

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200671Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

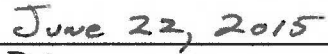
1.3.5.2 Patent Certification

Certification of No Relevant Patents

Pursuant to 21 USC § 355(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50(i)(1)(ii), in the opinion of and to the best knowledge of Silvergate Pharmaceuticals, Inc., there are no patents that claim the drug, Zestril® tablets (NDA 019777), on which investigations that are relied upon in this application were conducted or that claim a use of such drug.



Michael C. Beckloff
Chief Development Officer
Silvergate Pharmaceuticals, Inc.



Date

**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

208401

NAME OF APPLICANT/NDA HOLDER

Silvergate Pharmaceuticals, 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)

(b) (4) Oral Solution

ACTIVE INGREDIENT(S)

lisinopril

STRENGTH(S)

1 mg/mL

DOSAGE FORM

Oral solution

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

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

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

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

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 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	
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) <i>Michael C. Beckloff</i> Michael C. Beckloff (Jun 23, 2015)	Date Signed 6/30/2015
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 ☐ Patent Owner	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official ☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Michael C. Beckloff	
Address 7300 W 110th St, Ste 950	City/State Overland Park, KS
ZIP Code 66210	Telephone Number 913.871.1247
FAX Number (if available) 913.871.0168	E-Mail Address (if available) michael.beckloff@silvergatepharma.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 <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>	

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

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

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

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

2. Drug Substance (Active Ingredient)

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

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

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

EXCLUSIVITY SUMMARY

NDA # 208401

SUPPL # --

HFD # 110

Trade Name Qbrelis

Generic Name Lisinopril

Applicant Name Silvergate Pharmaceuticals, Inc.

Approval Date, If Known: July 29, 2016

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)(2)

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.

The application relied on the Agency's previous finding of safety and effectiveness for the reference listed drug, Zestril[®] (lisinopril) tablets (NDA 019777, approved May 19, 1988), distributed by AstraZeneca Pharmaceuticals.

In support of this application, the applicant submitted two reports of studies that investigated the exposure measures of lisinopril with an oral solution containing 10 mg lisinopril and a 10 mg Zestril[®] tablet in healthy subjects in the fasted and fed state. The 10 mg lisinopril dose corresponds to the initial dose of Zestril[®] recommended in the label. The objective of the studies was to compare the rate of absorption and oral bioavailability of a test formulation of 10 mL of lisinopril oral

solution, 1 mg/mL, to an equivalent oral dose of the commercially available comparator product, Zestril® 10 mg tablet when administered under fasted and fed conditions.

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:

--

c) Did the applicant request exclusivity?

YES NO

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

Of note, the applicant requested 7 years of exclusivity at the time of NDA submission in anticipation of the FDA granting lisinopril oral solution orphan drug designation for the treatment of hypertension in pediatric patients 0 to 16 years of age. During the review cycle, orphan designation was granted on October 14, 2015, and then revoked on April 28, 2016, as the prevalence of pediatric hypertension was found to exceed the statutory threshold of 200, 000 persons.

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?

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# 019777 Zestril®

NDA# --

NDA# --

2. Combination product.

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

YES NO

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

NDA# --

NDA# --

NDA# --

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1

YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

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

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

Name of person completing form: Sabry Soukehal
Title: Regulatory Project Manager
Date: July 28, 2016

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
07/28/2016

NORMAN L STOCKBRIDGE
07/28/2016

1.3.3 Debarment Certification

Silvergate Pharmaceuticals, Inc. (Silvergate), 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 (the Act) in connection with this application.

Silvergate certifies that, during the previous 5 years, it has not sustained a conviction that is described in sections 306(a) or (b) of the Act. In addition, no person affiliated with Silvergate, nor affiliated persons responsible for the development or submission of this application, have been convicted of an offense described in sections 306(a) or (b) of the Act.

Furthermore, Silvergate agrees to notify FDA of any changes in status of any employee with respect to sections 306(a) or (b) of the Act.



Michael C. Beckloff
Chief Development Officer
Silvergate Pharmaceuticals, Inc.

June 22, 2015
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208401 BLA # --	NDA Supplement # -- BLA Supplement # --	If NDA, Efficacy Supplement Type: -- <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: QBRELIS Established/Proper Name: Lisinopril Dosage Form: Solution		Applicant: Silvergate Pharmaceuticals, Inc. Agent for Applicant (if applicable): Michael C. Beckloff
RPM: Sabry Soukehal		Division: Cardiovascular and Renal Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> 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) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: June 13, 2016 <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>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>July 30, 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ 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 _____		☐ 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 3 – New Dosage Form
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ 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 required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	☐ Yes ☐ No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ 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.	☒ Verified ☐ 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>	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s): Approval, July 29, 2016
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	- Letters: 12/30/15, 8/28/15 - Reviews: 12/28/15, 8/17/15
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: 09/10/15 DMEPA: 10/09/15, 12/07/15, 2/2/16, 6/27/16 DMPP/PLT (DRISK): ☒ None OPDP: 4/6/16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	RPM reviews: 8/29/15, 7/28/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	505 (b)(2): 7/25/16
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

