CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208401Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

NDA: 208401

Drug: Qbrelis (Lisinopril) Oral Solution

Class: Angiotensin-Converting Enzyme (ACE) Inhibitor

Applicant: Silvergate Pharmaceuticals, Inc.

Proposed Indications:

1) Treatment of hypertension in adults and pediatric patients 6 years of age and older
2) Adjunct therapy for heart failure
3) Treatment of Acute Myocardial Infarction

Date of submission: June 30, 2015

PDUFA date: July 30, 2016[1]

Target Action date: July 29, 2016

II. REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Product

Cross Discipline Team Leader (CDTL) and Medical Reviewer: Aliza Thompson
Pharmacology & Toxicology: Elizabeth Hausner
Regulatory Health Project Manager: Sabry Soukehal

Office of Pharmaceutical Quality

Drug Product and Drug Substance: Rao Kambhampati
Microbiology: Erika Pfeiler
Process: Sung Kim
Facilities: Ebern Dobbin

Office of Clinical Pharmacology

Peter Hinderling
Rajanikanth Madabushi

Office of Surveillance and Epidemiology

DPV: Amy Chen and Monica Munoz
DMEPA: Tingting Gao and Sarah Thomas

[1] The original PDUFA date was April 30, 2016. On April 28, 2016, a major amendment was received; as a result, the goal date was extended by three months.

III. BACKGROUND

Lisinopril Oral Solution is an ACE inhibitor developed by Silvergate Pharmaceuticals, Inc. for the treatment of hypertension in adult patients and pediatric patients 6 years and older to lower blood pressure as well as for the (b) (4) 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. The proposed dose is 1mg/ml.

This Application followed a 505(b)(2) pathway utilizing Zestril® (Lisinopril) tablets (NDA 19777, approved May 19, 1988) as the reference listed drug.

A type B Pre-IND meeting was requested by the Applicant in September 2012 (Pre-IND 116486). The Division provided preliminary responses on November 2012. Because the Division's responses adequately addressed the Applicant's questions, the meeting was subsequently cancelled.

Two randomized, open-label, single-dose, 2-period, 2-treatment, 2-way crossover studies were conducted under fasted (SG03-01) and fed (SG03-02) conditions to compare the rate of absorption and oral bioavailability of Lisinopril Oral Solution to Zestril® tablets. Those studies served as a basis for this NDA submission.

On August 24, 2015, the Applicant requested orphan drug designation for the treatment of hypertension in pediatric patients 0 to 16 years of age on the basis that the oral solution is clinically superior to the approved drug (tablets). On October 14, 2015, the Applicant was granted orphan designation (#15-4819).

However, at the request of the Division, the prevalence estimate of pediatric hypertension requiring pharmacological therapy was assessed by the Division of Pediatric and Maternal Health (DPMH). There was a concern that, at the time of the orphan designation request, the estimated number of pediatric patients with hypertension exceeded the 200,000 threshold.

After a thorough review of the published and other publicly available data, DPMH concluded that at the time the Applicant applied for orphan drug designation, the estimated number of pediatric patients with hypertension who needed pharmacological therapy exceeded 200,000 and recommended the removal of the orphan drug designation.

On April 28, 2016, the Office of Orphan Drug Product Development revoked Lisinopril oral solution orphan drug designation for the treatment of hypertension in pediatric patients 0 through 16 years of age.

Because of the orphan designation was revoked, the Applicant submitted a revised Pediatric Study Plan on April 28, 2016. This submission constituted a major amendment and extended the goal date by three months.

The review of the application in general met all of the 21st century review guidelines.

IV. APPLICATION REVIEW

1. User Fee

The user fee for this application was paid in full on June 26, 2015. User Fee ID 3015182.

2. Pediatric Review Committee (PeRC)

The Applicant initially submitted a request for a partial waiver and deferral of pediatric studies in hypertension and a full waiver for heart failure and myocardial infarction indications in pediatric patients aged 0 to 16 years. Following NDA submission, the Applicant received orphan drug designation for the treatment of hypertension in pediatric patients 0-16 years of age. The Applicant intended to revise the proposed pediatric study plan, as PREA no longer applied to the hypertension indication. The PeRC meeting to discuss this proposal was held on March 16, 2016. At the meeting, the committee agreed to the full waiver requests (b) (4) signs and symptoms of systolic heart failure and the reduction of mortality in the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction). Because, the product had orphan drug designation for the treatment of hypertension in pediatric patients 0-16 years of age, an assessment for pediatric hypertension was not required and hence, was not reviewed at the March meeting.

Following revocation of orphan drug designation and the submission of a revised pediatric study plan, a PeRC meeting was held on May 11, 2016, with a focus on the hypertension indication and the Applicant's proposal for a partial waiver in patients less than 2 years of age and a deferral in patients 2 to 6 years old. The committee agreed to grant a partial waiver in patients less than 2 years old because studies are impossible or highly impractical and to the deferral in patients 2 to 6 years old.

3. Advisory Committee

There was no Advisory Committee meeting for this NDA because the application did not raise significant issues regarding the safety or effectiveness of the drug.

4. Trade name

The Applicant originally submitted the proposed name (b) (4) to PIND 116486 on March 31, 2015, and to NDA 208401 on July 14, 2015. This name was denied on August 28, 2015, as it was deemed orthographically and phonetically similar to another product. The Applicant then submitted the proposed name QBRELIS to NDA 208401 on October 16, 2015. This name was considered conditionally acceptable. A grant letter was issued on December 30, 2015.

5. Facilities Inspections

The Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance recommended accepting the data without an on-site inspection because the analytical site was recently inspected and the inspection was classified as No Action Indicated.

The Division of Generic Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance conducted an inspection of the clinical portion of the bioavailability studies at Worldwide Clinical Trials Early Phase Services, San Antonio, Texas during December 08-18, 2015. No significant deficiencies were observed. The final classification for this inspection was No action Indicated.

6. Regulatory Timeline

Pre-NDA Meeting: scheduled on December 5, 2012 but cancelled by the Applicant after receiving preliminary comments on November 30, 2012.
NDA Receipt Date: June 30, 2015

Filing Day 60: August 29, 2015
Filing 74-Day Letter: September 11, 2015
Advisory Committee: N/A
PDUFA Date: July 30, 2016[2]

7. Reviews

Below are the conclusions reached by the QBRELIS team members.

a) Divisional Memorandum - July 20, 2016

Dr. Stockbridge recommended approval. His memo documented his concurrence with the CDTL conclusion and noted that there were no new findings that could raise concerns. Please refer to his memo for further details.

b) Cross-Discipline Team Leader Review - July 17, 2016

Dr. Thompson recommended approval. Her review summarized each disciplines findings (CMC, nonclinical, and clinical pharmacology). She agreed with the reviewers' assessments and stated that the major issue that arose during the review of this application was the product's orphan designation that was granted and then revoked during the review cycle. Her review noted that the literature search done by the Applicant to characterize the safety profile of Lisinopril in children did not raise concerns. Her review discussed the Applicant's PREA requirements, including the need for deferred pediatric studies in children age 2 to 6 years with hypertension as well as the Division's rationale for waiving studies in children < 2 years of age with hypertension. Please see her review for further details.

c) Clinical Pharmacology Review - March 24, 2016

Dr. Madabushi found the data demonstrating bioequivalence of Lisinopril between the oral solution and Zestril® tablets to be supportive of approval.

