transit time, you cite a study by Olausson et al. This publication shows faster emptying of a small particle meal (80% in 3 hours) as compared to a large particle meal in patients with diabetic gastroparesis. Given the ^(b)(4) size of patiomer, you conclude that patiomer would exit well before 6 hours in patients with gastroparesis. While we agree that 6 hours provides adequate separation, we do not agree with your conclusion that ^(b)(4) hours is adequate. We note that all of the patients in this study were medicated with the gastrokinetic drug cisapride, hence it is difficult to extrapolate the findings in this study to the target population, which likely includes patients with untreated or undertreated gastroparesis.
3. A key premise of your submission is that patiomer's behavior can be extrapolated from the experience (published literature and modeling exercises) with the gastric emptying of liquids. As stated in our first comment, it's not clear that patiomer behaves like a liquid.

We also note that some have questioned the practice of measuring the gastric emptying of liquids to determine gastric emptying times. For example, Couturier et al (Nuclear Medicine Communications: 2004, Vol 25 No 11) state that in their study, gastric emptying of liquids provided poor and unreliable information with regard to discriminating patients with gastroparesis from controls and with regard to drawing pathological profiles of abnormal gastric emptying.

If you have any questions or would like to schedule a teleconference to discuss this issue further, please contact Sabry Soukehal, Consumer Safety Officer, at (240) 402-6187.

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 L STOCKBRIDGE
09/16/2015



NDA 205739

LABELING PMR/PMC DISCUSSION COMMENTS

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) dated October 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We also refer to our December 24, 2014, letter in which we notified you of our target date of July 3, 2015 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017.”

On May 20, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by July 17, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, please call me, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Sabry Soukehal
Consumer Safety Officer
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE: PI

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SABRY SOUKEHAL
07/02/2015



NDA 205739

GENERAL ADVICE

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We also refer to your May 7, 2015, submission of a revised Pediatric Study Plan containing your requests for deferral of the required pediatric assessments and (b) (4)

(b) (4)
Please see the attached document for our comments on your May 7, 2015, submission. You should submit your revised pediatric study plan to your NDA within 30 days or less of receipt of this communication. We would be happy to speak with you regarding our comments if needed.

If you have any questions, please contact Sabry Soukehal, Consumer Safety Officer at (240) 402 6187.

Sincerely,

{ See appended electronic signature page }

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Pediatric Study Plan with comments from the Division

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/s/

NORMAN L STOCKBRIDGE
07/01/2015

Folkendt, Michael M

From: Folkendt, Michael M
Sent: Tuesday, June 09, 2015 9:28 AM
To: 'Sarah McNulty'
Subject: RE: NDA 205739: Quality IR Letters

Dear Ms. McNulty,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following recommendation.

- During our methods validation analysis, we noticed that for the proposed Total Potassium Exchange Capacity Test, (b) (4)

Please let me know when you can respond to this recommendation. If you have any questions, please contact me either via phone at 301-796-1670 or email at Michael.folkendt@fda.hhs.gov.

Sincerely,
Michael

Michael Folkendt
Associate Director for Regulatory Affairs (ADRA)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
301-796-1670

From: Sarah McNulty [<mailto:smcnulty@relypsa.com>]
Sent: Monday, June 08, 2015 6:20 PM
To: Folkendt, Michael M
Subject: NDA 205739: Quality IR Letters

Hi Michael,

Thank you very much for your message. This email is to request that quality IR letters related to NDA 205739 be sent to me via email.

Regards,

Sarah

Sarah McNulty

Vice President, Regulatory Affairs

Relypsa, Inc | 100 Cardinal Way | Redwood City | CA 94063

T 650.421.9570 | F 650.421.9770 | smcnulty@relypsa.com | www.relypsa.com

Notice: This e-mail message, together with any attachments, contains information of Relypsa, Inc. that may be confidential, proprietary, copyrighted, privileged and/or protected work product, and is meant solely for the intended recipient. If you are not the intended recipient, and have received this message in error, please contact the sender immediately, permanently delete the original and any copies of this email and any attachments thereto.

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/s/

MICHAEL M FOLKENDT
06/09/2015



NDA 205739

GENERAL ADVICE

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4), 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We also refer to your October 21, 2014 submission, containing draft carton and container labels.

We have reviewed the referenced material and have the following comments:

DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS

General Comments (Container Labels and Carton Labeling)

1. Revise the presentation of the proprietary name from all upper case (i.e. VELTASSA) to title case (i.e. Veltassa) to improve the readability of the name.
2. Ensure that the established name is expressed in a font size that is at least half the size of the font used in the proprietary name in accordance with 21 CFR 201.10(g)(2).
3. Remove the trailing zero in the (b) (4) strength expression (b) (4) on all labels and labeling panels to avoid a ten-fold misinterpretation.
4. The proposed container labels and carton labeling include usual dose language under the header "Directions for Use". However, a separate Usual Dosage statement is required per 21 CFR 201.55. To address this issue, revise and move the sentence "See full Prescribing Information (b) (4)", which is currently under the header titled "Directions for Use", to a new header titled "Usual Dosage". The revised statement should read as "Usual Dosage: See prescribing information".
5. Ensure that the placeholder "[active ingredient]" on all container labels and carton labeling will be updated to the correct nomenclature for the active ingredient.

Carton labeling

1. The text under "Directions for Use" should include instructions on what to do if powder remains in the glass after drinking. Based on the current language in Section 2.2 of the full prescribing information, we recommend adding the following text: "If powder remains in the

glass after drinking, add more water, stir, and then drink immediately. Repeat as needed to ensure the entire dose is administered”

2. For the (b) (4) size, relocate the “Directions for Use” statements from the side panel to the back panel and increase the font size of the text.
3. Remove or provide a rationale for the (b) (4) statement (b) (4) dispense as 1 box”.

If you have any questions, please contact Sabry Soukehal, Consumer Safety Officer, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
05/01/2015



NDA 205739

MID-CYCLE COMMUNICATION

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We also refer to the teleconference between representatives of your firm and the FDA on April 2, 2015. The purpose of the teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please contact Sabry Soukehal, Consumer Safety Officer, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD
Clinical Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: 02 April 2015, 11:00 a.m. – 12:30 p.m. Eastern Time

Application Number: 205739
Product Name: VELTASSA (patiromer sorbitex calcium)
Indication: Treatment of Hyperkalemia
Applicant Name: Relypsa, Inc.

Meeting Chair: Aliza Thompson, MD
Meeting Recorder: Sabry Soukehal, RQAP-GLP

FDA ATTENDEES

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Mike Monteleone, MS, RAC	Associate Director for Labeling
Aliza Thompson, MD	Clinical Team Leader
Shen Xiao, MD	Clinical Reviewer
Albert Defelice, PhD	Non-Clinical Team Leader
William Link, PhD	Non-Clinical Reviewer
Alexis Childers, RAC	Sr. Regulatory Health Project Manager
Quynh Nguyen, PharmD, RAC	Sr. Regulatory Health Project Manager
Sabry Soukehal, RQAP-GLP	Consumer Safety Officer

*Office of Clinical Pharmacology

Mehul Mehta, PhD	Director
Rajnikanth Madabushi, PhD	Team Leader
Ju-Ping Lai, PhD	Clinical Pharmacology Reviewer

*Office Pharmaceutical Quality

Kasturi Srinivasachar, PhD	Acting Branch Chief
Mohan Sapru, PhD	CMC Team Leader
Raymond Frankewich, PhD	CMC Reviewer

*Office of Scientific Investigations/Office of Compliance

Sharon Gershon, PharmD	Regulatory Reviewer
------------------------	---------------------

*Office of Surveillance and Epidemiology

Amy Chen, PharmD	Safety Evaluator
------------------	------------------

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou
Marc Goldstein

Independent Assessor
Independent Assessor

APPLICANT ATTENDEES

Claire Lockey

Sr. Vice President, Pharmaceutical Development
and Regulatory Affairs

Wilhelm Stahl

Sr. Vice President, Pharmaceutical Operations

Martha Mayo, PharmD

Vice President, Clinical Development

Arpad Simon

Vice President, Drug Safety & Pharmacovigilance

Charles Du Mond, PhD

Vice President, Biometrics

Sarah McNulty

Vice President, Regulatory Affairs

Betty Clark

Senior Director, Regulatory Affairs

Lydie Yang

Director, Regulatory Affairs

Regulatory Consultant

Clinical Pharmacology Consultant

1.0 INTRODUCTION

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 or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

CMC:

Dr. Srinivasachar discussed two issues related to the drug substance and one issue related to the drug product.

The first drug substance issue related to the acceptance criterion for (b) (4) impurities of (b) (4) ppm. The concern is that one acceptance criterion for all (b) (4) is not appropriate because it would not distinguish (b) (4) of higher toxicity from those of lower toxicity. Dr. Srinivasachar indicated that the Applicant should apply separate acceptance criteria to each impurity instead of using the aggregate criterion of (b) (4) ppm. The Applicant agreed to address this issue and asked if the Division had specific limits in mind. Dr. Srinivasachar encouraged the Applicant to refer to the available guidances on the subject.

The second drug substance issue related to the United States Adopted Name (USAN). The review team indicated that an email received from the Applicant on March 31, 2015 and an official submission received on April 1, 2015 addressed the original concern about not having an assigned USAN. Hence, the original concern is no longer considered an issue. However, the review team suggested removing all references to the word (b) (4) as it implies (b) (4). Use of the term (b) (4) could be misleading and could lead to labeling issues. The review team would not be able to suggest an alternative name but would be able to provide guidance to the Applicant upon request.

As for the drug product issue, Dr. Srinivasachar stated that there did not appear to be any discussion of the product's (b) (4) in the application. He noted that sorbitol was added as a (b) (4) for the drug substance, but not as a (b) (4). Hence, it remains unclear whether (b) (4). He noted that (b) (4) could lead to non-compliance. The Applicant indicated that in the clinical trials, compliance was good overall and no complaints about (b) (4) were noted. The Applicant added that they were exploring whether the drug could be (b) (4) but they did not have the (b) (4)-testing completed prior to the NDA submission. However, the Applicant does not believe that (b) (4). Dr. Srinivasachar requested that the Applicant submit a justification to the NDA.

CLINICAL PHARMACOLOGY:

Three issues were discussed with the Applicant.

The first issue was the Applicant's proposal to incorporate language on once daily dosing in the Dosage and Administration section of the label. Dr. Lai indicated that she believes that the findings in study RLY5016-102 support the use of a QD regimen. Dr. Lai noted that the draft label proposal that was submitted via email seemed reasonable as a concept but that the specifics of the labeling language would be determined as a part of the labeling review in consultation with the signatories. The Applicant was advised to submit their revised label to the NDA. The Applicant had no questions regarding this point.

The second issue was dosing based on baseline serum potassium levels. Dr. Lai stated that based on her review of study RLY5016-205, and specifically the findings in Cohort 3, she does not see a need for a higher starting dose in patients with a baseline serum potassium ≥ 5.5 mEq/L. Her analyses indicate that a subject's baseline serum potassium level was the most significant predictor of the effect on serum potassium; in contrast, the dose of patiromer was not. Dr. Lai stated that these findings may have implications for the Dosing and Administration section of the label.

The Applicant emphasized that a starting dose of 8.4 g was not studied in subjects with high potassium levels. The Applicant also stated that when looking at the average daily dose, it does appear that those with higher potassium levels need the higher dose. The Applicant asked how the Agency envisioned dose titration in these patients. Dr. Madabushi responded by saying that the increments should not be different given that the dose-response relationship is flat. Dr. Madabushi also stated that these are the review team's initial thoughts on the matter, and encouraged the Applicant to submit additional information addressing the need for different

starting doses based on baseline serum potassium levels as well as the need for titration.