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

- This application is on the AIP - 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>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC 3/16/16 and 5/11/16 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
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>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ 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 OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	7/21/15, 9/11/15, 10/28/15, 12/15/15, 1/05/16, 2/22/16, 3/01/16, 4/29/16, 6/03/16, 6/29/16, and 6/30/16
❖ 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)	RPM memo: 4/29/16 DPMH memo (consult review): 3/24/16
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) – Meeting cancelled after the applicant received our preliminary comments dated 11/30/12	☒ No mtg
EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	N/A
❖ Advisory Committee Meeting(s) Date(s) of Meeting(s)	☒ No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	7/20/16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	7/17/16
PMR/PMC Development Templates (<i>indicate total number</i>)	One on 7/11/16 (safety review tab)
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	N/A
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Memo completed on 7/29/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management - 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>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	3/24/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	2/10/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ 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>)	3/23/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ 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>)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done (note: there are no planned communications from the Press Office)
❖ 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	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

SABRY SOUKEHAL
07/29/2016

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 208401

Submission Date(s): June 30, 2015

Applicant: Silvergate Pharmaceuticals, Inc

Product: Qbrelis / Lisinopril Oral Solution

Reviewer: Aliza Thompson

Date of Review: July 29, 2016

Covered Clinical Study (Name and/or Number): SG03-01 and SG03-02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>9 (1 Principal Investigator; 8 Subinvestigators)</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. The provided information does not raise questions about the integrity of the data.

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/s/

ALIZA M THOMPSON
07/29/2016



NDA 208401

LABELING PMR/PMC DISCUSSION COMMENTS

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qbrelis (lisinopril) Oral Solution 1mg/ml.

We also refer to our April 29, 2016 letter in which we notified you of our target date of July 01, 2016 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 April 20, 2016 we received your April 20, 2016 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 08, 2016**. 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 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.

These revisions have been reviewed and cleared to the level of Division Director.

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

Sincerely,

{See appended electronic signature page}

Sabry Soukehal
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE: Qbrelis Prescribing Information

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

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/s/

SABRY SOUKEHAL
06/30/2016



NDA 208401

GENERAL ADVICE

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qbrelis (Lisinopril) Oral Solution 1mg/ml.

We also refer to your June 23, 2016 submission containing revised draft container and carton labels.

The Division of Medication Error Prevention and Analysis (DMEPA) has reviewed the referenced materials and has the following comments and recommendations.

A. Container Label:

1. As currently presented, there are two barcodes on the container label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers.¹ Clarify the purpose and intent of the second barcode, and consider if the second barcode is necessary on the container label or if it can be removed to prevent confusion.

B. Carton Labeling:

1. Revise the presentation of the proprietary name and established name on the top flap of the carton labeling to include the dosage form, as follows: "Qbrelis (lisinopril) Oral Solution."²
2. Revise the temperature range in the storage information presented on the carton labeling [20-25°C ((b) (4))] to match that presented on the container label and in section 16 of the PI [20-25°C (68-77°F)].

¹ Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-3.

²Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, 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
06/29/2016

PeRC Meeting Minutes
May 11, 2016

PeRC Members Attending:

Lynne Yao
Meshاون Payne
Dianne Murphy
Gerri Baer
Peter Starke
Gil Burckart
Raquel Tapia
Greg Reaman
Dionna Green
Robert “Skip” Nelson
Kevin Krudys
Barbara Buch
Rosemary Addy
Shrikant Pagay
Adrienne Hornatko-Munoz
Wiley Chambers
Jackie Yancy
Thomas Smith
John Alexander
Karen Davis-Bruno

Agenda

NON-RESPONSIVE					
9:30	NDA 208401	Lisinopril (Partial Waiver/Deferral/Plan)		DCRP Sabry Soukehal	(1) Treatment of hypertension in adult and pediatric patient 6 years and older (2) (b) (4) signs and symptoms of systolic heart failure (3) Reduction of mortality in the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction

NON-RESPONSIVE

NON-RESPONSIVE

NON-RESPONSIVE

Lisinopril (Partial Waiver/Deferral/Plan)

- Proposed Indication: (1) Treatment of hypertension in adult and pediatric patient 6 years and older (2) (b) (4) signs and symptoms of systolic heart failure (3) Reduction of mortality in the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction
- This product triggers PREA as a new dosage form and has a PDUFA goal date of June 30, 2016.
- The division previously met with the PeRC on March 16, 2016 to discuss this pediatric plan for NDA 208401. At the meeting, PeRC agreed to a waiver for the following proposed indications: (1) (b) (4) heart failure and (2) (b) (4) treatment (b) (4) acute myocardial infarction. Because, the liquid formulation of the product had orphan drug designation for the treatment of hypertension in pediatric patients 0-16 years of age, a pediatric assessment for pediatric hypertension was not

required and therefore, was not reviewed at the March PeRC meeting. On April 28, 2016, the Office of Orphan Products Development revoked orphan designation for lisinopril for the treatment of pediatric hypertension, noting that the prevalence of pediatric hypertension was in excess of the statutory threshold. Hence, a pediatric assessment for the hypertension is now required. This pediatric assessment template focuses on the pediatric plan and assessment for the hypertension indication.