The review of study SG03-01 titled "A Randomized Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Study to Determine the Relative Bioavailability of 10 mL of Lisinopril Oral Solution, 1 mg/mL, versus Zestril® 10 mg Tablets under Fasted Conditions in Healthy Adults" concluded that the geometric means and 90% confidence intervals for the log transformed C_{max}, AUC_{last} and AUC_{inf} were within the 80 to 125% bioequivalence limits.

The review of study SG03-02 titled "A Randomized Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Study to Determine the Relative Bioavailability of 10 mL of Lisinopril Oral Solution, 1 mg/mL, versus Zestril® 10 mg Tablets under Fed Conditions in Healthy Adults" concluded that the confidence intervals for the log transformed C_{max}, $AUC_{last,}$ and AUC_{inf} were within the 80 to 125% bioequivalence limits. Please see his review for further details.

d) Pharmacology & Toxicology Review - February 10, 2016

Dr. Hausner reported that the application can be approved from a nonclinical perspective. She did not have labeling or additional recommendations.

However, given the potential for substantial off-label use in children younger than 6 years of age, Dr. Hausner asked the Applicant to provide justification for the safety of the excipients at the

[2] The original PDUFA date was April 30, 2016. On April 28, 2016, a major amendment was received; as a result, the goal date was extended by three months.

proposed levels in the pediatric population in general, and specifically in [redacted] (b) (4) As a response, the Applicant provided a list of all excipients, none of which were novel. The Applicant also clarified that each excipient was calculated using body weight data from the CDC.

Dr. Hausner concluded that no information was found pertaining to the effects or lack of effects of combination of excipients in young children. She also concluded that the Applicant had provided reasonable support for the levels of excipients in the new formulation. In her opinion, any remaining concern is for low birth weight infants receiving extra- label treatment with Lisinopril. Please see her review for details.

e) Office of Pharmaceutical Quality Review - March 23, 2016

An integrated summary was written for product quality. Approval is recommended from a quality perspective.

i. *Drug Substance*: Lisinopril is described as a white to off-white, crystalline powder that is not [redacted] (b) (4). It is soluble in water, sparingly soluble in methanol, and practically insoluble in [redacted] (b) (4) ethanol. Its molecular weight is 441.52 and its molecular formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$.

ii. *Drug Product*: Lisinopril Oral Solution, 1 mg/mL, is a ready-to-use aqueous formulation. Each 1 mL of the solution contains 1.09 mg of Lisinopril dihydrate, equivalent to 1 mg of Lisinopril, and the following inactive ingredients: purified water, xylitol, sodium citrate, citric acid, sodium benzoate. Hydrochloric acid or sodium hydroxide is added for pH adjustment.

iii. *Expiration date and storage conditions*: the review noted that the proposed shelf-life of 24 months is acceptable. The proposed storage conditions (room temperature 20ºC - 25ºC, protected from freezing and excessive heat) were also deemed acceptable.

iv. *Microbiology*: The review indicated that the antimicrobial effectiveness testing (AET) specifications and microbial limits of Lisinopril oral solution are acceptable.

v. *Biopharmaceutics*: As the application did not include a biowaiver request or a dissolution method, a biopharmaceutics review was not necessary.

8. Consults

a) Office of Surveillance and Epidemiology – Division of Medication Error Prevention and Analysis – October 09, 2015, December 07, 2015, February 02. 2016, and June 27, 2016

Dr. Gao then Dr. Thomas reviewed the carton and container labels and prescribing information using the principles of human factors and Failure Mode and Effects Analysis, along with post-market medication error data. The risk assessment performed on the PI and container labels identified deficiencies that may lead to medication errors and areas for improvement.

Additionally, Dr. Thomas reviewed several iterations of the carton and container labels.

Full details on DMEPA's recommendations can be found in the reviews. DMEPA's comments were sent to the Applicant. The Applicant made the requested revisions. DMEPA found them acceptable. Final agreed upon container labels were received June 23, 2016 and final carton labels were received July 08, 2016.

b) Office of Prescription Drug Promotion - April 06, 2016

Dr. Patel reviewed the draft prescribing information and carton and container labeling and did not have any comments.

c) Division of Pediatric and Maternal Health - March 24, 2016

Dr. Khurana reviewed the prevalence estimate for pediatric hypertension requiring pharmacologic therapy that would have been available to the Applicant at the time they applied for orphan designation. The purpose was to determine whether the statutory threshold of 200, 000 cases was exceeded. Based on the information she reviewed, she recommended the removal of orphan designation granted to Lisinopril oral solution. Please see her review for full details.

9. Labeling

Labeling discussions occurred with the Applicant. The final agreed-upon labeling will be attached to the approval letter.

V. CONCLUSION

The review team recommended approval. An approval letter will be signed by Dr. Stockbridge.

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

505(b)(2) ASSESSMENT

Application Information		
NDA # 208401	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Qbrelis Established/Proper Name: Lisinopril Dosage Form: Solution Strengths: 1mg/mL		
Applicant: Silvergate Pharmaceuticals, Inc.		
Date of Receipt: June 30, 2015		
PDUFA Goal Date: July 30, 2016	Action Goal Date (if different):	
RPM: Sabry Soukehal		
Proposed Indication(s): - Treatment of hypertension in adults and pediatric patients 6 years of age and older - Adjunct therapy for heart failure - Treatment of Acute Myocardial Infarction		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 019777 "Zestril" (lisinopril tablets)	FDA's previous finding of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Two dedicated bioequivalence studies (fasted and fed) were conducted to demonstrate the bioequivalence of 10 mL dose of lisinopril oral solution (1 mg/mL) to a 10 mg Zestril tablet (RLD) in healthy adults. The geometric mean ratio and 90% confidence intervals for Cmax and AUCtlast in both studies were within the 80 to 125% bioequivalence limits indicating bioequivalence of lisinopril oral solution and Zestril tablet.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Zestril® (lisinopril tablets)	019777	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form, from oral tablets to oral solution.

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

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

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

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

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

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

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

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

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

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDA 19558 (Prinivil); NDA 19777 (Zestril)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

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

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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
07/25/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA# 208401 – Qbrelis (lisinopril oral solution 1mg/ml)
Product Name:

PMR/PMC Description: Deferred pediatric study under PREA: An efficacy, safety and dose-finding study of Qbrelis in hypertensive pediatric patients two years to less than six years of age.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	12/31/2016
Study/Trial Completion:	06/30/2020
Final Report Submission:	12/31/2020
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The product is ready for approval for use in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The study is intended to address the applicant's PREA requirement.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An efficacy, safety and dose-finding study of Qbrelis in hypertensive pediatric patients two years to less than six years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

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/s/

Lori A WACHTER
07/11/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 27, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 208401
Product Name and Strength:	Qbrelis (Lisinopril) Oral Solution, 1 mg/mL
Submission Date:	June 23, 2016
Applicant/Sponsor Name:	Silvergate Pharmaceuticals, Inc.
OSE RCM #:	2015-1748-3
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Qbrelis submitted on June 23, 2016 for the risk of medication error (Appendix A).

2 CONCLUSION

We find the revised container label and carton labeling submitted by Silvergate Pharmaceuticals, Inc. to be unacceptable from a medication safety perspective. We note the presence of two barcodes on the container label, which can be confusing to healthcare providers. We also note newly added storage information on the container label and carton labeling that is not present in the prescribing information (PI) (b) (4) On the carton labeling, the dosage form is missing on the top flap, and the temperature range provided in the storage information is not consistent with that provided on the container label or in section 16 of the PI. Therefore, we provide the associated recommendations in Section 3 to Silvergate Pharmaceuticals, Inc.