The third discussion point was DDI liability. Dr. Thompson stressed that patiromer's DDI liability was a significant safety issue that needed to be addressed by the Applicant. Since this patient population is typically taking multiple medications, the review team believes that it is critical to adequately address this potential risk. While available data allow for mitigation of this risk for those drugs that were screened, it is also important to address the potential risk associated with drugs that were not screened. Dr. Madabushi indicated that the available information does not allow one to provide "universal" instructions on mitigating this risk for drugs that were not studied. A QD regimen of patiromer, (b) (4) would help address this issue in some settings, but not for drugs that are to be administered BID. In this situation, adequate spacing of drugs could be considered. The review team advised the Applicant to propose a strategy that adequately addressed patiromer's potential to interact with other administered drugs.

The review team indicated that it is considering options to communicate this risk as a part of the Dosing and Administration and Warnings and Precautions sections of the label, in addition to the Drug Interactions and Clinical Pharmacology sections of the label. Dr. Thompson also stated that a boxed warning and Medication Guide (outside of a REMS) may be needed to address this risk. Another option that is being considered by the review team is approval of patiromer (b) (4). The Applicant stated that the (b) (4) Dr. Thompson explained that a Medication Guide would be required to be dispensed to patients whereas an (b) (4) would not.

Dr. Thompson also requested additional information on any guidance that was given to investigators regarding the use of concomitant medications in study subjects.

ADDITIONAL DISCUSSION DURING MEETING:

The Applicant asked if they could get feedback on labeling, including carton and container labeling, as they would like to start printing soon. Dr. Thompson replied that the Division is not able to provide comments on labeling at this time. The Applicant would be printing at their own risk.

The Applicant asked if they will be receiving a GMP inspection as a BIMO GCP and PAI inspection has occurred already. Dr. Thompson indicated that the CMC reviewers had already left the meeting. She also reminded the Applicant that the purpose of the Mid-Cycle Communication meeting is to provide the Applicant with an update on the status of the review, not to field questions.

The Applicant asked when they could expect to receive comments on their Pediatric Study Plan (PSP). Mr. Soukehal replied that he expects to send the Division's comments on the PSP by the end of the following week.

3.0 INFORMATION REQUESTS

Dr. Srinivasachar indicated that the Applicant will receive additional CMC comments in an Information Request Letter.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

See discussion about DDI liability under Section 2.0.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee Meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The LCM is scheduled for June 29, 2015.

Label negotiations are set to begin by July 3, 2015.

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/s/

ALIZA M THOMPSON
05/01/2015



NDA 205739

INFORMATION REQUEST

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

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

- Regarding the composition of RLY5016 for Oral Suspension, the formulation does not involve the use of any (b) (4), and it is not clear whether the calcium-sorbitol counterion exhibits (b) (4). To address the (b) (4), provide justification, with supporting data, for omitting the use of any (b) (4) in RLY5016 for Oral Suspension.
- Remove any references to Veltassa or to RLY5016S in its labeling as a (b) (4) sorbitol. Phrases such as (b) (4) should be removed from the labeling.
- Establish separate acceptance criteria in the Release Specification for RLY5016S drug substance for each of the Class (b) (4) metals determined in the test for Elemental Impurities. These individual acceptance criteria should be consistent with the recommendations of ICH Q3D.
- Provide a commitment to file a prior-approval supplement (PAS) to this NDA to qualify any change to the (b) (4) RLY5016S drug substance.

- Submit information that demonstrates that all fluoride present in a sample of RLY5016S as fluoride ion or as CaF_2 is completely released from the sample and measured as fluoride, using your analytical procedure for Determination of Fluoride in RLY5016S by ISE. It is important to know that this analytical procedure is capable of releasing all fluoride in a sample which may be present as CaF_2 , given the low solubility of CaF_2 .
- Since you have not provided for [REDACTED] (b) (4) of this drug substance, confirm that no [REDACTED] (b) (4) will be performed for material that does not meet IPC or release specification.
- Clarify whether or not the test for Potassium Binding Capacity (PBC) is part of the stability specification for RLY5016S drug substance. In the footnotes of the stability specification provided in sec. 3.2.S.8.1, it is stated that the commercial (release) analytical procedure for this test was implemented at the [REDACTED] (b) (4) time point. However, PBC is not part of the release specification for RLY5016S. The only test for potassium capacity in the commercial (release) specification is the test for TKEC, which is also part of the stability specification. If a test for PBC is part of the stability specification, provide a description of the analytical procedure used and provide validation data for the procedure.
- Submit information that demonstrates that the [REDACTED] (b) (4) index of RLY5016S [REDACTED] (b) (4) is low compared to other polymers, and is indicative of extensive crosslinking.
- Provide validation data for the following two analytical procedures, which are part of the proposed stability specification of RLY5016S:
 - Determination of Impurities in RLY5016S by GC-FID Method 1.
 - [REDACTED] (b) (4) Impurities in RLY5016S by LC-UV Method 1.
- Provide a complete explanation of the experiment used to validate Accuracy for the analytical procedure for Calcium Identity and Calcium Content of RLY5016S by IC. In the validation report a [REDACTED] (b) (4) spiking solution is mentioned, but results obtained for all the sample preparations were close to [REDACTED] (b) (4). Accuracy should be demonstrated by application of the procedure to an analyte of known purity / content.
- Regarding the demonstration of Accuracy for the analytical procedure for Total Potassium Exchange Capacity (TKEC) of RLY5016S: Provide a complete explanation of the experiment used, and provide the complete validation data. In addition, explain how RLY5016S samples containing [REDACTED] (b) (4) would generate results in the middle of the acceptance criterion range (results reported for such samples were [REDACTED] (b) (4) [REDACTED] (b) (4)).
- Provide the raw data and the curve produced in the evaluation of Linearity for the TKEC procedure for RLY5016S. The position of the y-intercept should be evaluated.

If you have any questions, please contact Sabry Soukehal, Consumer Safety Officer, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
04/15/2015



NDA 205739

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Relypsa, Inc.
Attention: Ms. Sara McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your Drug Application (NDA) dated October 21, 2014, received October 21, 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Veltassa (patiromer) Powder for Oral Suspension, (b) (4), 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is October 21, 2015.

We have reviewed your (b) (4), and even if one were to conclude that the form of hyperkalemia addressed by this therapy represents a serious condition, it is not obvious that Veltassa provides a significant improvement in safety or effectiveness over available therapies. You note that Kayexalate has been associated with some serious complications which have not been seen with your therapy (i.e., severe constipation and life-threatening intestinal impactions, and colonic necrosis when administered with sorbitol). However, these appear to be rare/uncommon events in sick patients (e.g., neonates). (b) (4)

You also assert that your therapy provides a (b) (4), based on historical data and post-marketing reports of safety events. To support such a conclusion, however, you will need to test (b) (4) in clinical trials.

We are reviewing your application according to the processes for a standard review as described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as

described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 3, 2015.

We are not currently planning to hold an advisory committee meeting to discuss this application.

We request that you submit the following to us:

1. Please submit several samples of your drug product, and in each strength proposed for marketing, directly to:

Food and Drug Administration
Division of Cardiovascular and Renal Products
Attn: Edward Fromm, R.Ph., RAC
10903 New Hampshire Ave.
WO Building 22, Rm. 4162
Silver Spring, MD 20993

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a (b) (4) deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the (b) (4) (b) (4) deferral request is denied.

If you have any questions, please call Sabry Soukehal, Consumer Safety Officer, at (240) 402-6187.

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 L STOCKBRIDGE
12/24/2014



NDA 205739

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Relypsa, Inc.
Attention: Ms. Sara McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
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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 L STOCKBRIDGE
12/24/2014



NDA 205739

**METHODS VALIDATION
MATERIALS RECEIVED**

Relypsa, Inc.
Attention: Sarah McNulty, Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Sarah McNulty:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Veltassa (patiromer) powder for oral suspension and to our December 3, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 17, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/17/2014



NDA 205739

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063
smcnulty@relypsa.com

Dear Sarah McNulty:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Veltassa (patiromer) Powder for Oral Suspension.

We will be performing methods validation studies on Veltassa (patiromer) Powder for Oral Suspension, as described in NDA 205739.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Identity of RLY5016S by Fluorine Content Using Oxygen Combustion with ISE
Determination of Fluoride in RLY5016S by ISE
Calcium Identity and Calcium Content of RLY5016S by IC
Total Potassium Exchange Capacity of RLY5016S by IC
Sorbitol Content in RLY5016S by LC-RI
Particle Size Distribution of RLY5016S by Laser Diffraction
Total Potassium Exchange Capacity of RLY5016S For Oral Suspension by IC

Samples and Reference Standards

2 x 1 g RLY5016H reference standard
30 g RLY5016S
(b) (4) USP sorbitol reference standard
(b) (4) USP mannitol reference standard

Equipment

- 1 (b) (4) column, 250 x 4 mm
- 1 (b) (4) guard column, 50 x 4 mm
- 10 syringe filters 13 mm (b) (4)
- 10 syringe (b) (4)
- 1 (b) (4) particle size
- 1 package (b) (4)
- 1 package pH test strips, (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/03/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 075615
NDA 205739

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Relypsa, Inc.
700 Saginaw Drive
Redwood City, CA 94063

ATTENTION: Sarah McNulty
Executive Director, Regulatory Affairs

Dear Ms. McNulty:

Please refer to:

- Your Investigational New Drug Application (IND) submitted under section 505 (i) of the Federal Food, Drug, and Cosmetic Act for Patisomer Powder For Oral Suspension 4.2 g, 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g
- Your New Drug Application (NDA) dated and received October 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Patisomer Powder For Oral Suspension (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g

We also refer:

- Your June 19, 2014, correspondence, received June 20, 2014, requesting review of the proposed proprietary name, Veltassa
- Your June 30, 2014, correspondence, received July 1, 2014, clarifying the starting dose and how dose increments will be determined
- Your correspondence, dated and received November 3, 2014, requesting review of your proposed proprietary name, Veltassa

We have completed our review of the proposed proprietary name, Veltassa and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your June 19, 30, and November 3, 2014, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Russell Fortney, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/25/2014



NDA 205739

NDA ACKNOWLEDGMENT

Relypsa, Inc.
Attention: Ms. Sara McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: RLY5016 for Oral Suspension, (b) (4), 8.4, (b) (4) 16.8, (b) (4), 25.2 grams patiomer

Date of Application: October 21, 2014

Date of Receipt: October 21, 2014

Our Reference Number: NDA 205739

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 20, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Russell Fortney, R.Ph.
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

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

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/s/

EDWARD J FROMM
10/27/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 75615

MEETING MINUTES

Relypsa, Inc.
Attention: Claire J. Lockey
Senior Vice President, Pharmaceutical Development
5301 Patrick Henry Drive
Santa Clara, CA 95054

Dear Ms. Lockey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RLY5016.