- The division stated they do not agree with the number of patients to be studied as the study is not adequately powered and the sponsor has not adequately addressed this problem.

- *PeRC Recommendations:*
 - The PeRC agreed with the division's plan to waive studies in patients less than 2 years of age because studies are impossible or highly impractical and to the deferral in patients 2-6 years of age.
 - The PeRC agreed to the timelines as outlined by the division.

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
06/08/2016



NDA 208401

GENERAL ADVICE

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution 1 mg/ml.

We also refer to your April 28, 2016, submission containing a Pediatric Study Plan.

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

CLINICAL PHARMACOLOGY

1. We do not agree with the proposed doses.

(b) (4)

We are open to working with you to develop a dosing strategy that would result in better matching of exposures to those observed in adults.

2. Sparse pharmacokinetic sampling should be conducted at the end of the 2-week treatment phase of the trial. Samples do not need to be collected in all subjects; however samples should be collected in a sufficient number of subjects to ensure precision for pharmacokinetic parameter estimates within a range of 60 to 140%.

(b) (4)

STATISTICAL

1. The trial must have sufficient power for assessment of dose-response as well as for assessment of a clinically meaningful treatment effect in the randomized withdrawal phase of the study. Your proposal does not adequately address this issue. With regard to the randomized withdrawal phase, the study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary endpoint. A clinically meaningful treatment benefit is generally considered to be a 3-mmHg effect (placebo-subtracted change from baseline) on either systolic or diastolic pressure. This requires you to show that if the true treatment effect for one of the treatment groups were minimally "clinically meaningful", the pre-planned analysis would have at least 90% power to infer that at least one dose or the high dose is significantly different from placebo.
2. The statistical analysis should be a slope analysis for the first period. If the first period fails to reveal a statistically significant non-zero slope, an analysis of the second period (the randomized withdrawal phase) would determine whether there was, or was not, a blood pressure effect. No alpha adjustment would be required for testing these two hypotheses. In the second period, you may allocate alpha to each active arm or to some combination of treatment arms (e.g., the highest two dose levels).

CLINICAL

1. You propose to exclude subjects with a baseline potassium value $> \text{█}^{(b)}_{(4)}$ mEq/L. We agree that patients with elevated potassium values should be excluded from the study, but are concerned that the proposed threshold could expose subjects to unreasonable risk. You should lower the potassium value used to exclude subjects and provide support from the literature and/or guidelines for whatever threshold you propose.
2. You propose to perform laboratory tests, including "chemistry" tests at the screening visit $\text{█}^{(b)}_{(4)}$. We do not agree with your proposal; serum potassium and creatinine concentrations should be monitored closely during the study.
3. From a safety perspective, your study should be well-designed to characterize the risks of your product in children and specifically, the risks of hyperkalemia, acute elevations in serum creatinine, and hypotension. See also our prior comment regarding laboratory monitoring.
4. The trial must consistently measure both systolic pressure and diastolic pressure in all patients. Measurements of blood pressure should be collected throughout the inter-dosing interval and include measurements at peak lisinopril concentrations. Patients should be followed at least weekly in the randomized withdrawal phase, so that unacceptable increases in blood pressure can be detected and treated promptly.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, 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
06/03/2016



NDA 208401

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qbrelis (Lisinopril) Oral Solution 1 mg/ml.

On April 28, 2016, we received your April 28, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 30, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 01, 2016.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, 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
04/29/2016

**PeRC Meeting Minutes
March 16, 2016**

PeRC Members Attending:

John Alexander
Gil Burckart
Thomas Smith
Gettie Audain
Meshaun Payne
Wiley Chambers
Freda Cooner
Barbara Buch
Raquel Tapia
Greg Reaman
Kevin Krudys
Robert "Skip" Nelson
Jerri Bauer
Peter Starke
Dionna Greene
Ikram Ilean

Agenda

NON-RESPONSIVE

10:30	NDA 208401	Qbrelis (lisinopril) Full Waiver	DCRP	Sabry Soukehal	(2) (b) (4) signs and symptoms of systolic heart failure (3) Reduction of mortality in the treatment of hemodynamically stable patients within 24 hrs of acute myocardial infarction

NON-RESPONSIVE

NON-RESPONSIVE

NON-RESPONSIVE

Obrelis (lisinopril) Full Waiver

- Proposed Indication: (2) (b) (4) signs and symptoms of systolic heart failure (3) Reduction of mortality in the treatment of hemodynamically stable patients within 24 hrs of acute myocardial infarction.
- This product has a PDUFA goal date of April 30, 2016.
- The division indicated they are working with DPMH and the division of orphan drugs about rescinding the orphan drug designation for the pediatric hypertension indication.
- The division further explained that the applicant initially submitted a request for a partial waiver and deferral of pediatric studies in hypertension. Following NDA submission, the applicant received orphan drug designation, recently, for proposed indication (1) the treatment of hypertension in pediatric patients 0-16 years of age. The applicant intends to revise the proposed pediatric study plan, since, as the applicant understands, PREA no longer applies to the hypertension indication. The review division stated that the applicant no longer plans to conduct the pediatric hypertension studies that were previously included in the PSP.
- PeRC discussed concerns that this orphan designation would be a way of avoiding the pediatric studies under PREA.
- *PeRC Recommendations:*
 - The PeRC agreed with the waiver of pediatric patient's ages 0 to 16 years of age for proposed indications (2) and (3) as studies are impossible and highly impractical

NON-RESPONSIVE

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/s/

GETTIE AUDAIN
03/25/2016



NDA 208401

GENERAL ADVICE

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution 1 mg/ml.