3 RECOMMENDATIONS FOR SILVERGATE PHARMACEUTICALS, INC.

We recommend the following be implemented for the Qbrelis container label, carton labeling, and PI prior to approval of this NDA:

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.

[2] Draft 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.

C. Prescribing Information

1. Add the storage statement [redacted](b) (4)." to section 16 of the PI, in order to maintain consistency with the storage information presented on the container label and carton labeling.

APPENDIX A. LABEL AND LABELING SUBMITTED ON JUNE 23, 2016

Container Label

Carton Labeling

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/s/

SARAH E THOMAS
06/27/2016

CHI-MING TU
06/27/2016

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCT

NDA 208401 Memorandum

Date: April 29, 2016

On April 28, 2016, the Office of Orphan Products Development (OOPD) informed Silvergate Inc. (the Applicant) that their orphan drug designation for the "treatment of hypertension in pediatric patients 0 through 16 years of age" (# 15-4819) was revoked.

This memo provides the various communications that led to this decision.

Attached are copies of the following:

- The letter granting the Applicant orphan designation.
- The Division of Pediatric and Maternal Health Review recommending the removal of the orphan drug designation.
- The letter informing the Applicant of OOPD's intent to revoke the designation.
- The letter confirming the revocation of the orphan designation.

Sabry Soukehal

Regulatory Health Project Manger

Division of Cardiovascular and Renal Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5295
Silver Spring, MD 20993

OCT 14 2015

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

Attention: Susan J. Prather
Director, Regulatory Affairs

Re: Designation request # 15-4819
Amendment dated: August 24, 2015
Amendment received: August 25, 2015

Dear Ms. Prather:

This letter responds to your amended request for orphan-drug designation of lisinopril oral solution for "treatment of hypertension in pediatric patients 0 to 16 years of age."

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of lisinopril oral solution is granted for *treatment of hypertension in pediatric patients 0 through 16 years of age.*

Your designation is based on a *plausible hypothesis* that your drug may be clinically superior to the same drug that is already approved for the same orphan indication. *See* 21 CFR 316.3(b)(3) & (14) (defining "clinically superior" and "same drug" in this context). In order to obtain orphan-drug exclusivity upon approval, you will need to demonstrate that your drug is clinically superior to this already approved same drug (and any other versions of the same drug approved for the same orphan indication before your drug is approved). Failure to demonstrate clinical superiority over the already approved same drug(s) will result in your drug not receiving orphan-drug exclusivity. 21 CFR 316.34(c).

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug's orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted. 21 CFR 316.26.

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval. 21 CFR 316.30.

Please notify this Office within 30 days of submitting a marketing application for the drug's designated use. Once your marketing application is approved, please contact Jeffrey Fritsch, RPh, MPH, at 301-796-8682 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact Erica K. McNeilly, RPh, at 301-796-8679 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

/s/ for Gayatri R. Rao

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Mona Khurana, M.D., Medical Officer
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV

Through: Lynne Yao, M.D., Director

To: Division of Cardiovascular and Renal Products

Drug Name: Lisinopril

Drug Category: Angiotensin converting enzyme inhibitor

Subject: Revised Proposed Pediatric Study Request

Sponsor: Silvergate Pharmaceuticals

Materials Reviewed

- Materials accompanying February 24, 2016 consult from the Division of Cardiovascular and Renal Products (including referenced publications) (DARRTS Reference ID 3892435)
- Relevant documents related to lisinopril approval history accessed at Drugs@FDA
- Currently marketed lisinopril drug products accessed at Orange Book
- FDA Orphan Designation Search Page (search term: lisinopril)
- The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (including referenced publications). National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 114 (2): 555-576, 2004.
- PubMed database search (search terms: prevalence AND hypertension; prevalence AND hypertension AND US; prevalence AND pediatric hypertension AND American [limits: English, human, child]); including referenced publications from retrieved articles.

Consult Request

The Division of Cardiovascular and Renal Products (DCaRP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 24, 2016 to provide a prevalence estimate for pediatric hypertension requiring pharmacologic therapy based on information that would have been available to each of the sponsors of antihypertensive drug products which have already received orphan drug designation for treatment of pediatric hypertension. The purpose of this request is to determine if the prevalence estimates available to the sponsors at the time of their requests were higher than that required to be considered for orphan drug designation (200,000). Higher prevalence estimates than those reported at the time of the sponsor's requests could be a basis to revoke orphan drug designation for these products. DCaRP is requesting this information first for lisinopril oral solution since the Prescription Drugs User Fee Act (PDUFA) due date for the submitted new drug application (NDA) 208401 is April 30, 2016.

I. Relevant Background

Lisinopril was initially approved by FDA in 1987 under NDA 19558 in a tablet formulation with the trade name Prinivil[1] and then in 1988 as Zestril tablet under NDA 19777. Multiple abbreviated NDAs (ANDAs) have subsequently been approved for the oral tablet formulation only.[2]

In January 2015, (b) (4). received orphan drug designation for lisinopril oral solution in the treatment of primary hypertension with complications and secondary hypertension in pediatric patients 0 through 16 years of age.[3] The prevalence of pediatric hypertension at the time the application was submitted in February 2012 was established to be 196, 453.[4] The orphan drug designation was transferred to (b) (4) in March 2015.

FDA received a request for orphan drug designation for lisinopril oral solution on May 5, 2015 from Silvergate Pharmaceuticals, Inc. FDA granted orphan designation for the treatment of hypertension in pediatric patients 0 to 16 years of age on October 14, 2015.[5] There is currently

[1] December 29, 1987 approval letter: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2003/19558se5-043ltr.pdf (accessed March 4, 2016)

[2] Orange Book: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm?firstRec=101 (accessed March 4, 2016)

[3] Orphan Designation Search Page (search term: lisinopril; application number 12-3655): http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=365512 (accessed March 4, 2016)

[4] June 11, 2015 Review of a Request for Orphan Drug Designation

[5] Orphan Designation Search Page (search term: Lisinopril): http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=481915 (accessed March 4, 2016)

no FDA-approved ready-to-use liquid formulation of lisinopril for use by pediatric patients who have difficulty swallowing or cannot consume tablets.

II. Prevalence of Pediatric Hypertension

A. Diagnostic Considerations

Prevalence estimates of hypertension in the U.S. pediatric population should ideally be based on how hypertension is defined in the 2004 National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents consensus-based guidelines.[6] These guidelines have been endorsed by the American Academy of Pediatrics and by the American Heart Association. The NHBPEP guidelines recommend interpretation and categorization of systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements in children 3 years to 18 years of age based on the child's age, height, and sex in order to classify BP according to body size (see Table 1). Importantly, the NHBPEP's definition of pediatric hypertension is based on mean SBP and DBP measured on at least three separate occasions to allow for a more precise characterization of the blood pressure (BP) level.

Table 1. Definition of Pediatric Hypertension according to the NHBPEP Guidelines

BP Category	BP Percentile for Sex, Age, Height
Normal	SBP and DBP < 90th
Pre-Hypertension	Mean SBP or DBP: > 90th but ≤ 95th; OR BP > 120/80 mmHg but < 95th in adolescents
Hypertension	Mean SBP or DBP > 95th on at least 3 separate occasions
Stage 1	Mean SBP or DBP: > 95th but ≤ 99th plus 5 mmHg
Stage 2	Mean SBP or DBP: > 99th plus 5 mmHg

(Source: created by this reviewer from [6])

Depending on a child's age, up to 85% of confirmed pediatric hypertension can be due to a secondary cause. See Table 2.