We also refer to the meeting between representatives of your firm and the FDA on November 22, 2011.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: November 22, 2011 2:00 PM
Meeting Location: White Oak Campus

Application Number: IND 75615
Product Name: RLY5016
Indications: Treatment of hyperkalemia
Sponsor/Applicant Name: Relypsa

Meeting Chair: Robert Temple
Meeting Recorder: Russell Fortney

FDA ATTENDEES

Office of Drug Evaluation I

Robert Temple, MD Director
 Ellis Unger, MD Deputy Director

Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD Director
 Stephen Grant, MD Deputy Director
 Aliza Thompson, MD Medical Team Leader
 Shona Pendse, MD Medical Reviewer
 Al DeFelice, PhD Pharmacology Team Leader
 William Link, PhD Pharmacologist
 Russell Fortney Regulatory Project Manager

Office of Clinical Pharmacology

Rajanikanth Madabushi, PhD Team Leader
 Peter Hinderling, MD Reviewer

Office of Biostatistics, Division of Biometrics I

Jim Hung, PhD Director
 Fanhui Kong, PhD Statistician

Office of Medical Policy

Patrick Archdeacon, MD Medical Officer
 Jun Li, JD Regulatory Counsel Staff Fellow

RELYPSA ATTENDEES

Gerrit Klaerner, PhD President and Chief Operating Officer
 Claire Lockey Sr. Vice President, Pharmaceutical Development and Regulatory Affairs

 Jerry Buysse, PhD Chief Scientific Officer and Sr. Vice President, Research
 I-Zu Huang, MD Vice President, Clinical Development
 Sarah McNulty Director, Regulatory Affairs

Consultants

(b) (4)

BACKGROUND

RLY5016 is a non-absorbed polymeric drug that binds potassium in the gastrointestinal tract and is being developed as a treatment for hyperkalemia. This purpose of this meeting is to discuss the design of Relypsa's two proposed Phase 3 protocols. Preliminary responses to the sponsor's questions were communicated to the sponsor prior to the meeting and are copied below, followed by any additional discussion that took place during the meeting.

DISCUSSION

The following questions were discussed:

1. Relypsa is conducting a Phase 2 study (RLY5016-205) in up to 300 diabetic nephropathy patients with CKD who require treatment for hyperkalemia caused by their current RAAS inhibitor therapy or become hyperkalemic while receiving maximum (within label) doses of RAAS inhibitor therapy during the run-in period. Study RLY5016-205 utilizes an open-label, dose-ranging, titration-to-effect design with treatment duration of up to one year and a RLY5016 withdrawal period of up to 28 days. Patients are assigned to one of two serum potassium strata (Stratum 1: serum K⁺ > 5.0 – 5.5 mEq/L and Stratum 2: serum K⁺ > 5.5 – < 6.0 mEq/L), each with three different starting doses, two of which overlap. This study is currently being conducted outside the US (Western and Eastern Europe). The protocol and a summary of preliminary results as of October 25, 2011 are provided in this Meeting Package.
 - a. An interim analysis of study RLY5016-205 is intended to define the starting dose of RLY5016 for each of the two serum potassium strata based on data from 10 patients per dose group (three dose groups per stratum, two overlapping doses in each) for a total of 60 patients treated for 4 weeks. The interim analysis will examine the primary endpoint of change in serum potassium from baseline to 4 weeks or first titration of RLY5016 dose, whichever occurs first. Should the interim analysis not provide an unambiguous starting dose, dose ranging will be continued and based on the open-label nature of the RLY5016-205 study the data will be analyzed in 60 patient increments (10 patients per dose group) going forward. Does the Agency agree that the design and planned interim analysis of study RLY5016-205 can be used to define the starting doses for both potassium strata?

Preliminary Agency Response: Your approach seems reasonable.

Additional discussion during meeting: No additional discussion.

- b. Does the Agency agree that Relypsa can initiate Phase 3 studies once the RLY5016-205 interim analysis to define the starting dose of RLY5016 is complete and a dose is selected for each of the two serum potassium strata as outlined in 1a?

Preliminary Agency Response: Yes, assuming you are able to identify a reasonable starting dose based on the interim analysis.

Additional discussion during meeting: No additional discussion.

- c. Does the Agency agree that, if necessary, additional dose ranging can be conducted in the Phase 3 studies, either in parallel with or after the 8-week treatment period of study RLY5016-205 is completed?

Preliminary Agency Response: Yes.

Additional discussion during meeting: No additional discussion.

- d. Does the Agency agree that data from study RLY5016-204 and preliminary data from study RLY5016-205 support the titration algorithm proposed for the Phase 3 studies (same algorithm currently used in study RLY5016-205)?

Preliminary Agency Response: The time course for drug effects on potassium is not clear to us. We suggest that you further characterize the time course of effects on potassium to better inform a strategy for titration (i.e., the times at which the initial effect and maximum effect is expected).

Additional discussion during meeting: Dr. Thompson reiterated the importance of determining how soon RLY5016 begins to reduce potassium levels, so that labeling can properly inform physicians. The sponsor noted that their phase 3 trials are not designed to determine the timing of the onset of action. Dr. Temple suggested that getting early potassium levels (six and 12 hours) in a small number of patients would probably be sufficient and that this could be done in a separate trial. The sponsor will consider this suggestion and agreed to provide data to characterize the time course.

- e. Does the Agency agree that the RLY5016 withdrawal period employed in study RLY5016-205 is appropriately designed to obtain the withdrawal data requested during Relypsa's June 18, 2010 meeting with the Agency?

Preliminary Agency Response: The data from subjects with $K^+ > 5.0$ mEq/L, in whom you propose to withdraw both the RLY5016 and the RAAS inhibitor therapy, will be hard to interpret. However, for reasons of subject safety, this approach is perhaps justified. Whether or not the specified timing for obtaining follow up data is sensible depends on how soon after drug withdrawal one would expect the drug lowering effects on potassium to abate, and when a subject would be expected to achieve a new steady state with regard to potassium levels.

Additional discussion during meeting: No additional discussion.

- f. Based on data from previously conducted trials of RLY5016 and preliminary data from study RLY5016-205, is a minimum mean change in serum K^+ of -0.3 to -0.4 mEq/L from baseline to 4 and 8 weeks (initial treatment period) following administration of RLY5016 in all patients with serum K^+ levels > 5.0 mEq/L (i.e., combined Strata 1 and 2) clinically meaningful?

Preliminary Agency Response: A critical issue is whether RLY5016 has an important effect on K^+ in those subjects with the highest levels of K^+ . In addition to determining the mean effect on K^+ , you should also characterize the distribution of these effects. We will also be interested in whether or not patients with the highest levels of K^+ can be brought down to within the normal range.

Additional discussion during meeting: No additional discussion.

- g. Assuming successful determination of a starting dose of RLY5016 and demonstration of clinically meaningful lowering of serum potassium levels with RLY5016, does the Agency agree that study RLY5016-205 may be considered a Phase 2/3 trial and serve as one of two pivotal studies?

Preliminary Agency Response: This trial could potentially be used to support approval as one of two pivotal trials. In order for the study to be considered a pivotal study, the type I error rate of the study needs to be properly controlled. It is unclear from the description of this study how the type I error issue will be addressed. It is also important for you to submit the statistical analysis plan as soon as possible.

Additional discussion during meeting: The Agency noted that a major impediment to considering the 205 study as an adequate and well-controlled study supporting approval is the fact that the statistical analysis plan of this open-label trial has not yet been finalized. However, the Agency noted that the 301 trial, as designed (with a randomized withdrawal phase), could be considered two distinct trials, both of which can be used to support approval.

2. Relypsa proposes to conduct two Phase 3 trials similar in design to study RLY5016-205, enrolling a similar patient population (CKD, T2DM, HF patients) with hyperkalemia due to treatment with RAAS inhibitors. One Phase 3 study (approximately 200 patients) will be an open-label study in normokalemic patients who will receive maximum labeled doses of RAAS inhibitors for up to 4 weeks (run-in period). Once serum K⁺ is ≥ 5.1 mEq/L, patients will receive RLY5016 for 8 weeks. After the initial 8-week RLY5016 treatment period, patients will be randomized to continue RLY5016 or withdraw RLY5016 and receive placebo (as a safety comparator) for up to 4 additional weeks. The second proposed Phase 3 study will also have an 8-week RLY5016 treatment period but will not require a run-in period as patients in this study must be hyperkalemic at screening.

Patients in each study will be assigned to one of two potassium strata (as defined in study RLY5016-205) and receive a starting dose of RLY5016 based on their level of hyperkalemia (determined by the interim analysis of study RLY5016-205). Doses of RLY5016 will be titrated as needed to maintain serum potassium levels in the target range (serum K⁺ 3.8 – 5.0 mEq/L) at follow-up intervals.

One of the key considerations in designing the Phase 3 studies was ensuring that the necessary data are obtained to define dosing instructions that will inform physicians on how to use RLY5016 in treatment of their patients. At the June 2010 FDA/Relypsa meeting, the Agency indicated that the development program should provide the following: 1) information on dose-response; 2) data showing how administration of RLY5016 lowers serum potassium levels as a function of baseline values; and 3) data showing the time-course and stability of resulting changes in serum potassium levels.

The Agency also indicated at the meeting that given the non-absorbed nature of RLY5016, nonclinical and clinical experience to date, and objectivity of the serum potassium endpoint, open-label studies might be acceptable. Furthermore, it was agreed that a placebo arm should be included in one of the pivotal trials for safety evaluations.

- a. Does the Agency agree that the proposed Phase 3 study designs will provide the necessary information to define dosing instructions for RLY5016 use by physicians?

Preliminary Agency Response: The proposed studies may provide the necessary information. However, we have the following recommendations and requests for clarification:

1. The study population you propose to enroll seems reasonable. However, you may want to consider expanding your study to all subjects with hyperkalemia of a given severity, regardless of etiology.
2. We encourage you to consider an algorithm for titrating the dose based not only on the most recent K^+ but also on recent rate of change of K^+ . From a practical standpoint, one could consider providing a table(s) with rows and columns corresponding to the present and prior K^+ values, with dosing instructions provided at the intersection of the row and column.
3. We suggest that you include in your protocol methods for identifying spurious K^+ levels secondary to hemolysis so as to minimize the risk of inappropriately uptitrating the dose.
4. We also suggest that you assess the kinetics of the change in potassium, and include early time points (i.e., 12 hours and 24 hours). This may not be necessary if you already have such data on the time course of effects.

Additional discussion during meeting: No additional discussion.

- b. Does the Agency agree with the proposed primary endpoint for the pivotal studies as mean change from baseline in serum potassium levels to week 8?

Preliminary Agency Response: The primary endpoint can be a mean change from baseline, however, we are also interested in the distribution of the effects and the effects as a function of baseline potassium level (Please also refer to our response to question 1f.). The Week 8 time point is acceptable; an earlier time point might also be reasonable.

For the evaluation of efficacy in Study 301, it is not clear what the control group is at Week 8, given that subjects will be randomized to either continue active treatment or go on placebo at Week 8.

Additional discussion during meeting: See slides 14 -- 16 for a description of the 301 study. For the randomized withdrawal phase the Agency recommended using an endpoint of change from new baseline (beginning of the withdrawal phase) in serum potassium. The sponsor agreed to consider this suggestion.

- c. One of the proposed Phase 3 studies will employ a RLY5016 randomized withdrawal period, where patients will be randomized to continue RLY5016 or replace RLY5016 with placebo for up to 4 weeks after an initial 8-week RLY5016 treatment period. Does the Agency agree that this is an acceptable design for one of the Phase 3 studies and adequate to obtain safety comparator data?

Preliminary Agency Response: The design is acceptable, though as noted in our response to question 1e, the data from subjects with a $K^+ > 5.0$ mEq/L will be difficult to interpret. Furthermore, it is not clear that comparison of RLY5016 with placebo in the randomized withdrawal phase will provide any useful safety data.

Additional discussion during meeting: There was some discussion regarding the amount of safety data needed, as well as the various methods of obtaining such data. Dr. Archdeacon suggested enrolling patients on RAAS inhibition and randomizing to groups that either continue on RAAS inhibition with RLY5016 added, or discontinue RAAS (because of elevated potassium). The sponsor noted that they have considered that option, but decided against it as the no-RAAS group would have lower potassium levels than the RASS/RLY5016 group, creating a sub-optimal comparison for safety purposes. In addition, they feel their current proposal is acceptable for a non-absorbed drug. Dr. Temple noted that the sponsor can increase the size of the

safety comparator group by pooling all data for pre- and post-RLY5016 use. In addition, the post-RLY5016 data can be increased by extending the follow-up periods.