We also refer to your February 16, 2016, email (attached below) requesting that your label be modified to include an indication for the treatment of hypertension in children (b)(4) of age and older.

The Division of Cardiovascular and Renal Products has reviewed your request and has the following response.

In your email, you reference the “FDA’s response to the 2002 Zestril and Prinivil Written Request” and assert that (b)(4)

(b)(4)

- Qbrelis is indicated for the treatment of hypertension, to lower blood pressure in adults and children older than (b)(4).
- Qbrelis is not recommended (b)(4) in pediatric patients with glomerular filtration rate $<30 \text{ mL/min/1.73 m}^2$, as no data are available.

You also note that such labeling would be consistent with your “assessment based on Zestril and Prinivil SBoA for pediatric use as well as a comparison to the enalapril package insert for pediatric patients with $\text{GFR} <30 \text{ mL/min/1.73m}^2$.”

Although there may be precedent (i.e., the enalapril label) for using PK data to provide dosing recommendations for the use of blood pressure lowering agents in very young children, we no longer believe that an understanding of PK alone is sufficient to write dosing recommendations for these products in very young children. Since the enalapril approval, we have learned that PK-PD relationships for blood pressure reduction can be altered in children. Moreover, adequate

information on the safety and tolerability of the intended dose of a product in children less than 6 years of age would also be needed to support a claim in this population.

Hence, we do not believe that the information cited thus far is sufficient to expand the indication of your product to include the treatment of hypertension in children as young as [REDACTED] ^{(b) (4)} of age.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, 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: Mr. Beckloff's email dated February 16, 2016

From: [Michael Beckloff](#)
To: [Soukehal Sabry](#)
Cc: [Susan Prather](#)
Subject: Follow up Question on Qbrelis NDA 208401
Date: Tuesday, February 16, 2016 12:21:14 PM

Sabry:

I wanted to follow up with you on a question that we have regarding the pediatric labeling and age ranges for our Qbrelis NDA 208401.

Please refer to my e-mail of November 3, 2015 (copy below) regarding issues and questions we have regarding a potential pediatric study in children under the age of 6 years with a GFR <30 mL/min/1.73m².

We have reviewed the FDA's response to the 2002 Zestril and Prinivil Written Request. It indicates one of FDA's primary concerns was the comparative PK study in children less than 6 years old and the fact that it did not include patients with impaired renal function, specifically a GFR < 30 mL/min/1.73 m². This was the primary reason for our initially proposed study.

However, we have consulted medical experts in nephrology and have learned that due to lisinopril's long half-life with renal clearance and the high risk of serious adverse events, lisinopril would rarely be the ACE-I selected for pediatric patients less than 6 years of age with reduced renal function (GFR < 30 mL/min/1.73 m²). There are also several publications available that confirm the concern for high risk of serious adverse events in this CKD patient population (e.g. patients less than 6 years of age). Consequently, based on this information, it is not feasible to conduct a clinical study in patients less than 6 years of age with a GFR < 30 mL/min/1.73 m².

In summary, because we have found that lisinopril is rarely used in pediatric patients less than 6 years of age with a GFR < 30 mL/min/1.73 m² and given there is substantial evidence that lisinopril is safe and effective in children less than 6 years old with a GFR > 30 mL/min/1.73 m² based on the existing PK and PD data as discussed by FDA in the response to the Written Request, we would like to request that our Qbrelis label to be expanded to include children (b) (4) and older as follows:

Qbrelis is indicated for the treatment of hypertension, to lower blood pressure in adults and children older than (b) (4)

Qbrelis is not recommended in (b) (4) pediatric patients with glomerular filtration rate <30 mL/min/1.73 m², as no data are available.

This labeling would be consistent with our assessment based on Zestril and Prinivil SBoA for pediatric use as well as a comparison to the enalapril package insert for pediatric patients with GFR <30 mL/min/1.73m².

We would appreciate receiving FDA's input as to whether it would be possible to expand the age range for our current Qbrelis NDA labeling.

Thank you for your assistance.

Best regards.