Table 2. Reported Proportions of Confirmed Pediatric Hypertension that is Secondary with the Most Common Underlying Etiologies

[6] The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 114 (Suppl 4th Report): 555-576, 2004.

Pediatric Age Group	Proportion of Secondary Hypertension	Most Common Etiologies[7] (Listed in Order of Frequency)
Birth to < 6 years	70%-85%[8]	Renal Parenchymal Disease Renovascular Disease Endocrine Disease Cardiac/Pulmonary/CNS disease Iatrogenic Genitourinary
6 years to < 12 years	70%-85%[8]	
12 years to 18 years	5%-15%[8]	

(Source: adapted by this reviewer from[7, 8]); CNS: central nervous system

Prevalence estimates of pediatric hypertension based on large community-based screening studies published before the 2004 NHBPEP guidelines have limited relevance for the following reasons: (1) inconsistent definitions of hypertension that relied on a single set of BP measurements; (2) narrow pediatric age ranges; and (3) limited race distributions. While more recently published studies have captured a broader pediatric age range and racial distribution that are potentially more representative of the U.S. pediatric population, these studies also have limited utility because they used claims-based[9,10] approaches or survey data based on a single set of BP measurements[11,12] to define pediatric hypertension rather than the more rigorous diagnostic approach recommended by the NHBPEP.

B. Pharmacologic Treatment Considerations

Prevalence estimates of hypertension in the U.S. pediatric population should capture all patients for whom pharmacologic treatment would be recommended. The NHBPEP guidelines recommend initiating pharmacologic therapy in pediatric patients with the following:[6]

- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite non-pharmacologic measures

[7] Brady TM and Feld LG. Pediatric Approach to Hypertension. Seminars in Nephrology 29: 379-388, 2009.

[8] Flynn JT. Evaluation and Management of Hypertension in Childhood. Progress in Pediatric Cardiology 12: 177-188, 2001.

[9] Dobson CP, Eide M, Nylund CM. Hypertension Prevalence, Cardiac Complications, and Antihypertensive Medication use in Children. Journal of Pediatrics 167: 92-97, 2015.

[10] Welch WP, Yang W, Taylor-Zapata P, et al. Antihypertensive Drug Use by Children: Are the Drugs Labeled and Indicated? The Journal of Clinical Hypertension 14(6): 388-395, 2012.

[11] Kit BK, Kuklina E, Carroll MD, et al. Prevalence of and Trends in Dyslipidemia and Blood Pressure Among US Children and Adolescents, 1999-2012. JAMA Pediatrics 169(3): 272-279, 2015.

[12] Din-Dzietham R, Liu Y, Bielo M, et al. High Blood Pressure Trends in Children and Adolescents in National Surveys, 1963 to 2002. Circulation 116: 1488-1496, 2007.

DPMH Comments: In their amended prevalence estimates, the sponsor failed to specifically address each of these pediatric hypertensive sub-populations for whom pharmacologic therapy would be appropriate. Rather, the sponsor's calculations included only the following three sub-populations in need of pharmacologic intervention:

- *Stage 1 primary hypertension associated with left ventricular hypertrophy (LVH) (This approach does not capture all pediatric patients with primary hypertension who did not have LVH but who would still be candidates for pharmacologic intervention if they failed dietary and lifestyle modifications).*
- *All patients with stage 2 primary hypertension (These patients will likely overlap with those in the secondary hypertension group since Stage 2 hypertension in the majority of pediatric patients is less likely to be primary and most likely to be due to an underlying cause).*
- *All patients with secondary hypertension*

C. Available Prevalence Data on Pediatric Hypertension

According to a 2013 U.S. Preventive Services Task Force (USPSTF) publication, the prevalence of pediatric hypertension in the United States has been reported to range from 1% to 5% and the prevalence of hypertension among obese U.S. children and adolescents is estimated at 11%.[13] Since the USPSTF's prevalence estimates[14,15,16] did not appear to be entirely based on pediatric hypertension diagnosed using the 2004 NHBPEP guidelines, DPMH searched the PubMed database for studies published since the 2004 NHBPEP guidelines that have reported the prevalence of pediatric hypertension using the NHBPEP's definition of hypertension (based on three sets of elevated BP measurements). DPMH's search retrieved four publications reporting prevalence estimates consistent with those reported in the 2013 USPSTF publication. These three studies reported prevalence rates of 2.5% among high school students,[17] 3.2% among 11-17 year olds,[18] 4.5% among 10-19 year olds,[19] and 3.6% among 3-18 years olds.[20] These four studies are briefly summarized in this section.

[13] Moyer VA. U.S. Preventive Services Task Force. Screening for Primary Hypertension in Children and Adolescents. U.S. Preventive Task Force Recommendation Statement. Annals of Internal Medicine 159: 613-619, 2013.

[14] Lurbe E, Alvarez J, Redon J. Diagnosis and Treatment of Hypertension in Children. Current Hypertension Rep 12: 480-486, 2010.

[15] Obarzanek E, Wu CO, Cutler JA, et al. Prevalence and Incidence of Hypertension in Adolescent Girls. Journal of Pediatrics. 157(3): 461-467, 2010.

[16] Flynn JT and Falkner BE. The Importance of Blood Pressure Screening in Children. Journal of Pediatrics 155(2): 299-300, 2009.

[17] Acosta AA, Samuels JA, Portman RJ, et al. Prevalence of Persistent Prehypertension in Adolescents. The Journal of Pediatrics 160:757-761, 2012.

One study by Hansen et al. was previously used to support the orphan designation request for lisinopril.[20] This was a retrospective cohort study to determine the prevalence of pre-hypertension and hypertension, on the basis of International Classification of Diseases Ninth Revision (ICD-9) codes, among 14,187 children and adolescents 3 years to 18 years of age from a large academic urban medical system in northeast Ohio who received well-child care from June 1999 to September 2006. The authors identified 507 children and adolescents (3.6%) who met the NHBPEP's criteria for hypertension.

DPMH Comments: Demographic characteristics were not clearly described to determine if the study population was fully representative of the U.S. pediatric population. However, this was the only study identified by DPMH that used the NHBPEP guidelines and included younger pediatric patients less than 10 years of age.

The other three studies were school-based screenings conducted to determine the prevalence of pre-hypertension and hypertension, based on the NHBPEP guidelines, among children and adolescents from Houston area schools who were 10 years of age and older.[17,18,19]

- Acosta et al screened 1,020 students from a Houston area high school in 2007 and identified 2.5% with hypertension.[17] The study population was 49.2% Hispanic, 25.2% Caucasian, and 16.1% African-American.
- McNiece et al[18] screened 6,790 adolescents 11 years to 17 years of age from nine Houston area schools from 2003 to 2005 and identified 3.2% with hypertension. The study population was 37% Caucasian, 28% African-American, 8% Asian, and 27% Hispanic. A greater proportion of the study population was African-American compared to the total U.S. population (28% vs. 14.3%[8]).
- Sorof et al[19] screened 5,102 school-aged children 10 years to 19 years of age from eight Houston area schools from May 2002 to November 2002 and identified 4.5% with hypertension. The overall prevalence of overweight (body mass index [BMI] $\geq 95^{th}$ percentile) was 20%. The study population was 44% Caucasian, 22% African-American, 7% Asian, 2% other, and 25% Hispanic. A greater proportion of the study population was African-American compared to the total U.S. population (22% vs. 14.3%). The higher prevalence of pediatric hypertension in this study appeared to be strongly determined by the high proportion of the study population that had BMIs greater than normal. The prevalence of hypertension in this study among students with a normal BMI ($< 85^{th}$ percentile) was 2.6% compared to 10.7% in those with obesity (BMI $\geq 95^{th}$ percentile).