- d. Does the Agency agree that data from the proposed overall clinical development program (study RLY5016-205 with data for up to 52 weeks and Phase 3 trials with changes from baseline in serum potassium levels for up to 12 weeks), are adequate to support acute and chronic treatment of hyperkalemia?

Preliminary Agency Response: We agree.

Additional discussion during meeting: No additional discussion.

- e. Does the Agency agree that data from the randomized withdrawal period in one of the Phase 3 studies are adequate to support chronic treatment by demonstrating that fewer patients receiving placebo than those administered RLY5016 after 12 weeks can continue to receive maximum labeled recommended doses of RAAS inhibitors?

Preliminary Agency Response: Data on the adjustment of RAAS inhibition will be difficult to interpret. We will be interested in seeing the effects on potassium levels following withdrawal.

Additional discussion during meeting: See discussion under question 2b. If the endpoint is related to potassium levels, Dr. Stockbridge said that a successful 301-randomized withdrawal trial would likely support a claim of allowing more patients to continue on maximum RAAS inhibition.

There was a discussion about the submission of the protocol as a request for Special Protocol Assessment (SPA). Dr. Stockbridge said the Division is willing to review a protocol synopsis in order to provide some guidance prior to submission of the actual SPA. The Agency noted that the statistical analysis plan should be submitted prior to patient enrollment.

3. Does the Agency agree that no other clinical studies are required beyond our current planned clinical development program? For example, a QT/QTc or absorption/distribution/ metabolism/excretion (ADME) study will not be required due to the lack of systemic exposure of RLY5016 and a food effect study will not be required because the potassium binding of RLY5016 occurs predominantly in the colon?

Preliminary Agency Response: If you can provide data demonstrating that potassium adsorption at the pH conditions of the duodenum under fed and fasted conditions does not occur, a food interaction study *in vitro* is not necessary. Absorption and distribution studies in humans are not required. Regarding metabolism studies see "Additional Agency Comments/Questions" Section point 4.

Additional discussion during meeting: There was some discussion of the potential for absorption of RLY5016. Dr. Hinderling noted that the radiolabeled ADME study indicated some amount of absorption. The sponsor explained that they believe the ^{(b)(4)} recovered in urine was excess isomer that was absorbed, and not indicative of absorption of RLY5016. Dr. Hinderling suggested that the sponsor attempt to identify the labeled compound by TLC (see slides 19 and 20).

The sponsor asked for clarification on whether or not a QT/QTc study will be required. Dr. Stockbridge said a QT study will not be required.

4. Relypsa is considering the evaluation of QD dosing as a treatment option, either before or after anticipated NDA approval. Would a single trial (as outlined in Section 14.3) demonstrating that QD and BID dosing of the optimal starting dose(s) of RLY5016 results in comparable lowering of serum potassium levels be adequate to support once a day, in addition to twice a day, administration of RLY5016?

Preliminary Agency Response: In order to answer this question we need to understand whether you are planning to give the same total daily dose in the QD regimen as in the BID regimen, and whether or not you have data supporting the safety of a dose of that strength when administered once.

Additional discussion during meeting: No additional discussion.

5. Given that hyperkalemia occurs mainly in patients with compromised renal function and that CKD is very infrequent in the pediatric population, Relypsa plans to request a full waiver of the pediatric assessment requirement. Does the Agency agree that RLY5016 may qualify for a full waiver of the pediatric assessment requirement?

Preliminary Agency Response: This may be reasonable but a request along with associated rationale will need to be submitted at the time of the NDA.

Additional discussion during meeting: No additional discussion.

6. To date, approximately 160 subjects have been exposed to RLY5016 in five completed studies (two Phase 1 and three Phase 2). Upon completion of study RLY5016-205, another 300 patients will be exposed to RLY5016. The two proposed Phase 3 studies are anticipated to enroll 200 and 100 patients, respectively. Together these are expected to result in a total projected safety exposure of approximately 760 subjects, consistent with what was agreed to in the June 18, 2010 FDA/Relypsa meeting, i.e., approximately 800 subjects in the safety database to support a NDA submission and approval.

- a. Relypsa plans to treat approximately 75 – 100 patients for at least one year and 100 – 150 patients for at least six months. Assuming that RLY5016 continues to demonstrate a similar safety profile as it has in the approximately 160 subjects exposed to date, does the Agency agree that this amount of patient exposure will be sufficient to assess the long-term safety of RLY5016 and adequate for filing the NDA?

Preliminary Agency Response: You should plan to expose enough subjects for a long enough time to determine the frequency of common adverse events and to exclude some increase in frequency of events resulting in mortality or severe morbidity. We note that three of the 63 subjects enrolled in the 8 week study RLY5016-204 died suddenly. We understand that the subjects enrolled (NYHA class 2-3 HF with CKD) were at risk for sudden death. However, fluctuations in serum potassium levels may provoke serious ventricular arrhythmias. Therefore we are uncertain as to the number of subjects and duration of exposure required to provide adequate reassurance on the potential for serious ventricular arrhythmias in a population predisposed to their occurrence.

Additional discussion during meeting: The sponsor discussed the three deaths in the 204 trial (see slide 12). The 204 trial enrolled relatively sick patients (diabetes, heart failure and chronic renal disease). Two of the three patients were off RLY5016 at the time of death, and none had experienced wild fluctuations in potassium levels. In addition, they noted that an extensive heat wave in the region may have contributed; they have not seen similar SAEs at those same study sites in current trials.

- b. All efforts will be made to minimize the drop-out rate in the long-term maintenance period of the Phase 2 study RLY5016-205. However, the attrition rate is a projection only. If patients discontinue treatment at a higher rate than anticipated will the Agency accept the NDA filing with a fewer number of patients for long-term exposure, e.g., 50 patients exposed for one year and 100 patients for six months?

Preliminary Agency Response: This may be acceptable for a treatment indication provided that no new safety signals arise that need to be further explored. Of particular interest will be effects of therapy on vitamin and electrolyte levels such as magnesium, calcium, and fluoride. The label will likely also describe the extent to which there is long-term experience.

Additional discussion during meeting: No additional discussion.

- c. Most (if not all) of the long-term safety exposure data will be derived from the current Phase 2 study RLY5016-205 being conducted outside the US (Western and Eastern Europe). Is this acceptable?

Preliminary Agency Response: This is acceptable provided that you can make the case that the study findings are generalizable to medical practice in the US (e.g., study practices reflect U.S. standards of care/background therapy, etc).

Additional discussion during meeting: No additional discussion.

- d. If study RLY5016-205 is considered a pivotal trial and Relypsa does not conduct the Phase 3 study RLY5016-302, expected to enroll 100 patients, will a total safety database of approximately 650 patients be acceptable?

Preliminary Agency Response: Please see our response to question 6a.

Additional discussion during meeting: See discussion under question 1g.

7. The majority of study sites in the pivotal studies will be located outside the US (primarily Western and Eastern and Europe). Although there is no specific requirement to enroll patients from the US, we plan to enroll approximately 10 – 20% of patients from North American sites. In addition, we plan to assess regional impact, if any, on efficacy and safety analyses. Is this acceptable to the Agency?

Preliminary Agency Response: Please see our response to question 6c.

Additional discussion during meeting: No additional discussion.

8. Given the mechanism of action of RLY5016 and its lack of systemic absorption, and absence of any evidence in the medical literature to indicate that hyperkalemic patients of different races or ethnicity will respond differently to a colonic potassium binder, it is not expected that there will be notable differences in efficacy or safety between racial and ethnic groups. While all efforts will be made to include patients of different races, Relypsa anticipates that the percentage of these patients in the RLY5016 clinical program may be too small to perform a subgroup analysis of efficacy and safety on serum potassium endpoints. Is this acceptable to the Agency?

Preliminary Agency Response: Your approach seems reasonable.

Additional discussion during meeting: No additional discussion.

9. Relypsa conducted an in vitro drug-drug interaction study with 6 drugs chosen in view of their common use in the patient population that would most frequently receive RLY5016 (patients with CKD, DM, HF and hypertension) and 18 in vivo drug-drug interaction studies in rats. Based on the results of these studies, which indicated no significant interactions between RLY5016 and any of the drugs tested, does the Agency agree that no further drug-drug interaction studies are required?

Preliminary Agency Response: You selected the drugs to be tested according to the likelihood of their co-administration with RLY5016. Given that RLY5016 is an anion it would be important to test basic drugs with $pK_a(s) > 9.0$. Please list acid or base characteristics and pK_a of the already tested drugs. Please list mean C_{max} and AUC as well as SD of the compounds tested in the presence and

absence of RLY5016 in the rat. The *in vivo* studies in the rat used concentrations of the tested compounds that were greater than those in humans if the maximum approved dose were administered. Also, the RLY5016 dose used in the rat experiments was lower than the maximum dose of 60 g administered in humans. Please provide supporting evidence indicating the results obtained for the tested co-administered drugs can be extrapolated to therapeutic levels and the lower concentrations tested for RLY5016 can be extrapolated to the higher levels expected after a 60 g dose. The requested information will inform the decision on the need for additional studies.

Additional discussion during meeting: The sponsor noted that they plan to request a teleconference in the future to discuss this issue.

10. Relypsa met with FDA reviewing chemists from the Office of New Drug Quality Assessment (ONDQA) during an End of Phase 2 (EOP2) Type B chemistry, manufacturing and controls (CMC) meeting on December 15, 2010. The reviewing chemists agreed with the proposed attributes and acceptance criteria for Phase 3 clinical material and commercial drug product, with the caveat that the final determination will occur during NDA review. One of the attributes tested is fluoride, with a proposed specification of (b) (4). Relypsa provided information and data that the calcium fluoride impurity in RLY5016 is poorly absorbed. Since this specification was one of the topics discussed at the pre-IND meeting and fluoride, when absorbed, is a potential safety concern, Relypsa requests review of our proposed specification by the pharmacology/toxicology and clinical reviewers.

Assuming that future clinical trials demonstrate similar serum fluoride results to those observed in the completed 4 and 8 week Phase 2 studies, do the pharmacology/toxicology and clinical reviewers agree with the proposed fluoride specification of (b) (4) as a release and end-of-shelf life specification for RLY5016 in Phase 3 clinical studies and commercial drug product?

Preliminary Agency Response: Yes.

Additional discussion during meeting: No additional discussion.

11. Relypsa has completed a number of nonclinical studies, including in vitro/in vivo pharmacology studies, safety pharmacology studies, radiolabeled ADME studies in rats and dogs, DDI studies, repeat dose toxicology studies (short-term and chronic studies in rats and dogs), genotoxicity studies, reproductive toxicity studies, and a fluoride safety assessment study. No additional nonclinical studies are planned. Does the Agency agree that no additional toxicology studies are needed to support the NDA?

Preliminary Agency Response: Yes.

Additional discussion during meeting: No additional discussion.

12. RLY5016 has not been associated with any significant toxicological effects even at high doses in nonclinical studies performed to date. Given its non absorbed nature, Relypsa does not believe carcinogenicity studies are needed to support the NDA and intends to submit a waiver for carcinogenicity testing to the Agency. Does the Agency have any comments or concerns in regards to this plan?

Preliminary Agency Response: No.

Additional discussion during meeting: No additional discussion.