Michael

Michael C. Beckloff
Chief Development Officer
Silvergate Pharmaceuticals, Inc.
7300 West 110th Street, Suite 950
Overland Park, Kansas 66210

Mobile: (b) (6)
michael.beckloff@silvergatepharma.com

November 3 e-mail

From: Michael Beckloff [<mailto:michael.beckloff@silvergatepharma.com>] **Sent:** Tuesday, November 03, 2015 5:20 PM **To:** Soukehal, Sabry **Subject:** Re: NDA 208401 question about pediatric study plan

Sabry:

I hope your week is going well. I wanted to follow-up with you on the topics we discussed during our telephone call on November 2, 2015 regarding our pediatric study plan.

(b) (4)

(b) (4) We await the Agency's response to the full waiver requests for the adult indications of adjunct therapy for heart failure and treatment of acute myocardial infarction. Please confirm this will be acceptable.

However, as indicated in the NDA, our original plan was to submit the study protocol during the month of October. A number of issues that we did not anticipate have developed that have resulted in a delay in finalizing the protocol. These issues are summarized below:

1. There is a question as to appropriate lower age limit for the study. Our protocol synopsis defines the lower limit to be (b) (4). Therefore, we are attempting to better understand what the lower age limit should be for this study.
2. There is also now a question regarding the glomerular filtration rate (GFR) eligibility criteria, specifically in the narrow range of (b) (4). We are in the process of assessing the GFR eligibility criteria to understand if it will be possible to identify an adequate number of these patients for participation in the study.
3. There are also questions as to the number and extent of the exclusion criteria that will be appropriate for this type of study. This will likely have a direct impact enrollment and the ability to identify an adequate number of patients for the study.
4. We are also considering the possibility of expanding the study to include pharmacodynamics

through blood pressure assessment over the course of the study.

5. Because of these questions, we are consulting with experts in pediatric nephrology to help us answer these questions and appropriately modify the study design. Once the study design has been finalized, we have contracted with Worldwide Clinical Trials to conduct a feasibility study that will allow us to assess our ability to identify appropriate patients to participate in this study.

Given our waiver requests and because of the above issues, we anticipate that our protocol will not be finalized until the second half of 2016. Before the protocol is finalized, we would like to meet with the Agency to discuss our overall clinical development plan and the specific IND requirements for this product.

Thank you.

Michael

Michael C. Beckloff
Chief Development Officer
Silvergate Pharmaceuticals, Inc.
7300 West 110th Street, Suite 950
Overland Park, Kansas 66210

Mobile: (b) (6)
michael.beckloff@silvergatepharma.com

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/s/

NORMAN L STOCKBRIDGE
03/01/2016



NDA 208401

GENERAL ADVICE

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution 1 mg/ml.

We also refer to our January 05, 2016, general advice letter containing the Division of Medication Error Prevention and Analysis comments and recommendations on your carton and container labels, and to your submission dated January 19, 2016, containing your response to the above-mentioned advice letter.

The Division of Medication Error Prevention and Analysis has reviewed your response and the referenced materials and has the following recommendation.

1. Ensure the barcode on the container label is able to be scanned as presented in the horizontal orientation. If not, reorient the barcode on the container label to a vertical position to ensure that the barcode can be scanned. Barcodes placed in a horizontal position on cylindrical medication containers may not scan due to curvature.

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
02/22/2016



NDA 208401

GENERAL ADVICE

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution 1 mg/ml.

We also refer to your September 30, 2015, submission containing a revised draft package insert, and to your October 16, 2015, submission containing draft carton and container labels with the proposed proprietary name QBRELIS.

The Division of Medication Error Prevention and Analysis (DMEPA) has reviewed the referenced materials and has the following comments and recommendations.

1. General Recommendations for Container label and Carton labeling

- a. Remove the statement “Ready to use” from the container label and carton labeling. The term appears promotional in nature, and does not add to the usage instruction for this product.
- b. Section 16 of the proposed Prescribing Information (PI) states that the product should be stored at “controlled room temperature 20°C-25°C (68°F-77°F) [see USP]...” In contrast, the container label and carton labeling refer to storage at (b) (4) room temperature, (b) (4). Section 16 of the PI and the container label and carton labeling should contain consistent information on storage conditions. Submit revised labeling addressing this discrepancy.
- c. Ensure the actual barcode is provided in the indicated place-holder on the container label and carton labeling.
- d. Since the proposed pediatric dose is 0.07 mg/kg once daily, some patients may not need the entire 150 mL in each bottle. Therefore, remove the statement (b) (4) (b) (4) so that pharmacies may dispense the prescribed amount (b) (4)

2. Container label

- a. As currently presented, the principal display panel (PDP) is too crowded and lacks white space, thus decreasing readability for important information on the PDP. Consider relocating the storage statement to the side panel above the statement “(b) (4)” and reducing the size of the company name and logo or relocate it.
- b. The statement (b) (4) is misleading as the “Boxed Warnings” section in the proposed prescribing information does not communicate complete directions for use. Revise this statement so it is not misleading, or remove this statement from the side panel.

3. Carton labeling

- a. Remove the word (b) (4) in the statement (b) (4) KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.”
- b. Non-affirmative language is used in the following statement present on the carton labeling: (b) (4) which may potentiate inappropriate use if the word (b) (4) is missed while the end-user is reading the label. Therefore, we recommend changing the phrase to an affirmative statement as follows: “Ensure seal is present and intact before using.”