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[18] McNiece KL, Poffenbarger TS, Turner JL, et al. Prevalence of Hypertension and Pre-Hypertension among Adolescents. Journal of Pediatrics 150: 640-644, 2007.

[19] Sorof JM, Lai D, Turner J, et al. Overweight, Ethnicity, and the Prevalence of Hypertension in School-Aged Children. Pediatrics 113(3): 475-482, 2004.

[20] Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of Hypertension in Children and Adolescents. JAMA 298(8): 874-879, 2007.

DPMH Comments: Although the racial distributions of the study populations in these three studies were representative of the 2000 Houston census, they may not be fully representative of the general U.S. pediatric population (see Section II.D.). Additionally, the authors in these studies appeared to include Hispanic as a race rather than as an ethnicity, so comparisons with 2014 U.S. census data could not be made to determine if Hispanics were disproportionately represented in the study populations.

D. U.S. Pediatric Population Data

In 2014, the total U.S. population was estimated to be 318,907,401 including 73.6 million (23.1%) children and adolescents from birth to 17 years of age.[21] Among the estimated 73.6 million U.S. youth in 2014, 25.0 million were adolescents 12 years to 17 years of age, 24.7 million were children 6 years to 11 years of age, and 23.9 million were children 0 to 5 years of age.[22] In 2014, 52% of U.S. youth were White, non-Hispanic; 24% were Hispanic; 14% were Black, non-Hispanic; 5% were Asian, non-Hispanic; and 5% were non-Hispanic "all other races".[23]

DPMH Comments: These 2014 U.S. census data were issued March 2015 and were, therefore, publicly available to the sponsor for inclusion in their prevalence calculations prior to their May 5, 2015 re-submission for orphan drug designation.

The prevalence of obesity among U.S. youth was 17.0% in 2011-2014 and was highest among adolescents 12 years to 19 years of age (20.5%) than among younger children 6 years to 11 years of age (17.5%) and pre-school aged children 2 years to 5 years of age (8.9%).[24]

DPMH Comments: Although the reference supporting these numbers was published in November 2015 (after the sponsor's re-submission), these numbers are relatively consistent with those previously published by the same authors. A 2014 publication[25] from the same authors, analyzing the same database, found the prevalence of obesity in the U.S. youth from 2011-2012 to be 16.9%; the prevalence among children 2 years to 5 years of age was 8.4%, those 6 years to 11 years of age was 17.7%, and for those 12 years to 19 years of age was 20.5%.

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[21] Projections of the Size and Composition of the U.S. Population: 2014 to 2060 by Sandra L. Colby and Jennifer M. Ortman; issued March 2015 and accessed at www.census.gov on March 7, 2016

[22] http://www.childstats.gov/americaschildren/tables/pop1.asp?popup=true; accessed March 7, 2016

[23] http://www.childstats.gov/americaschildren/demo1.asp; accessed March 10, 2016

[24] Ogden CL, Carroll MD, Fryar CD, et al. Prevalence of Obesity Among Adults and Youth: United States, 2011-2014. NCHS Data Brief 219: 1-8, 2015.

[25] Ogden CL, Carroll MD, Kit BK, et al. Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. JAMA 311 (8): 806-814, 2014.

III. DPMH's Prevalence Estimate based on Data Available to the Sponsor at the May 5, 2015 Orphan Designation Request for Lisinopril Oral Solution

See Table 3 for DPMH's calculated prevalence estimate for pediatric hypertension in the United States based on the following information:

- 2014 U.S. census data[21]
- The range of prevalence of pediatric hypertension reported in published studies which followed the NHBPEP guidelines[17,18,19,20]
- The reported proportion of confirmed pediatric hypertension that is secondary[8]
- The estimated prevalence of obesity in U.S. youth based on 2014 published values[25]
- The 11% reported prevalence of hypertension among obese U.S. youth.[13,19]

Table 3. Prevalence Estimate of Pediatric Hypertension in the United States

Description	Percent	Denominator	Total	Source
2014 U.S. Census Population (based on report issued March 2015)				
Total Population	--	--	318,907,401	21
Pediatric Population	23.1%	318,907,401	73,600,000 (approximately)	21
0-5 Years	--	--	23,900,000	22
6 Years-11 Years	--	--	24,700,000	22
12 Years-17 Years	--	--	25,000,000	22
Prevalence of Hypertension in U.S. Youth				
0—5 Years	3.6%	23,900,000	860,400	20
6 Years-11 Years	3.6%	24,700,000	889,200	20
12 Years-17 Years	2.5%-4.5%	25,000,000	625,000-1,125,000	17,18,19,20
Total			2,374,600-2,874,600	
Prevalence of Non-WCH				
0-5 Years	47%-56%	860,400	404,388-481,824	26
6 Years-11 Years	47%-56%	889,200	417,924-497,952	26
12 Years-17 Years	47%-56%	625,000-1,125,000	293,750-630,000	26
Total			1,116,062-1,609,776	
Secondary Hypertension in U.S. Youth				
0-5 Years	70%-85%	404,388-481,824	283,071-409,550	8
6 Years-11 Years	70%-85%	417,924-497,952	292,546-423,259	8
12 Years-17 Years	5%-15%	293,750-630,000	14,687-94,500	8
Total			***590,304-927,309***	
Prevalence of Obese U.S. Youth				
0-5 Years	8.4%	23,900,000	2,007,600	25
6 Years-11 Years	17.7%	24,700,000	4,371,900	25
12-17 Year Olds	20.5%	25,000,000	5,125,000	25
Total			11,504,500	
Prevalence of Hypertension Among Obese U.S. Youth				
0-5 Years	11%	2,007,600	220,836	13,19

6 Years-11 Years	11%	4,371,900	480,909	[13,19]
12 Years-17 Years	11%	5,125,000	563,750	[13,19]
Total			***1,265,495***	

(Source: created by this reviewer)

DPMH's calculated combined prevalence of primary hypertension (1,265,495) and secondary hypertension (590,304-927,309) exceed the maximum of 200,000 required for orphan designation.

DPMH Comments:

If only 15.8% (199,949) of the estimated 1,265,495 obese U.S. children (less than 18 years of age) required pharmacologic intervention, then the number of pediatric patients would exceed the criterion for orphan drug designation. DPMH staff (including this reviewer) has clinical experience in pediatric nephrology and hypertension and note that the actual percentage of obese U.S. youth with primary hypertension needing pharmacologic intervention far exceeds 15.8%.

There are no published reports in the U.S. describing the prevalence of pediatric patients with primary hypertension who require pharmacologic intervention specifically due to failed dietary and lifestyle modifications. The only figure DPMH was able to identify is likely an underestimate because the prevalence was derived from a claims-based, cross-sectional study which relied on ICD-9 codes.[10] *This approach is problematic given the extent of under diagnosis of hypertension on this basis as noted in at least one publication*[20] *widely referenced by the sponsor. The study design and limitations of the claims-based study are described elsewhere in this document (see Section IV, DPMH Comment 4), but results showed a prevalence of primary hypertension of 0.18%; antihypertensive drug use among these pediatric patients was 34.1%. The reasons for why these patients required antihypertensive drug therapy (LVH, failed dietary and lifestyle modifications, both) were not captured in the study.*

Therefore, based solely on the likelihood that the number of primary hypertension patients in the U.S. less than 17 years of age who would require treatment is far greater than 200,000,the orphan designation for this product for pediatric hypertension should be removed. Moreover, if the prevalence of secondary hypertension is included in this estimate, the number of pediatric hypertension patients requiring pharmacologic therapy further increases.