13. Relypsa does not plan to perform a peri/post natal development study, due to lack of effects noted in the rat fertility and rat and rabbit embryo/fetal toxicity studies, the lack of systemic exposure of the drug, and restriction of the pharmacologic action of RLY5016 to the GI tract, where excreted

potassium is bound to the polymer. In addition, the intended patient population is generally elderly and seriously ill. Does the Agency agree that a rat peri/post natal development study is not needed for NDA submission?

Preliminary Agency Response: Yes.

Additional discussion during meeting: No additional discussion.

Additional Agency Preliminary Comments/Questions

1. A steady-state C_{max} of about 350 mcg/mL for RLY5016 can be calculated for a subject with a creatinine clearance of 15 mL/min/1.73 m² assuming the t_{1/2} in healthy humans is the same as that in dogs (mean 112 h), a 24 h dose interval, a dose of 60 g and renal excretion of the unchanged drug to be the major route of elimination. How much potassium is adsorbed by RLY5016 at this concentration?

Additional discussion during meeting: No additional discussion.

2. Is ILY105 used in the ADME studies the same as RLY5016?

Additional discussion during meeting: No additional discussion.

3. What is the position of ¹⁴C in labeled ILY105?

Additional discussion during meeting: See slide 19.

4. Please provide evidence that RLY5016 is metabolically stable after systemic absorption.

Additional discussion during meeting: See discussion under question 3.

5. What is RLY5016's adsorption of sodium, lithium, magnesium, and iron relative to potassium?

Additional discussion during meeting: No additional discussion.

ATTACHMENTS AND HANDOUTS

The sponsor presented the following slides during the meeting.

25 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ROBERT TEMPLE
12/22/2011

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2015. See instructions for OMB Statement, below.	
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm	
1. APPLICANT'S NAME AND ADDRESS RELYPSA INC Sarah McNulty 700 Saginaw Drive Redwood City CA 940634752 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 205-739
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 650-421-9570	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME RLY5016 for Oral Suspension	6. USER FEE I.D. NUMBER PD3014604
7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO PRIORITY REVIEW VOUCHER NUMBER:	
8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act	

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

Privacy Act Notice:

This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: <http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm>.

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PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE Sarah McNulty <i>Sarah McNulty</i>	TITLE Vice President, Regulatory Affairs	DATE 10/15/14
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 \$2,335,200.00

Form FDA 3397 (03/12)

**INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET
FORM FDA 3397**

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at https://userfees.fda.gov/OA_HTML/pdufaCAcdLogin.jsp. If you need assistance in completing the form call 301-796-7200 or email: userfees@fda.gov.

NOTE: Form FDA 3397 need not be submitted for:

CDER

- 505(j) applications
- Supplements to 505(j) applications
- 351(k) applications

CBER

Any supplement that does not require clinical data for approval.
Applications and supplements for:

- * Products for further manufacturing use only
- * Whole blood or blood components for transfusion
- * Bovine blood product for topical application licensed before September 1, 1992
- * A crude allergenic extract product
- * An in vitro diagnostic biological product licensed under Section 351 of the PHS Act
- * 351(k) applications

ITEM NO.	INSTRUCTIONS
1-2.	Self-explanatory
3.	PRODUCT NAME: Include generic or proper name and trade name, as applicable.
4.	BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) - Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A SUPPLEMENT enter the BLA STN. FOR DRUG PRODUCTS: Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm .
5.	CLINICAL DATA: The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf .
6.	USER FEE I.D. NUMBER: Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	PRIORITY REVIEW VOUCHER: If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA's Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA's guidance can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf .
8.	EXCLUSIONS: The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	WAIVER: Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.

Form FDA 3397 (03/2012)(BACK)

Close Print Cover sheet



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 75615

MEETING MINUTES

Relypsa, Inc.
Attention: Sarah McNulty
Executive Director, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RLY5016.

We also refer to the meeting between representatives of your firm and the FDA on March 27, 2013. The purpose of the meeting was to CMC topics.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Margaret Whittaker, Regulatory Project Manager at (301) 796-2911.

Sincerely,

{See appended electronic signature page}

Margaret V. Whittaker
Regulatory Project Manager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Pre-NDA

Meeting Date and Time: March 27, 2013, 12:30 – 2:00 PM
Meeting Location: CDER WO Bldg 22, Room 1419

Application Number: IND 75615
Product Name: RLY5016
Indication: Treatment of Hyperkalemia
Sponsor/Applicant Name: Relypsa, Inc.

Meeting Chair: Ramesh Sood, PhD
Meeting Recorder: Margaret V. Whittaker

FDA ATTENDEES

Ramesh Sood, Branch Chief, ONDQA
William Link, Pharmaceutical Toxicology Reviewer, OND
Okpo Eradiri, Biopharmaceutical Reviewer, ONDQA
Kasturi Srinivasachar, CMC Reviewer, ONDQA
Thomas Wong, CMC Reviewer, ONDQA

SPONSOR ATTENDEES

Jerry Buysse, Chief Scientific Officer, Relypsa Inc.
Wilhelm Stahl, Supervisory Pharmaceutical Operations, Relypsa Inc.
Sally Look, Regulatory Interlix, Relypsa Inc.
Gargi Choudhary, Analytical Development, Relypsa Inc.
Elizabeth Anne Clark, Senior Director of Regulatory Affairs, Relypsa Inc.
Sarah McNulty, Executive Director, Regulatory Affairs, Relypsa Inc.
Son Nguyen, Senior Director, Analytical Development, Relypsa Inc.
Vinita Kumar, Senior Director, Quality Assurance, Relypsa Inc.
Gerrit Klaerner, President, Relypsa Inc.
Claire Lockey, Supervisor Regulatory Affairs, Relypsa Inc.

1.0 BACKGROUND

Relypsa is developing RLY5016 or Patiromer (as a powder for oral suspension) for the treatment of hyperkalemia. The polymeric drug binds potassium in the lumen of the colon and therefore does not need systemic exposure for its therapeutic or pharmacologic effect. The firm held an EOP2 meeting with the Agency in December 2010 and discussed among other issues, their desire to categorize (b) (4) calcium and sorbitol with RLY516 (named RLY516S) as the API. One of Relypsa's main objectives is to get confirmation of the (b) (4) acceptance as API by the Agency in this meeting. In addition, the firm would like to "reach agreement on a

plan for the types of manufacturing changes whereby bioequivalence testing on the drug product would be required.

2. DISCUSSION

2.1. CMC Questions

Question 1: Does the Agency agree with Relypsa's drug substance impurity control strategy whereby we establish the amount of impurity allowed in the drug substance at only one of the (b) (4) proposed control points (b) (4)? (b) (4)?

FDA Response to Question 1: The control point of all impurities will depend on the place where impurities are being generated in the synthesis, the levels at which they are controlled and the demonstration of the capability of removal/purging of the impurity downstream in the manufacturing process, if needed. In this case, only one control point should be sufficient for controlling the impurities. The acceptance of the impurity level will be determined during NDA review based on safety considerations, analytical methodology and manufacturability.

Discussion: The control strategies for impurities are review issues and will be examined during the formal NDA review. The control strategy appears reasonable; however, Relypsa will need to demonstrate the controls are implemented at the correct point in the process and to make sure that impurity levels do not change after the control point.

Question 2: Does the Agency agree that impurities controlled at (b) (4) drug substance intermediate need only appear on the specification and certificate of analysis at the respective control point, i.e., if the impurity is controlled in drug substance intermediate it need not appear on the drug substance specification?

FDA Response to Question 2: See response for question #1

2.2. Minor Drug Substance and Process Changes

Question 3: Relypsa plans to implement four minor process changes that are required for commercial production of the drug substance; implementation of the changes was identified as necessary after production of the registration stability batches of drug substance. The manufacturing process for drug substance to be described in NDA Section 3.2.S.2.2 will reflect the process with the changes implemented. The changes are supported by extensive risk assessments and design of experiment (DOE) studies, as well as manufacturing experience at laboratory scale. The results of the evaluations will be described in Section 3.2.S.2.6 of the NDA. The changes will be implemented as part of the process validation campaign. Does the Agency agree with Relypsa's plans to implement (b) (4) process changes determined to be necessary for commercial manufacturing at the time of process validation?

FDA Response to Question 3: This issue is a review issue and will be decided at time of NDA review.

Discussion: Pending review, the lab testing approach looks sufficient to demonstrate equivalence. Lab testing results should be included in the NDA submission for review. If stabilizers are added, Relypsa must demonstrate in lab studies the comparative stability of the starting material before and after the addition of the stabilizer. Data on lab testing should be included in the NDA for review.

Question 4: As follow up to the 15 December 2010 EOP2 meeting and 09 September 2011 IND amendment (SN 0030) and in preparation for the NDA submission, Relypsa requests confirmation that RLY5016S is accepted as the drug substance. Does the Agency agree with the designation of RLY5016S as the drug substance?

FDA Response to Question 4: You may include the manufacture and control of the patiromer calcium-sorbitol (b)(4) in the Module 3.2.S. The Module 3.2.S should include the following information:

- The evidence to support the structure of the patiromer calcium.
- The characterization of the patiromer calcium (b)(4)
- In-process quality control of patiromer calcium (b)(4)

Discussion: The sorbitol (b)(4) does not need to be isolated and characterized. Sufficient information for the process should be submitted in the final submission. FDA recommended that Relypsa, Inc. begin to consider labeling of the product following the new USP Salt nomenclature policy.

2.3 Drug Substance Comparability

Question 5: Does the Agency agree that the (b)(4) testing plan will be adequate to demonstrate equivalence of drug substance batches and does the Agency agree with our proposed applications of the (b)(4) testing plan, i.e., to support major post-approval changes such as the addition of new drug substance suppliers?

FDA Response to Question 5: This is a review issue. A (b)(4) protocol should be included in the NDA submission.

2.4 Elemental Impurities

Question 6: Analysis for heavy metals is not currently performed for the drug product. Instead, Relypsa proposes testing of heavy metals in the drug substance and in xanthan gum which are the only two components in the drug product. The list of metals to be tested and their specification limits to be proposed for commercial drug substance and xanthan gum will be based on the new USP<232> and USP <233> monographs. Does the Agency agree with

the proposed plan for controlling heavy metals in drug substance and xanthan gum instead of drug product?

FDA Response to Question 6: Yes.

2.5 Potential Genotoxic Impurities

Question 7: Does the Agency agree with Relypsa's proposal for setting a specification for the potentially genotoxic impurities based on compound-specific risk assessments and the resulting permitted daily exposure levels that are calculated?

FDA Response to Question 7: In principle, the proposal is acceptable. It is recognized that extraction of these impurities from the drug product required non-physiological methods and that exposure in patients is likely less than the total of extractables. Any further information, regarding what physiological conditions were attempted and the apparent partition coefficients observed, would aid in assessing the expected human exposure to these impurities.

Discussion: (b) (4) organic compounds can be of concern. The final NDA will include data from studies that mimic conditions in the gastrointestinal track and demonstrate that impurities are not extracted during testing under physiological conditions.

2.6 Ordinary Impurities of Special Toxicological Concern

Question 8: Does the Agency agree with Relypsa's proposal for setting a specification for ordinary impurities of special toxicological concern based on compound-specific risk assessments and the resulting safe human doses that are calculated?

FDA Response to Question 8: The same principle applies as in Response 7 above.

2.7 CMC/Pharmacology/Toxicology – Potential Genotoxic Impurities

Question 9: Does the Agency agree with the acceptance criterion and control point proposed for each potential genotoxic impurity?

- a. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) in the drug substance intermediate?
- b. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) in the drug substance intermediate?