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
01/05/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208401

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Silvergate Pharmaceuticals, Inc.
7300 W 110th St
Ste 950
Overland Park, KS 66210

ATTENTION: Michael C. Beckloff
Chief Development Officer

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution, 1 mg/mL.

We also refer to your October 16, 2015, correspondence, received October 16, 2015, requesting review of your proposed proprietary name, Qbrelis.

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

If any of the proposed product characteristics as stated in your October 16, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Sabry Soukehal, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

IRENE Z CHAN on behalf of TODD D BRIDGES
12/30/2015



NDA 208401

INFORMATION REQUEST

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution 1mg/ml.

We are reviewing the clinical pharmacology section of your submission and have the following information request. We request a written response by January 15, 2016 in order to continue our evaluation of your NDA.

CLINICAL PHARMACOLOGY

The report of study SG-03-01 on page 9 states that “ the established long-term stability at -20 ° C for lisinopril in human K2-EDTA plasma is 91 days and covers the period of study sample storage (16 and 27 days)”. However, data supporting this claim could not be found in your submission. The study report SG-03-01 states that lisinopril stored at -20 ° C is stable for 15 days. If the relevant stability information covering the period of study sample storage has been submitted, please point us to specific section where this information can be found. If not, please submit this information at the earliest to facilitate a timely review. In case you do not have this information, provide a discussion of the consequences this may have for the assessment of the bioequivalence of lisinopril oral solution.

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
12/15/2015



NDA 208401

INFORMATION REQUEST

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution 1mg/ml.

We are reviewing the non-clinical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

NON CLINICAL

- 1) Given the potential for substantial off-label use in children younger than 6 years of age, please provide justification for the safety of the excipients at the proposed levels in the pediatric population in general, and specifically in (b) (4)

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
10/28/2015



NDA 208401

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

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (Lisinopril) Oral Solution 1mg/ml.

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**. Therefore, the user fee goal date is April 30, 2016.

We are reviewing your application according to the processes 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 March 25, 2016.

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

We request that you submit the following information:

CMC

1. The stability data provided in the initial NDA submission for the drug product do not support the proposed expiration dating period of 24 months. In addition, the NDA submission did not contain any in-use stability data for the drug product. Please provide updated stability data for the primary registration batches including results for the (b) (4) storage condition and regression analysis of the real-time stability data along with results from the in-use stability studies conducted on the drug product.
2. Please provide test methods and acceptance criteria to demonstrate the product is free of *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

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

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

Formatting Comments:

In Highlights

1. All text in the Boxed Warning must be bolded.
Comment: Only the heading was bolded.
2. The Boxed Warning must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment: The statement was aligned to the left and not centered.

In addition, the following labeling issues were identified:

1. Please review the approved lisinopril label (NDA 019777) which was updated on August 25, 2015 and incorporate revisions to your proposed label as appropriate.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 02, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in 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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Cardiovascular and Renal Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for the treatment of signs and symptoms of systolic heart failure and for the reduction of mortality in the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

We acknowledge receipt of your request for a partial waiver of pediatric studies for the treatment of hypertension in patients birth to less than (b) (4). Once we have reviewed your request, we will notify you if the partial waiver request is denied

We acknowledge receipt of your request for a (b) (4) deferral of pediatric studies for the treatment of hypertension in patients (b) (4) to 6 years of age. Once we have reviewed your request, we will notify you if the partial deferral request is denied

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
09/11/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 116486
NDA 208401

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Silvergate Pharmaceuticals, Inc.
7300 W 110th Street
Suite 950
Overland Park, KS 66210

ATTENTION: Michael C. Beckloff
Chief Development Officer

Dear Mr. Beckloff:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and to your New Drug Application (NDA) dated and received June 30, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lisinopril Oral Solution, 1 mg/mL.

We also refer to:

- Your March 31, 2015, correspondence to your IND, received April 1, 2015, requesting review of your proposed proprietary name, (b) (4)
- Your correspondence to your NDA, dated and received July 14, 2015, requesting review of your proposed proprietary name (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, (b) (4), is orthographically and phonetically similar to the currently marketed prescription product, (b) (4). Both names are identical in length and share the same five letters (b) (4) in identical positions within each name. Although the names contain different letter strings (b) (4) in the second and third positions of the names, these letter strings may not provide adequate distinction between the names given that both names begin with the letter (b) (4) and ends with the letter string (b) (4). See writing sample below:



Phonetically, the names (b) (4) and (b) (4) contain (b) (4) syllables each. The first syllable of each name shares the same letter (b) (4) sound. The second syllable of each name sounds similar because (b) (4) are both bilabial plosive consonants. This is supported by the results from our simulated voice prescription study, where 3 participants misinterpreted the (b) (4). Lastly, the (b) (4) syllables of both names are identical.