IV. DPMH's Re-Examination of Sponsor's Amended Calculations

DPMH re-examined the prevalence estimates provided by the sponsor at the time of their May 5, 2015 re-submission for orphan drug designation. Each of the sponsor's assertions is reviewed with DPMH comments in Table 4 below.

Table 4. DPMH Comments about Sponsor's Population Estimate Strategy

Sponsor's Approach	DPMH Comments
U.S. Pediatric Population based on 2010 U.S. Census	2014 U.S. census data should have been used; see Table 3.

Prevalence of Hypertension (3 years-18 years) based on 3.6%[20] prevalence in the U.S. pediatric population	3.6%[20] is appropriate to use for U.S. youth 0-11 years of age but the reported prevalence ranges from 2.5%-4.5%[17,18,19,20] in older U.S. youth 12-17 years of age; see Table 3.
Non-WCH estimate based on 54%[26] prevalence	Using the reported range of prevalence estimates for WCH from all available published studies – rather than a single published estimate - may have been more appropriate. See DPMH comment 2 in Section IV. See Table 3.
Non-obese hypertension estimate based on prevalence of 49%[27]	Both values do not help inform the number of pediatric patients in whom pharmacologic therapy would be needed since these categories do not distinguish between primary vs. secondary hypertension See DPMH comment 3 in Section IV about limitations in the referenced study.[27]
Prevalence of stage 1 hypertension[20]	
Prevalence of Primary Hypertension[10]	See DPMH comment 4 in Section IV about limitations in the referenced study that should preclude use of these study data for the estimate calculation.
Prevalence of LVH in Stage 1 Primary Hypertension[27]	This number may overlap with prevalence estimates for primary and/or secondary hypertension.
Prevalence of Secondary Hypertension[10]	See DPMH comment 4 in Section IV about limitations in the referenced study that should preclude use of these study data for the estimate calculation.
Prevalence of Stage 2 Hypertension[20]	This number may overlap with prevalence estimates for primary and/or secondary hypertension.

(Source: created by this reviewer) WCH: white coat hypertension

DPMH Comments: DPMH notes that verifying the accuracy of the sponsor's calculations is difficult because the different categories delineated by the sponsor are not necessarily mutually exclusive with other categories. For instance, non-obese hypertension is presumably all secondary but can also be classified as stage 1 or stage 2 hypertension. Therefore, the sequential calculation approach used by the sponsor to derive a final prevalence estimate is flawed and would likely underestimate the total number of pediatric hypertension patients who would require pharmacologic treatment.

DPMH independently reviewed the publications referenced by the sponsor in support of their calculations and has the following comments:

DPMH Comment 1:

The sponsor considered the prevalence estimate of 3.6% reported by Hansen and colleagues in 2007[20] to be the high-end of the pediatric hypertension prevalence spectrum.

DPMH agrees with reliance on this estimate.

DPMH Comment 2:

The sponsor referenced a retrospective chart review[26] to determine the prevalence of non-white coat hypertension (WCH). This study identified 267 pediatric patients, ages 1 month to 20 years, who were referred to a pediatric hypertension sub-specialty clinic for initial evaluation of elevated BP. Results showed that, among the 128 patients who underwent ambulatory BP monitoring (ABPM), 46% had white coat hypertension (WCH), 49% had stage 1 hypertension, and 5% had stage 2 hypertension. The sponsor combined the percentage of patients with stage 1 and 2 hypertension (54% of the study population) in their prevalence estimate, but a range from other available studies may be more appropriate. The authors of this publication noted that the prevalence of WCH noted in their study was consistent with previously published ranges for the prevalence of WCH (44%-53%). If 44%-53% of prevalent pediatric hypertension is WCH, then the remaining percentage (47%-56%) should be considered non-white coat hypertension.

DPMH disagrees with use of a single estimate of 54% and suggests that the range of published values (47%-56%) be used instead. DPMH notes that the racial distribution of the study population (43% white, 34% black, 22% Hispanic, 1% Asian) was representative of the Houston metropolitan area but is not fully representative of the U.S. pediatric population. Blacks were overrepresented in the study population compared to the U.S. pediatric population (34% vs. 14%) and Asians were underrepresented in the study population compared to the U.S. pediatric population (1% vs. 5%)

DPMH Comment 3:

The sponsor estimated the prevalence of non-obese hypertension (49%) from a retrospective cohort study which found a 0.3% prevalence of hypertension among pediatric patients 3 years to 17 years of age receiving well-child care in community-based practices and having 1 or more outpatient visits between July 1, 2007 and December 31, 2009 with an initial (index) BP measurement.[27] Follow-up BP measurements obtained in the index cases at subsequent outpatient visits were used to classify hypertension per the NHBPEP guidelines over a total follow-up period of 3.5 years. The authors found the prevalence of patients with normal BPs,

[26] Swartz SJ, Srivaths PR, Croix B, et al. Cost-Effectiveness of Ambulatory Blood Pressure Monitoring in the Initial Evaluation of Hypertension in Children. Pediatrics 122: 1177-1181, 2008.

[27] Lo JC, Sinaiko A, Chandra M, et al. Prehypertension and Hypertension in Community-Based Pediatric Practice. Pediatrics 131: e415-e424, 2013.

pre-hypertension, and hypertension to be 83.4%, 12.0%, and 0.3% (257/85,780), respectively. The sponsor's prevalence estimate for non-obese hypertension of 49% (127/257) reflects the proportion of the study population who met the criteria for hypertension and had a BMI percentile < 85th for sex and age. Although the remaining 51% of hypertensive patients were obese, this publication did not specify if or how primary versus secondary causes of hypertension were distinguished among the hypertensive cohort. The data source for this study appropriately included large urban and suburban community populations from Northern California, Colorado, and Minnesota. However, 37.9% (4,109) of pediatric patients with a BP reading ≥ 95th percentile for sex, age, and height at the index visit did not have subsequent BP measurements taken during the follow-up period and were, therefore, not included in the prevalence estimate; 65% of these patients were less than 12 years of age. Compared with patients with follow-up measurements, a slightly greater proportion of those without follow-up BP were overweight or obese (52.3% vs 48.5%, P < 0.01).

This study may underestimate the true prevalence of pediatric hypertension in this population, particularly among younger pediatric patients because more than 1/3 of patients with an elevated BP at the index visit were excluded from the final analysis due to the lack of repeated BP measurements in the follow-up period.

DPMH Comment 4:

The sponsor estimated the prevalence of primary hypertension as 89% from a claims-based analysis of pediatric use of antihypertensive drugs in 2008 using data from a national commercial insurer.[10] Using de-identified inpatient, outpatient, physician, and pharmacy claims data from Ingenix's UnitedHealth Group Analytics Platform database, the authors identified 1.45 million children less than 18 years of age in the database who had had continuous coverage for both medical and pharmacy benefits for the entire year. The authors included pediatric patients whose hypertension episode started prior to or in 2008 and analyzed their drug utilization in 2008 only. The authors used ICD-9 codes for primary hypertension to define patients with primary hypertension and considered all other hypertensive pediatric patients to have secondary hypertension. With their approach, the authors found that the prevalence of primary and secondary hypertension was 0.18% (2607/1.4 million) and 0.02% (308/1.4 million), respectively. The combined prevalence rate was 0.20%. Results showed the percentage of all pediatric patients with hypertension who used an antihypertensive drug was highest in those 0 to less than 6 years of age (44.3%), followed by those 12 years to less than 18 years of age (38.1%), and then by those 6 years to less than 12 years of age (30.9%). Angiotensin-converting enzyme inhibitors (ACEi) were the most commonly used antihypertensive drug class in all pediatric age groups, and lisinopril was the most commonly used ACEi.