- c. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) in the drug substance intermediate?
- d. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % only in the (b) (4) material without further testing of the drug substance intermediate or drug substance?
- e. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) in the drug substance intermediate?
- f. Does the Agency agree with the specification of NMT (b) (4) for (b) (4) in the drug substance?

FDA Response to Question 9: See Response for question #1.

2.8 CMC/Pharmacology/Toxicology – Ordinary Impurities of Special Toxicological Concern (1)

Question 10: Does the Agency agree with acceptance criterion and control point proposed for each impurity of special toxicological concern?

- a. Relypsa proposes a specification for the theoretical impurity, (b) (4) in the drug substance based on published literature of studies which define the No Observable Effect Level (NOEL), establish the Human Equivalent Dose (HED), and recommend a safe reference dose for chronic exposure. Does the Agency agree with Relypsa's proposed specification of NMT (b) (4) for (b) (4) (b) (4) in the drug substance?
- b. Does the Agency agree with the proposal for control of (b) (4) impurity of special toxicological concern with reactivity similar to (b) (4) in the (b) (4) (b) (4) material at a limit of NMT (b) (4) %?
- c. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?
- d. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?

FDA Response to Question 10: See Response for question #1.

2.9 CMC/Pharmacology/Toxicology – Ordinary Impurities of Special Toxicological Concern (2)

Question 11: Acceptable levels for ordinary organic impurities in drugs administered at >2 g/day are addressed in the ICH Q3A (R2) guideline. Per the ICHQ3A (R2) guideline, Relypsa will report ordinary impurities present above (b) (4)% ((b) (4)) and will limit each ordinary impurity to NMT (b) (4)% ((b) (4)) in RLY5016S drug substance. Does the Agency agree with Relypsa's proposal for control of ordinary organic impurities in the drug substance?

FDA Response to Question 11: Yes. The Agency agrees with your proposal.

Question #12: Does the Agency agree with the acceptance criterion and control point proposed for each of the 13 ordinary organic impurities?

- g. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4)% in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?
- h. Does the Agency agree with Relypsa's proposal to control (b) (4) with a specification range of (b) (4) in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance for (b) (4)?
- i. Does the Agency agree with Relypsa's proposal to control (b) (4) in the drug substance intermediate instead of the drug substance with a specification limit of NMT (b) (4) in the intermediate?
- j. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4)% in the (b) (4) material?
- k. Does the Agency agree with Relypsa's designation of extractable (b) (4) substances as ordinary impurities and the proposed specification of NMT (b) (4) in drug substance?
- l. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4)% in the drug substance intermediate, without further testing of the drug substance?
- m. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4)% in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?

- n. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the drug substance intermediate, without further testing of the drug substance?
- o. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?
- p. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the drug substance intermediate, without further testing of the drug substance?
- q. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?
- r. Does the Agency agree with Relypsa's proposal to treat the unidentified (b) (4) impurity as "specified unidentified Impurity (4)" in the (b) (4) material and only control it in the (b) (4) material with a limit of NMT (b) (4) %?
- s. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?

FDA Response to Question 12: See response to question #1.

2.10 Residual Solvents

Question 13: Does the Agency agree with the acceptance criterion and control point proposed for each of the five Residual Solvents identified?

- a. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the (b) (4) material, without further testing of the drug substance intermediate or the drug substance?
- b. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the drug substance intermediate, without further testing of the drug substance?
- c. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the drug substance intermediate, without further testing of the drug substance?
- d. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the drug substance intermediate, without further testing of the drug substance?
- e. Does the Agency agree with Relypsa's proposal to control (b) (4) at a limit of NMT (b) (4) % in the drug substance?

FDA Response to Question 13: See response to question #1.

2.11 Fluoride Specification

Question 13: Relypsa proposes to establish an end-of-shelf-life specification for the drug product RLY5016 for Oral Suspension that is different from the release specification.

- t. Does the Agency agree with Relypsa's proposal to determine the end-of-shelf-life fluoride specification by 1) limiting the fluoride level in RLY5016 for Oral Suspension so that no more than (b)(4) of soluble fluoride (i.e., sodium fluoride equivalent) will be delivered to a patient from patiromer and 2) the amount of patiromer derived soluble fluoride will be determined from the 12-month RLY5016-205 clinical study change from baseline serum fluoride data as outlined in section 16?

Does the Agency agree with Relypsa's plan for room temperature labeling instructions?

FDA Response to 14: a) It will be determined during NDA review, b) agency agrees with the label storage conditions. The allowable excursion temperature and time will be determined during NDA review.

Discussion: FDA views this process in regards to stability studies as acceptable, i.e., refrigeration for 1 year, room temperature for 3-6 months as well as shelf life as acceptable and submittable for NDA review. FDA stated that 'in use' stability data should be included.

2.12 Biopharm/CMC

Question 15: Does the Agency agree that in vitro bioequivalence should be used to demonstrate equivalence between different dosage forms or to support significant changes to the drug product manufacturing process?

FDA Response to 15: An in-vitro equivalence approach may be acceptable for evaluating significant manufacturing changes for your RLY5016 drug product. However, it is your responsibility to provide confirmatory data that RLY5016 is not systemically absorbed throughout the gastrointestinal tract.

Provide the protocols for the in-vitro studies that will be conducted to demonstrate the equivalence of the products manufactured before- and after-the proposed changes for our review and comments.

Discussion: Data from these studies should be included in the NDA. FDA agrees with Relypsa, Inc.'s plan of including particle size distribution as additional comparative test in the NDA. Binding assays appear acceptable for demonstrating equivalence for significant manufacturing changes.

2.13 General Information

Question 16: Does the Agency agree to accept for review additional stability data for the drug substance and drug product if submitted with the NDA 4-month safety update?

FDA Response for 16: No. According to PDUFA V, all additional information should be submitted within 30 days from the date of original NDA submission provided an agreement was reached and documented at the pre-NDA meeting.

Additional Discussion on Dissolution Testing:

FDA stated that dissolution testing of RLY5016, a polymer that is not intended to be absorbed and does not go into solution in order to bind potassium, may not be necessary.

Post-Meeting Comment:

The Sponsor should include in their NDA submission, the rationale for not developing a dissolution method for RLY5016.

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

/s/

MARGARET WHITTAKER
04/12/2013

RAMESH K SOOD
04/12/2013



IND 75,615

MEETING MINUTES

Relypsa, Inc.
Attention: Claire J. Lockey
Senior Vice President, Pharmaceutical Development and Regulatory Affairs
5301 Patrick Henry Drive
Santa Clara, CA 95054

Dear Ms. Lockey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RLY5016.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2010. The purpose of the meeting was to discuss CMC plans for clinical Phase 3 activities and for preparation of an anticipated NDA filing.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Khushboo Sharma, Regulatory Project Manager/me at (301)796-1270.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Relypsa, Inc.
Application Number:	IND 75,615
Product Name:	RLY5016
Meeting Requestor:	Relypsa, Inc.
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC) End of Phase 2 (EOP 2) Meeting
Meeting Date and Time:	December 15, 2010 14:30-15:30 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	November 16, 2010
Meeting Chair:	Ramesh Sood, Ph.D., Branch Chief
Meeting Recorder:	Khushboo Sharma, Regulatory Project Manger (ONDQA)

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of New Drug Quality Assessment I:

Ramesh Sood, Ph.D.; Branch Chief
Kasturi Srinivasachar, Ph.D., CMC Lead
Donghao Lu, Ph.D., Product Quality Reviewer
Patrick Marroum, Ph.D., Biopharmaceutics Supervisor
Khushboo Sharma, Regulatory Project Manager

EXTERNAL ATTENDEES:

Claire Lockey, Sr. Vice President, Pharmaceutical Development and Regulatory
Yip-Fong Chia, Vice President, Manufacturing

Sherin Halfon, Ph.D., Director, Project Management
Son Nguyen, Ph.D, Director, Analytical Sciences
Shiah-Yun Chen, Ph.D., Associate Director, Analytical Drug Development
Vinita Prasad Kumar, Associate Director, Regulatory and Quality Assurance
Gerrit Klaerner, Ph.D., President and Chief Operating Officer
Consultants

(b) (4)

1.0 BACKGROUND

The purpose of the Type B End of Phase 2 meeting regarding RLY5016 is to discuss CMC plans for clinical Phase 3 activities for preparation and anticipated NDA filing. As per the last discussion with the Agency on June 18, 2010, a clinical development path was defined and Relypsa is in the process for Phase 3 studies. They provided Phase 3 plans for CMC activities and obtain feedback and agreement from the agency on the plans. Additionally, Relypsa wanted to discuss unique CMC technical challenges associated with RLY5016 polymer.

2.0 DISCUSSION

2.1 Drug Substance

- 2.1.1 **Briefing Package Question 1:** Relypsa plans to use two manufacturers for the production of stabilized drug substance, RLY5016S, for formulation into Phase 3 clinical material, (b) (4) and (b) (4). Our intention is to identify both sites of manufacture for RLY5016S as commercial manufacturers of the drug substance and stabilized drug substance. Does the Agency agree with our plans to qualify (b) (4) and (b) (4) as commercial manufacturers of RLY5016S in the NDA?

FDA Preliminary Response:

RLY5016S should be considered a drug product intermediate; therefore, the two sites will be considered the sites for drug product intermediate. For the drug substance RLY5016, you will need to show equivalence (physical and chemical characterization) between the RLY5016 manufactured at the two sites.

Based on the available information in this package, your plans to qualify (b) (4) and (b) (4) as commercial manufacturers of RLY5016S (and similarly applied to RLY5016) in the NDA are acceptable (see response to Question 11c below regarding the suitability of the in vitro comparability studies).

Meeting Discussion:

- Relypsa, Inc. is proposing both RLY5016 (b) (4) as the Drug Substance. Agency does not agree with (b) (4) as the drug substance; (b) (4) (b) (4)
(b) (4) The Sponsor explained the difficulties in manufacturing RLY 5016 in large quantities with acceptable levels (b) (4) The Agency was not convinced that the Sponsor has explored all avenues to manufacture RLY5016 as most of these efforts were not explained in the meeting package. The Sponsor agreed that they will continue to explore the possibility of making RLY 5016 in large quantities with

acceptable purity and submit an amendment to the IND with details of all the efforts made to achieve this goal. The agency agreed that they will evaluate the Sponsor's rationale to designate (b)(4) as the drug substance.

- 2.1.2 **Briefing Package Question 2a:** Relypsa currently designates (b)(4) as the starting materials in the synthesis of drug substance. The starting materials are commercially available from multiple suppliers and the specifications for each starting material and its characterization are well established. Does the Agency agree with Relypsa's rationale and proposal for designation of (b)(4) as a starting material in the synthesis of the drug substance and does the Agency agree with our proposed specifications for this starting material?

FDA Preliminary Response:

Your proposal for starting material designations of (b)(4) is acceptable. However, the starting material needs to be tightly controlled. The limit for individual unspecified impurities should be controlled at NMT (b)(4)%. Additionally, potentially genotoxic impurities may be present in the starting materials. You need to control these potentially genotoxic impurities in the starting materials or in the downstream product at appropriate levels.

Meeting Discussion:

- Relypsa agreed that they will include the recommended controls for the impurities in the starting material specification and will also retrospectively analyze the starting materials that they have already used in the synthesis of the drug substance for these impurities.

- 2.1.3 **Briefing Package Question 2b:** Does the Agency agree with Relypsa's rationale and proposal for designation of (b)(4) as a starting material in the synthesis of the drug substance and does the Agency agree with our proposed specifications for this starting material?

FDA Preliminary Response:

Based on the available information in this package, the proposed specification for this starting material appears reasonable. However, you need to provide full justification in NDA submission. See 2a for additional comments.

Meeting Discussion:

- See Meeting Discussion for 2a.