In addition to the orthographic and phonetic similarities of these names, (b) (4) and (b) (4) share overlapping product characteristics in dose (b) (4). Although the dosage form and route of administration are different, post-marketing experience with other drug products demonstrate that name confusion can occur between similarly named prescription products such as (b) (4) despite differences in dosage form and route of administration. Likewise, both (b) (4) and (b) (4) have a single route of administration, which prescribers may omit from prescriptions. For example, the Institute for Safe Medication Practices (ISMP) describes a case of medication confusion where a healthcare professional misinterpreted a written order for (b) (4) since the prescriber did not note the route of administration.³

Thus, based on the aforementioned reasons, we find the proposed proprietary name, (b) (4) unacceptable.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

¹Institute for Safe Medication Practices. Safety briefs. ISMP Med Saf Alert Acute Care. 1999;4(4):1.

² Institute for Safe Medication Practices. Safety briefs: (b) (4) mix-ups. ISMP Med Saf Alert Acute Care. 2013;18(3):3.

³Institute for Safe Medication Practices, Safety Briefs. ISMP Med Safe Alert Acute Care 1999; 4(3):2.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Sabry Soukehay, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
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
08/28/2015



NDA 208401

NDA ACKNOWLEDGMENT

Silvergate Pharmaceuticals, Inc.
Attention: Mr. Michael C. Beckloff
Chief Development Officer
Commerce Plaza II, Suite 950
7400 W 110th Street
Overlook Park, KS 66210

Dear Mr. Beckloff:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Product: (b) (4) (Lisinopril) Oral Solution, 1 mg/mL

Date of Application: June 30, 2015

Date of Receipt: June 30, 2015

Our Reference Number: 208401

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 August 29, 2015, 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(1)(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. Additional information is available at <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:

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
07/21/2015

Bui Nguyen, Tri

From: Lyons, Darrell
Sent: Tuesday, July 07, 2015 7:38 AM
To: 'michael.beckloff@silvergatepharma.com'
Cc: Flowers, Louis; Bui Nguyen, Tri
Subject: Proprietary Name for NDA 208401

Dear Mr. Beckloff:

Please refer to your NDA 208401 for Lisinopril Oral Solution, 1 mg/ml.

We also refer to your correspondence, dated and received June 30, 2015, requesting review of your original NDA.

If you intend to have a proprietary name for the above-referenced product, you should submit a request for proprietary name review within 14 days of this communication.

Include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the new submission is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs,
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding any other aspects of the proprietary name review process, feel free to contact me directly.

Best Regards,

Darrell Lyons

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
FDA, Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office: (301) 796-4092
darrell.lyons@fda.hhs.gov

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/s/

DARRELL LYONS
07/07/2015



PIND (b) (4)
PIND 116486
PIND (b) (4)

MEETING PRELIMINARY COMMENTS

Beckloff Associates, Inc
Attention: Wayne Vallee, RPh, RAC
US Agent for Silvergate Pharma
Director, Managing Consultant
A Cardinal Health Company
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Dear Mr. Vallee:

Please refer to your Pre-Investigational New Drug Application (PIND) files for (b) (4),
(b) (4), lisinopril (PIND 116486) and (b) (4)

We also refer to your September 13, 2012, correspondences requesting Pre-IND meetings to discuss your development plans for these products.

Our preliminary responses to your meeting questions are enclosed.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: Cancelled
Meeting Location: Cancelled

Application Number: PINDs (b) (4) 116486; (b) (4)
Product Name: (b) (4)
lisinopril (PIND 116486)
(b) (4)

Indication: hypertension
Sponsor/Applicant Name: Silvergate

Introduction:

This material consists of our responses to your questions and any additional comments in response to your questions. We believe that our responses adequately address your questions and so we are cancelling the meeting scheduled for December 5, 2012.

1.0 BACKGROUND

The sponsor, Silvergate Pharmaceuticals, has requested a meeting to discuss their development program and planned submission of 505(b)(2) NDAs for pediatric formulations of amlodipine, lisinopril and losartan.

2. DISCUSSION



PIND 116486 - Lisinopril Questions
Chemistry, Manufacturing, and Controls

Question 1: *The specifications for related substances in the drug product are based on the USP monograph for Lisinopril Tablets. Details of the drug product manufacturing and the controls associated are provided in this meeting information package. The proposed NDA specification will comply with the USP monograph.*

Does the Agency agree that the current drug product specification is appropriate for the NDA?

Response: USP requirements are the minimum that should be met but may not be sufficient. The specification for the product should conform to ICH Q3B for reporting, identification and qualification thresholds for degradation products. The adequacy of the acceptance criteria will be determined during the review of the NDA submission.

Question 2: *The current plan is to submit the NDA with 6 months accelerated and room-temperature stability data on 3 registration batches, supplementing the stability data with 12-month data at the midpoint of the review cycle. Additionally, data from an in-use stability study conducted on the reconstituted products from the 3 registration batches will be submitted to support the in-use shelf life.*

Does the Agency agree that this plan is acceptable?

Response: No, you should submit the NDA with 12 months of long term and 6 months of accelerated stability data. In-use stability data should be generated using reconstituted product from batches which have been stored for the longest duration for which RT data are available. These in-use studies should be repeated on product batches which have reached the intended shelf-life to establish that critical attributes of the reconstituted solution have not changed upon storage of the oral powder.