This study's strength appears to be the ability of the claims-based data to allow a more precise collection of the specific antihypertensive drug prescribed, the drug dosage, and the prescription date in to inform detailed analyses of antihypertensive drug utilization patterns in the study cohort. However, the prevalence estimates for pediatric hypertension in this study are likely an underestimate for several reasons. First, the study's reliance on ICD-9 codes for diagnoses of primary hypertension, rather than through direct BP measurements, is problematic given the

extent of under diagnosis of hypertension on this basis as noted in at least one publication widely referenced by the sponsor.[20] *Second, the authors used a less rigorous definition for hypertension, including for primary and secondary hypertension, than that recommended by the NHBPEP. Third, the results may not adequately represent the U.S. pediatric population demographically and socioeconomically since the study population was limited to those with private health insurance provided by a single national commercial insurer. Since the data were derived from health insurance claims, data on race and ethnicity were not included for analyses.*

V. Conclusions

DPMH has reviewed the sponsor's amended estimates for the prevalence of pediatric hypertension and disagrees with the sponsor's conclusion that the estimate of the prevalence is less than 200,000.

Based on an independent review of available published and other publicly available data, DPMH's calculated combined prevalence of primary pediatric hypertension (1,265,495) and secondary pediatric hypertension (590,304-927,309) exceed the maximum of 200,000 required for orphan designation. These estimates are based on 2014 U.S. census data and peer-reviewed published data that were available to the sponsor prior to their May 5, 2015 re-submission.

VI. Recommendations

DPMH recommends the following:

1. Removal of the orphan designation granted to Silvergate Pharmaceutical's lisinopril oral solution. DPMH further recommends that orphan designation for this product should be removed prior to the PDUFA date of April 30, 2016.

2. Removal of any existing orphan designations for therapies intended to treat pediatric hypertension granted for pediatric hypertension after February 2014 based on availability of published prevalence data of childhood obesity in the United States at that time.

3. Future requests for orphan designation of therapies intended for treatment of pediatric hypertension should be declined unless additional data are shared providing conclusive evidence that the prevalence of pediatric hypertension is less than 200,000.

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/s/

MONA K KHURANA
03/24/2016

LYNNE P YAO
03/24/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5295
Silver Spring, MD 20993

APR 0 8 2016

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

Attention: Susan J. Prather
Director, Regulatory Affairs

Re: Designation #12-3767
Designation #15-4819

Dear Ms. Prather:

Reference is made to orphan-drug designation requests dated July 19, 2012 and May 1, 2015, for the use of enalapril and lisinopril for the treatment of hypertension in pediatric patients 0 through 16 years of age. Reference is also made to our letters dated January 30, 2013 and October 14, 2015, granting orphan-drug designation to your drugs enalapril and lisinopril for the treatment of hypertension in pediatric patients 0 through 16 years of age.

Based on additional information that has come to our attention, we have determined that, at the time you filed both of your requests for orphan-drug designation, the prevalence of hypertension in pediatric patients amenable to treatment with pharmacologic agents exceeded the statutory threshold of 200,000 persons in the United States (US). Thus, we believe that enalapril and lisinopril were not eligible for orphan-drug designation at the time the requests for orphan-drug designation were submitted. We are proposing to revoke your designation for these drugs pursuant to 21 CFR 316.29, and are giving you 14 calendar days, until **April 22, 2016**, to submit any comments on this proposal.

The basis for our determination is as follows:

The orphan-drug regulations at 316.21(b) note that "prevalence" is defined as the number of persons in the US who have been diagnosed as having the disease or condition at the time of the submission of the request for orphan-drug designation. Since the first request by Silvergate for orphan-drug designation for use in the treatment of pediatric hypertension was received by the Office of Orphan Products development (OOPD) on July 20, 2012, any population documentation supporting whether or not this use qualified for orphan-drug designation should be available on or before that date. A population estimate as of that date should also be provided. A Census Bureau PopClock calculation provides that the US population on February 14, 2012 was 313,243,466 and that children

age 0 through 16 years comprised 22.6% of the US 2010 Census.[1] This results in an estimate of 70,800,000 children age 0 through 16 years on that date.

Prevalence estimates of hypertension in the US pediatric population should be based on the definition of hypertension as articulated in the 2004 National High Blood Pressure Education Program (NHBPEP) guidelines since these guidelines were endorsed by both the American Academy of Pediatrics and the American Heart Association. Hansen et al 2007 used the 2004 NHBPEP guidelines to determine the criteria for hypertension.[2] Hansen et al specifies that while the criteria for hypertension were met by 3.6% of the children included in a retrospective cohort study (i.e., 507 children), only 26% of those, or 131 children, had a diagnosis of hypertension or elevated blood pressure documented in the electronic medical record. Hansen further notes that elevated blood pressure without hypertension (ICD-9 code 796.2) was the only code present in 51 of the 131 diagnosed with hypertension; therefore, only 80 of the 507 participants (15.8%) had a true hypertension diagnosis in the electronic medical record. As such, applying this information to an estimate of 70,800,000 children age 0 through 16 years,[3,4] results in a prevalence of 402,710 children age 0 to 16 years who have been diagnosed with hypertension as of February 14, 2012.

Prevalence estimates of hypertension in the US pediatric population for purposes of orphan drug-designation should capture all patients for whom pharmacologic treatment would be recommended. The NHBPEP guidelines recommend initiating pharmacologic therapy in pediatric patients with the following:[5]

- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (types 1 and 2); and
- Persistent hypertension despite non-pharmacologic measures.

Hypertension can be primary (essential) hypertension or can be due to a secondary disease process. There appear to be no published reports in the US that adequately describe the prevalence of pediatric patients with primary hypertension who require pharmacologic intervention due to failed dietary and lifestyle modifications. However, an estimate of the proportion of secondary hypertension among pediatric age groups is available. In 2001, Flynn et al estimated that the prevalence of secondary hypertension in US youth 0 to 11 years is between 70-85% of all hypertension, and between 5 to 15% of

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[1] US Census Bureau. http://www.census.gov

[2] Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of Hypertension in Children and Adolescents. JAMA 298(8): 874-879, 2007.

[3] US Census Bureau. http://www.census.gov.

[4] Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of Hypertension in Children and Adolescents. JAMA 298(8): 874-879, 2007.

[5] The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 114 (Suppl 4th Report): 555-576, 2004.

all hypertension in pediatric aged children 12 through 17 years.[6] From these percentages, and the prevalence of diagnosed pediatric hypertension calculated above on February 2012, 402,710, the prevalence of secondary hypertension in pediatric children can be estimated to be between 203,107 to 257,452. Of note, Flynn et al did not use NHBPEP Fourth report criteria to diagnose the hypertension since this publication was from 2001. A 2005 publication by Flynn et al, which also did not use NHBPEP Fourth Report criteria, found a prevalence of 51.7% secondary hypertension among 145 children less than 18 years of age with hypertension, which would correspond to a prevalence of 208,201 for pediatric secondary hypertension.[7] A January 2015 publication by Gupta et al described how the group used NHBPEP Fourth Report criteria to diagnose hypertension in 275 children 0 through 19 years, and once diagnosis was confirmed, the children underwent additional evaluation for secondary hypertension per the Fourth Working Group report.[8] Gupta et al also found a prevalence of 57% of secondary hypertension among all children diagnosed with hypertension. While this last publication was not available in 2012, it supports a determination that the prevalence of secondary hypertension in the United States in the pediatric population exceeded 200,000 in 2012.