- 2.1.4 **Briefing Package Question 2c:** Does the Agency agree with Relypsa's rationale and proposal for designation of (b)(4) as a starting material in the synthesis of the drug substance and does the Agency agree with our proposed specifications for this starting material?

FDA Preliminary Response:

Based on the available information in this package, the proposed specification for this starting material appears reasonable. However, you need to provide full justification in NDA submission. See 2a for additional comments.

Meeting Discussion:

- See Meeting Discussion for 2a.

2.1.5 **Briefing Package Question 2d:** Does the Agency agree with Relypsa's rationale and proposal for designation of (b) (4) as a starting material in the synthesis of the drug substance and does the Agency agree with our proposed specifications for this starting material?

FDA Preliminary Response:

Based on the available information in this package, the proposed specification for this starting material appears reasonable. However, you need to provide full justification in NDA submission. See 2a for additional comments.

Meeting Discussion:

- See Meeting Discussion for 2a

2.1.6 **Briefing Package Question 3:** Does the Agency agree with the planned attributes for release of the RLY5016 (b) (4) intermediate?

FDA Preliminary Response:

RLY5016 (b) (4) is a key intermediate and it is synthesized (b) (4) intermediate need to be carefully implemented, especially for impurities (including the potentially genotoxic impurities). You need to provide full characterization and justification for the impurity profile for RLY5016 (b) (4) in the NDA submission.

Meeting Discussion:

No meeting Discussion on this topic.

2.1.7 **Briefing Package Question 4a:** Relypsa may make minor changes to the process for synthesis of the stabilized drug substance (b) (4) for commercialization. Does the Agency agree with the plans to demonstrate (b) (4) of stabilized drug substance (b) (4)?

FDA Preliminary Response:

The Agency agrees with the plans to demonstrate (b) (4) RLY5016 (b) (4) (see response to Question 11c below regarding the in vitro (b) (4) studies).

Meeting Discussion:

- If the Agency subsequently agrees (b) (4) the Drug Substance, (b) (4)

- 2.1.8 **Briefing Package Question 4b:** Does the Agency agree that the process changes proposed are considered minor if we can demonstrate equivalence of the stabilized drug substance manufactured pre and post-change?

FDA Preliminary Response:

The Agency agrees. See response to Question 4a.

Meeting Discussion:

- If the Agency subsequently agrees [REDACTED] (b) (4) the Drug Substance, [REDACTED] (b) (4)

- 2.1.9 **Briefing Package Question 5a:** The intended attributes and acceptance criteria for release of stabilized drug substance for Phase 3 and the intended attributes to be tested at release for commercial stabilized drug substance are provided in the Meeting Package. Does the Agency agree with the proposed attributes and acceptance criteria for release of stabilized drug substance, RLY5016S, to be used in Phase 3 clinical studies?

FDA Preliminary Response:

The Agency agrees with the proposed attributes and acceptance criteria for RLY5016S (and similarly applied to RLY5016) to be used in Phase 3 clinical studies.

Meeting Discussion:

- If the Agency subsequently agrees [REDACTED] (b) (4) the Drug Substance, [REDACTED] (b) (4)

- 2.1.10 **Briefing Package Question 5b:** Does the Agency agree with the intended attributes to be tested at release for the commercial stabilized drug substance, RLY5016S?

FDA Preliminary Response:

Based on the available information in this package, the proposed test attributes for RLY5016S (and similarly applied to RLY5016) appear reasonable. The acceptance criteria for the commercial stage will be evaluated during NDA review. You need to provide full characterization and justification for the impurity profile (including the potentially genotoxic impurities) in the NDA submission.

The suitability of the RLY5016S will need to be demonstrated if this [REDACTED] (b) (4) is held for an extended period prior to its use in the drug product manufacturing.

Meeting Discussion:

- If the Agency subsequently agrees [REDACTED] (b) (4) the Drug Substance, [REDACTED] (b) (4)

- 2.1.11 **Briefing Package Question 5c:** Does the Agency agree with Relypsa's approach to controlling impurities in the stabilized drug substance, RLY5016S?

FDA Preliminary Response:

See response to Question 5b.

- 2.1.12 **Briefing Package Question 6a:** The stability plans to support a retest period for stabilized drug substance is outlined in the Meeting Package. Does the Agency agree that the overall stability plan is adequate to generate the data required to support the Phase 3 program using stabilized drug substance, RLY5016S, manufactured by (b)(4) and (b)(4)?

FDA Preliminary Response:

You should submit the available stability data for RLY 5016 drug substance to support your phase 3 studies. The RLY5016S will be considered as a drug product (b)(4) the drug substance. You will need to establish a retest period for the drug substance RLY5016 as per the ICH Q1A (R2) guidance prior to submitting NDA.

Meeting Discussion:

- If the Agency subsequently agrees to accept (b)(4) then there will be no need to establish retest period for RLY-5016.

- 2.1.13 **Briefing Package Question 6b:** Does the Agency agree that the overall stability plan is adequate to generate the data required to support submission of the NDA with stabilized drug substance, RLY5016S, manufactured by (b)(4) and (b)(4)?

FDA Preliminary Response:

You need to conduct stability studies on RLY5016 as per ICH Q1A (R2) to establish a retest period.

Meeting Discussion:

- See discussion for 6a

- 2.1.14 **Briefing Package Question 7a:** Due to the instability of the drug substance, the active ingredient, RLY5016, (b)(4)

FDA Preliminary Response:

RLY5016 is acceptable as the drug substance; (b)(4)
(b)(4)

Meeting Discussion:

- See meeting discussion for Question 1

2.1.15 **Briefing Package Question 7b:** Does the Agency agree with our plan to use RLY5016S as the reference standard for analysis of stabilized drug substance and drug product at Phase 3 and for commercial stabilized drug substance and drug product?

FDA Preliminary Response:

For identification of RLY5016 by IR spectroscopy you should use RLY5016 as the reference.

Meeting Discussion:

- No discussion.

2.1.16 **Briefing Package Question 7c:** Does the Agency agree that the structural characterization data to be submitted in the NDA can be obtained from analysis of (b) (4)?

FDA Preliminary Response:

No. Full structural characterization should be carried out on drug substance RLY5016.

Meeting Discussion:

- If the Agency agrees to accept (b) (4) then full characterization of RLY 5016 may not be needed.

2.1.17 **Briefing Package Question 7d:** Does the Agency agree that the RLY5016S reference standard is adequately characterized?

FDA Preliminary Response:

Yes. A comparable reference standard for RLY5016 should be established.

Meeting Discussion:

- If the Agency subsequently agrees to accept (b) (4) then a comparable reference standard for RLY 5016 may not be needed.

2.1.18 **Briefing Package Question 7e:** Does the Agency agree with the plan to enter (b) (4) into an ICH registration stability program and to establish a retest period for long-term storage of the stabilized drug substance, even though the drug substance is RLY5016?

FDA Preliminary Response:

See response to Question 6b.

Meeting Discussion:

- See discussion for 6a.

2.2 Drug Product

2.2.1 Briefing Package Question 8:

(b) (4)

(b) (4)

FDA Preliminary Response:

You need to optimize your process for the manufacture of

(b) (4)

(b) (4)

(b) (4) However, if this is not technically feasible, then this approach may be acceptable.

Meeting Discussion:

- The Sponsor agreed that they would optimize the manufacturing process to eliminate (b) (4)

2.2.2 Briefing Package Question 9: To date, (b) (4) has manufactured drug product for use in Phase 2 clinical studies. (b) (4) is the drug product manufacturing site that will produce Phase 3 clinical material and commercial product. Does the Agency agree with the proposed testing plans to include (b) (4) as the site for manufacture of Phase 3 clinical material and commercial drug product?

FDA Preliminary Response:

The proposed plan is acceptable.

Meeting Discussion:

- No meeting discussion.

2.2.3 Briefing Package Question 10: Relypsa may make changes to the process for manufacture of drug product between Phase 3 and process validation prior to commercialization. Does the Agency agree with the proposed plans to support the manufacturing changes for the drug product in the NDA?

FDA Preliminary Response:

At this stage, we cannot respond to this question. We will need to evaluate the specification and extent of the changes to the process.

Meeting Discussion:

- No meeting discussion.

2.2.4 **Briefing Package Question 11a:** The proposed attributes and acceptance criteria for release of drug product for Phase 3 and the intended attributes to be tested at release for commercial drug product are provided in the Meeting Package. Does the Agency agree with the proposed attributes and acceptance criteria for release of drug product for use in Phase 3 clinical studies?

FDA Preliminary Response:

The proposed attributes and acceptance criteria for release of drug product for use in Phase 3 clinical studies are acceptable.

Meeting Discussion:

- No meeting discussion.

2.2.5 **Briefing Package Question 11b:** Does the Agency agree with the intended attributes to be tested at release for the commercial drug product?

FDA Preliminary Response:

Based on the data provided, the intended attributes are acceptable at this stage; however, the final determination, including acceptance criteria, will be a review issue during NDA submission.

Meeting Discussion:

- No meeting discussion.

2.2.6 **Briefing Package Question 11c:** Does the Agency agree with our proposed *in vitro* equilibrium and kinetic binding tests, and the proposed acceptance criteria, to be used to support comparability and show bioequivalence in the event that manufacturing changes are made during development and/or post-approval?

FDA Preliminary Response:

This is acceptable.

Meeting Discussion:

- No meeting discussion.

2.2.7 **Briefing Package Question 11d:** Does the Agency agree with the approach to controlling impurities in the drug product?

FDA Preliminary Response:

See response to Question 5b.

Meeting Discussion:

- No meeting discussion.

2.2.8 **Briefing Package Question 12a:** The drug product dosage form is a powder for suspension packaged in (b) (4). The specific strengths to be made available commercially will be defined based on the results of the clinical trials. The (b) (4) that are under consideration are: (b) (4) (active ingredient). Does the Agency agree that the overall stability plan for drug product is adequate to generate the data required to support the Phase 3 program?

FDA Preliminary Response:

The overall stability plan is acceptable to support the Phase 3 program.

Meeting Discussion:

- No meeting discussion.

2.2.9 **Briefing Package Question 12b:** Does the Agency agree that the overall stability program for drug product is satisfactory to generate the data required to support submission of the NDA?

FDA Preliminary Response:

Based on the available information, we cannot respond to this question. You need to conduct stability studies on drug product as per ICH Q1A (R2).

Meeting Discussion:

- No meeting discussion.

2.2.10 **Briefing Package Question 12c:** Does the Agency agree with our stability bracketing plan proposed to support NDA submission?

FDA Preliminary Response:

We do not agree with your stability bracketing plan, as you stated that the dimensions of the (b) (4) will be adjusted to accommodate the increased fill weight of the drug product. You need to establish the bracketing plan as per ICH Q1D.

Meeting Discussion:

- No meeting discussion.

2.2.11 **Briefing Package Question 12d:** Does the Agency agree that as long as the intended commercial strengths of drug product are bracketed in the stability program, it is acceptable if the proposed commercial strengths are within the brackets but are not the actual strengths that were tested on stability?

FDA Preliminary Response:

The agency agrees.

Meeting Discussion:

- No meeting discussion.

2.2.12 **Briefing Package Question 12e:** Due to the increase in inorganic fluoride that is produced over time in the drug product with storage, drug product is currently stored long-term at (b) (4). In the NDA we plan to provide stability data at (b) (4) to support a label that would allow patients to store drug product at room temperature for limited periods of time. Does the Agency agree with the proposed plan?

FDA Preliminary Response:

The agency agrees.

Meeting Discussion:

- No meeting discussion.