Nonclinical

Question 3: *Silvergate plans to make reference to the nonclinical section of the ZESTRIL labeling (the reference listed drug) to fulfill the nonclinical requirements for the 505(b)(2) NDA. In addition, a literature search will be conducted to identify new pediatric information. Any significant findings will be included in the NDA.*

Please confirm that the nonclinical plan is acceptable and will meet the nonclinical requirements of the NDA.

Response: Yes.

Clinical

Question 4: *Silvergate plans to conduct a 3-way study in normal, healthy adult males and females comparing the bioavailability of a 10- or 20-mg dose of the 1-mg/mL lisinopril solution to a 10- or 20-mg ZESTRIL tablet under fasted conditions and a 10- or 20-mg dose of the 1-mg/mL lisinopril solution under fed conditions. The primary end points of the study are to demonstrate comparable bioavailability, not necessarily bioequivalence, between the formulations and to determine if there is a food effect for the 1-mg/mL lisinopril solution.*

Please confirm this type of study should provide suitable bioavailability information for review for approval and that no additional studies would be required if the bioavailability results are comparable.

Response: We recommend powering the study for bioequivalence to Zestril as that would be ideal. If the pharmacokinetic time course of the pediatric formulation differs significantly from that of Zestril in the peak to trough (inter-dosing interval) ratio or if the C_{min} of your product is less than that of Zestril, then you will have to establish effectiveness similar to Zestril.

Question 5: *The concentration of the Silvergate lisinopril pediatric product and ZESTRIL extemporaneous pediatric suspension is 1.0 mg/ml. The ZESTRIL reference listed drug is a 40-mg tablet, requiring a 40-mL dose volume. In AstraZeneca's ZESTRIL NDA 1977/S-044 and Study 037, a 20-mg dose (20-mL dose volume) was used to assess and support the comparative bioavailability of the extemporaneous pediatric suspension. The pharmacokinetics (PK) of lisinopril are linear with the dose (Beerman, 1989). Silvergate will use a 10- or 20-mg dose of the test product (10-mg dose pending bioanalytical method validated LLOQ) in the pivotal comparative bioavailability of test versus reference tablet. As the dose for the lisinopril pediatric product is dependent only on volume and there is linear PK, the lowest dose exposure to healthy volunteers will be used in this study.*

Please confirm that the proposed 10 or 20 mg dose is acceptable.

Response: Yes. Please also include information supporting linear pharmacokinetics in your NDA submission.

Question 6: *A literature search will be conducted to identify new clinical pediatric information. Any significant findings will be included in the NDA.*

Please confirm that the clinical plan is acceptable and will meet the clinical requirements of the NDA.

Response: Your approach is reasonable.

Submission-Specific Information

Question 7: *Because the planned study will not exceed the maximum single or total daily dose specified in the approved ZESTRIL labeling, the planned bioavailability study would not meet the requirements for an IND under 21 CFR 320.31—Applicability of requirements regarding an “Investigational New Drug Application.”*

Please confirm that an Investigational New Drug application would not be needed to conduct the proposed bioavailability study.

Response: An IND would not be required to conduct the proposed bioavailability study. However, conducting it under an IND would give the Division a chance to review your protocol and offer any advice or suggestions.

Question 8: *The application is planned as a 505(b)(2) NDA, referencing ZESTRIL 40-mg tablets, the reference listed drug.*

Please confirm the acceptability of the proposed application as a 505(b)(2) NDA.

Response: A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you

should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Please note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.1019)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Question 9: *The proposed draft labeling will be almost identical to the approved labeling for ZESTRIL tablets. Differences will be the inclusion of the bioavailability study results and revisions to the "How Supplied" section and manufacturing and distribution contact information. Approved ZESTRIL labeling regarding heart failure and acute myocardial infarction will be deleted, as will information regarding the preparation of a lisinopril suspension.*

Please confirm that the proposed draft labeling will be acceptable for review in the 505(b)(2) application.

Response: Your approach is reasonable. Regarding deletion of the other indication(s), your approach is acceptable, although we would be open to leaving them in place.

(b) (4)

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3.0 ADDITIONAL COMMENTS

Biopharmaceutics:

1. A dissolution method development report should be included in the NDA. The dissolution report should include the following information:
 - Solubility data for the drug substance covering the pH range
 - Detailed description of the dissolution method and the developmental parameters (equipment/apparatus selection, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions etc.) used to select the most appropriate method. The testing conditions used for each test should be clearly specified
 - The complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time, and
 - Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as validation data for the dissolution method and analytical method.

2. In the NDA submission, include the complete dissolution profile data (registration) stability batches supporting the selection of the proposed dissolution specification. For the select following points should be considered:
 - Use the dissolution profile data from the bio- and primary stability batches for setting the specification
 - The profiles should encompass the time frame over which at least 80% of the drug is dissolved or where the plateau in dissolution is occurring
 - For an immediate release product, the selection of the point should be where Q=80% dissolution occurs.

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/

NORMAN L STOCKBRIDGE
11/30/2012