2.3 General

2.3.1 **Briefing Package Question 13:** (b) (4) used in the production of (b) (4)

FDA Preliminary Response:

We encourage you to implement this plan before initiating Phase III. Also, additional CMC data may be needed depending on the proposed changes. You should seek input from other disciplines as well (Clinical, ClinPharm).

Meeting Discussion:

- No meeting discussion.

3 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit an amendment to IND 76,715 with the details justifying ^{(b)(4)} as the Drug Substance.	Relypsa, Inc.	Prior to initiating Phase III studies.

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/s/

RAMESH K SOOD
12/22/2010

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205739

LATE-CYCLE MEETING MINUTES

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) dated October 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b)(4) 8.4 g, (b)(4) 16.8 g, (b)(4) and 25.2 g.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 29, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Sabry Soukehal, Consumer Safety Officer, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD
Clinical Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: 29 June 2015, 1:30 p.m. – 3:00 p.m. Eastern Time
Meeting Location: Teleconference

Application Number: 205739
Product Name: VELTASSA (patiromer sorbitex calcium)
Applicant Name: Relypsa, Inc.

Meeting Chair: Aliza Thompson, MD
Meeting Recorder: Sabry Soukehal, RQAP-GLP

FDA ATTENDEES

*Office of Drug Evaluation I

Robert Temple, MD Deputy Director

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Mike Monteleone, MS, RAC	Associate Director for Labeling
Aliza Thompson, MD	Clinical Team Leader
Shen Xiao, MD	Clinical Reviewer
Albert Defelice, PhD	Non-Clinical Team Leader
William Link, PhD	Non-Clinical Reviewer
Edward Fromm, R. Ph., RAC	Chief, Regulatory Health Project Manager
Quynh Nguyen, PharmD, RAC	Sr. Regulatory Health Project Manager
Sabry Soukehal, RQAP-GLP	Consumer Safety Officer
Brian Proctor	Regulatory Health Project Manager

*Office of Clinical Pharmacology

Rajanikanth Madabushi, PhD	Team Leader
Ju-Ping Lai, PhD	Clinical Pharmacology Reviewer

*Office of Pharmaceutical Quality

Mohan Sapru, PhD	CMC Team Leader
Raymond Frankewich, PhD	CMC Reviewer
Michael Folkendt	Associate Director for Regulatory Affairs

*Office of Scientific Investigations/Office of Compliance

Sharon Gershon, PharmD	Regulatory Reviewer
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*Office of Surveillance and Epidemiology

Amy Chen, PharmD	Safety Evaluator
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2.0 DISCUSSION

1. Discussion of Substantive Review Issues

CMC:

Dr. Frankewich indicated that a preliminary review of the quality information amendments submitted on June 19, 2015 and June 25, 2015 did not raise significant concerns. However, a detailed review needs to be performed and will require some time. Dr. Frankewich stated that the analytical method to determine (b) (4) levels, to be submitted in September 2015, will need to be evaluated. The Applicant stated that they had already submitted the development data and asked if it was necessary to submit the analytical method and validation procedure for (b) (4) prior to taking an action on the NDA considering the fact that currently, the total (b) (4) impurities are about (b) (4) % and will be about (b) (4) % with the dose (b) (4) to QD dosing. Dr. Frankewich confirmed that the CMC group will need to review the analytical method and validation procedure for (b) (4) prior to making a recommendation on approval. The Applicant indicated that the analytical data would be submitted by July 10, 2015, except for the method validation data and related details.

Dr. Frankewich stated that it is not possible at this time to determine if the planned submission would extend the review clock. Dr. Frankewich commented that the drug substance stability specifications appeared acceptable. The Applicant confirmed that they had withdrawn submission of the (b) (4) as requested by the Division and stated that all CMC information requests up to this point had been addressed.

Clinical Pharmacology:

Dr. Madabushi acknowledged the Applicant's decision to (b) (4) the dosing regimen (b) (4) QD regimen and indicated that this change was an important first step in addressing the drug-drug interaction (DDI) issue. He had concerns, however, related to changes that were made to Table 2 (Drugs Tested in *In Vitro* Binding Studies with Veltassa) in section 7 of the draft label. The applicant provided their rationale for some of the changes that were made to the table, explaining that they removed (b) (4) and that amlodipine and metoprolol were added to the list of drugs that can be concomitantly administered because the clinical trial data did not suggest a clinically relevant interaction. Dr. Madabushi pointed out that using the clinical trial data to assess drug interactions is challenging, as in general the "experiment" is not adequately controlled to provide reliable information. He also stated that ciprofloxacin should be added back to Table 2 because the interaction is with one of the components of VELTASSA.

With regard to addressing potential drug interactions between VELTASSA and drugs that were not evaluated in the Applicant's *in vitro* studies, Dr. Madabushi commented that he did not believe it was appropriate to adopt the standard language used in phosphate binder labeling. Drs. Madabushi and Thompson noted that the available data indicate that VELTASSA has a greater DDI liability than recently approved phosphate binders and that the indicated population for VELTASSA is likely to be much larger than the indicated population for phosphate binders (i.e.,

patients with end-stage renal disease). Dr. Thompson stated that the approach taken with phosphate binders is not optimal and would not be sufficient to mitigate the risk with VELTASSA. Dr. Madabushi encouraged the Applicant to develop a better strategy to mitigate the risk.

The current draft label states that VELTASSA should be taken with food. The Applicant asked if labeling could indicate that VELTASSA can be taken at any time, (b) (4). Dr. Thompson noted that patiromer was taken with food in all of the clinical studies; (b) (4).

Dr. Thompson asked if the Applicant had considered the use of (b) (4) in patients taking VELTASSA. The Applicant said that (b) (4) did not rise to the 5% level of use based on their data but indicated that they will explore whether a “general instructions” statement would be able to address use with (b) (4). Dr. Madabushi advised the Applicant to develop labeling instructions that are easy to implement and unlikely to result in drug-drug interactions. He indicated that additional meetings would probably be needed to discuss the DDI issue.

2. Wrap-up and Action Items

Dr. Thompson stated that no Advisory Committee Meeting is planned.

Given the (b) (4) dosing (b) (4) the Applicant stated that they plan (b) (4) a 30-packet carton (for QD dosing). They plan to submit this change to the carton labeling by the end of July 2015. The Agency stated that DMEPA will need to review the change to the carton.

The Applicant asked whether the Division could share its analyses supporting a (b) (4). The Division agreed to share the information with the Applicant and sent a description of its analysis and findings on July 13, 2015.

The Division agreed with the Applicant’s proposed dosage strengths of 8.4 g, 16.8 g and 25.2 g in single-use packets. The Division stated that it would provide draft labeling by the end of the following week.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

ALIZA M THOMPSON
07/27/2015



NDA 205739

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Relypsa, Inc.
Attention: Sarah McNulty
Vice President, Regulatory Affairs
700 Saginaw Drive
Redwood City, CA 94063

Dear Ms. McNulty:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELTASSA (patiromer sorbitex calcium) Powder for Oral Suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 29, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, please contact Sabry Soukehal, Consumer Safety Officer, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
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ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: June 29, 2015 at 1:30 pm Eastern Time
Meeting Location: White Oak, Building 22, Room 4270 - Teleconference

Application Number: 205739
Product Name: VELTASSA
Indication: Treatment of Hyperkalemia
Applicant Name: Relypsa, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

CMC:

1. Please be advised that your proposal to provide analytical procedures and validation reports for analysis of Class (b) (4) elemental impurities in RLY5016 drug substance and xanthan

gum by September 4, 2015 may be considered a major amendment to this NDA which may result in an extension of the PDUFA Goal Date.

Clinical Pharmacology:

1. We have considered your proposal to mitigate the risk of drug-drug interactions, submitted on May 20, 2015. For the following reasons, we still believe this represents a substantive review issue that will need to be addressed before a regulatory action is taken.
 - For drugs that have evidence of binding based on *in vitro* studies, you propose administration prior to Veltassa and a time window for separation that ranges from (b) (4) hours depending on the medication. In some instances, an option to take the concomitant medication (b) (4) hours after the administration of Veltassa is also provided. We believe that the proposed strategy is too complex and will be difficult to implement in clinical practice. Your strategy should be relatively easy for patients to follow. It should also address the fact that multiple physicians are likely to be prescribing medications to patients.
 - You propose once daily dosing of Veltassa (b) (4). We agree that a once daily dosing regimen of Veltassa alleviates some of the concern for potential drug-drug interactions, especially for concomitant medications that are also administered once daily. (b) (4)
(b) (4)
f note, even a once-daily regimen may not adequately mitigate the risk since the target population is likely to be on multiple critical medications and since some of these medications may need to be separated from each other or require administration at set but different times each day (b) (4).

We encourage you to consider the aforementioned issues and propose a pragmatic strategy that can be applied to a wide spectrum of drugs that are relevant to the target population. The proposed strategy should be reasonably easy to implement and should be applicable to various oral dosage forms. We also request that you submit a list of drugs that are likely to be used in the proposed population that also meet either of the following criteria: (1) the drug requires twice-daily (or more frequent) administration or (2) the drug is an extended-release preparation.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

At this time, we believe a Medication Guide is needed to address the potential risk of drug-drug interactions. The proposed Medication Guide submitted on May 20, 2015 is under review.

INFORMATION REQUESTS

CMC:

1. In your amendment dated May 5, 2015, you indicated that the following tests, which were used to generate data provided in the primary stability study, will not be used to generate stability data for future batches: Impurities in RLY5016S by GC-FID Method 1; Impurities in RLY5016S by LC-UV Method 1; and Potassium Binding Capacity. Please update your stability protocol and specification in your NDA with regard to these tests.

2. Regarding your proposed  (b) (4)

3. Concerning your  (b) (4)

4. Concerning your  (b) (4)

 (b) (4)

MAJOR LABELING ISSUES

Clinical Pharmacology:

1. Section 2 (Dosage and Administration) recommends a starting dose of 8.4 grams daily in patients [REDACTED] (b) (4). The section also indicates that the dose may be increased or decreased by 8.4 grams daily, as necessary, to reach the desired range, but doesn't specify a maximum daily dose or the time interval between titration steps.
 - Based on our review of studies 205 and 301 and your response to the mid-cycle communication, [REDACTED] (b) (4).
 - Because most of the patients in the clinical trials achieved the target serum potassium level at a dose \leq 25.2 grams/day and because there is no long-term safety or tolerability experience with a unit dose greater than 25.2 grams, we believe that Section 2 should state that the dose can be titrated to 25.2 grams once daily based on response.
 - The label should also provide guidance on the time interval between dose titration steps. A [REDACTED] (b) (4) interval may not be sufficient to observe the full effect. We suggest an interval of at least 1 week before the first titration.
2. Section 3 (Dosage Forms and Strengths) indicates that Veltassa will be packaged in single-use packets containing [REDACTED] (b) (4) 8.4 grams, [REDACTED] (b) (4) 16.8 grams, [REDACTED] (b) (4) or 25.2 grams patiromer. Once agreement is reached on the dosing regimen, the available dosage strengths should be revised to reflect the agreed-upon dosing regimen.

Clinical:

1. In the proposed Veltassa preparation instructions [REDACTED] (b) (4) the amount of water that is added [REDACTED] (b) (4). We recommend that dosing instructions specify the same "initial" amount of water and "additional" amount of water for all of the doses (i.e., the amount required for the highest recommended dose).

LCM AGENDA

1. Introductory Comments
 - Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues
3. REMS or Other Risk Management Actions

4. Information Requests
5. Major labeling issues
6. Review Plans
7. Wrap-up and Action Items

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

/s/

MARY R SOUTHWORTH
06/17/2015
Signing for Norman Stockbridge