In February 2012, the number of children diagnosed with secondary hypertension exceeded the 200,000 threshold for orphan-drug designation. Since this is only one of several subsets of pediatric hypertension that are recommended to be pharmacologically treated, it is clear that the number of children age 0 through 16 years that are diagnosed with hypertension that are recommended to be pharmacologically treated well exceeds the threshold of 200,000 to qualify for orphan-drug designation.

Therefore, pursuant to 21 C.F.R. 316.29(a)(3), OOPD intends to revoke the orphan-drug designations for enalapril and lisinopril for the treatment of hypertension in pediatric patients 0 through 16 years of age.[9] If you have additional relevant information to address the aforementioned concerns, please submit it to the Office of Orphan Products Development by **April 22, 2016**, for our review.

---

[6] Flynn JT. Evaluation and Management of Hypertension in Childhood. Progress in Pediatric Cardiology 12: 177- 188, 2001.

[7] Flynn JT, Alderman MH. Characteristics of children with primary hypertension seen at a referral center. Pediatr Nephrol 20:961–966, 2005.

[8] Gupta-Malhotra M, Banker A, Shete S, et al. Essential Hypertension vs. Secondary Hypertension Among Children. American Journal of Hypertension 28(1): 73-80, 2015.

[9] We note that enalapril was approved on August 13, 2013, and did not obtain orphan drug exclusivity because it was not shown to be clinically superior to the previously approved same drug, Vasotec. Pursuant to 21 CFR 316.29(b), revocation of orphan drug designation does not implicate the drug's approval.

Should you have any questions, please contact Jeff Fritsch, RPh in this Office at 301-796-8682 or alternatively at 301-796-8660.

Sincerely,

Gayatri Rao

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

cc:

OOPD/File # 15-4819
OOPD/Chron

History:
J. Fritsch
E. McNeilly
G. Rao
DCRP /NDA 208401
DCRP/S. Soukehal/CSO

Intent to Revoke Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5295
Silver Spring, MD 20993

APR 2 8 2016

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

Attention: Susan J. Prather
Director, Regulatory Affairs

Re: Designation # 15-4819

Dear Ms. Prather:

Reference is made to your orphan-drug designation request dated May 1, 2015, for the use of Lisinopril for the treatment of hypertension in pediatric patients 0 through 16 years of age (Lisinopril's designation). Reference is also made to our designation letter dated October 14, 2015, and our letter of intent to revoke orphan designation dated April 8, 2016.

Our letter dated April 8, 2016, stated that upon reconsideration of Lisinopril's designation, we had determined that, at the time you filed the request, the prevalence of hypertension in pediatric patients amenable to treatment with pharmacologic agents exceeded the statutory orphan-drug designation qualification threshold of 200,000 affected persons in the United States. Thus, at the time you filed the request, Lisinopril was not eligible for orphan-drug designation. In our April 8, 2016, letter, we also informed you that, pursuant to 21 C.F.R. 316.29(a)(3), we intended to revoke Lisinopril's designation. We notified you that if you had additional relevant information to address the designation issue, you should submit it to the Agency for consideration by April 22, 2016. On April 21, 2016, by phone, you informed the Office of Orphan Products Development that you had decided not to respond to the letter of intent to revoke orphan designation.

Therefore, pursuant to 21 CFR 316.29(a)(3), we are revoking Lisinopril's designation for treatment of hypertension in pediatric patients 0 through 16 years of age, which was granted on October 14, 2015. Because Lisinopril was not eligible for orphan-drug designation at the time of submission of the request, and therefore not eligible for any benefits that accompany orphan-drug designation, any such benefits are hereby terminated as improperly granted.

Should you have any further questions, please contact Jeff Fritsch, RPh, in this Office at 301-796-8682 or alternatively at 301-796-8660.

Sincerely,

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

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/s/

SABRY SOUKEHAL
04/29/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: April 6, 2016

To: Sabry Soukehal
Consumer Safety Officer
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Qbrelis (lisinopril) Oral Solution**
NDA: 208401
Comments on draft product labeling

In response to your consult dated August 19, 2015, OPDP has reviewed the draft prescribing information (PI) and the proposed Carton and Container labeling for Qbrelis (lisinopril) Oral Solution. We have reviewed the attached substantially complete version of the draft PI emailed to us on April 3, 2016 as well as the proposed Carton and Container Labeling submitted by the sponsor on January 19, 2016. We do not have any comments on the draft PI or the proposed Carton and Container labeling at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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

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/s/

ZARNA PATEL
04/06/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Mona Khurana, M.D., Medical Officer
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV

Through: Lynne Yao, M.D., Director

To: Division of Cardiovascular and Renal Products

Drug Name: Lisinopril

Drug Category: Angiotensin converting enzyme inhibitor

Subject: Revised Proposed Pediatric Study Request

Sponsor: Silvergate Pharmaceuticals

Materials Reviewed

- Materials accompanying February 24, 2016 consult from the Division of Cardiovascular and Renal Products (including referenced publications) (DARRTS Reference ID 3892435)
- Relevant documents related to lisinopril approval history accessed at Drugs@FDA
- Currently marketed lisinopril drug products accessed at Orange Book
- FDA Orphan Designation Search Page (search term: lisinopril)
- The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (including referenced publications). National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 114 (2): 555-576, 2004.
- PubMed database search (search terms: prevalence AND hypertension; prevalence AND hypertension AND US; prevalence AND pediatric hypertension AND American [limits: English, human, child]); including referenced publications from retrieved articles.

Consult Request

The Division of Cardiovascular and Renal Products (DCaRP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 24, 2016 to provide a prevalence estimate for pediatric hypertension requiring pharmacologic therapy based on information that would have been available to each of the sponsors of antihypertensive drug products which have already received orphan drug designation for treatment of pediatric hypertension. The purpose of this request is to determine if the prevalence estimates available to the sponsors at the time of their requests were higher than that required to be considered for orphan drug designation (200,000). Higher prevalence estimates than those reported at the time of the sponsor's requests could be a basis to revoke orphan drug designation for these products. DCaRP is requesting this information first for lisinopril oral solution since the Prescription Drugs User Fee Act (PDUFA) due date for the submitted new drug application (NDA) 208401 is April 30, 2016.

I. Relevant Background

Lisinopril was initially approved by FDA in 1987 under NDA 19558 in a tablet formulation with the trade name Prinivil[1] and then in 1988 as Zestril tablet under NDA 19777. Multiple abbreviated NDAs (ANDAs) have subsequently been approved for the oral tablet formulation only.[2]

In January 2015, (b) (4) received orphan drug designation for lisinopril oral solution in the treatment of primary hypertension with complications and secondary hypertension in pediatric patients 0 through 16 years of age.[3] The prevalence of pediatric hypertension at the time the application was submitted in February 2012 was established to be 196, 453.[4] The orphan drug designation was transferred to (b) (4) in March 2015.

FDA received a request for orphan drug designation for lisinopril oral solution on May 5, 2015 from Silvergate Pharmaceuticals, Inc. FDA granted orphan designation for the treatment of hypertension in pediatric patients 0 to 16 years of age on October 14, 2015.[5] There is currently

[1] December 29, 1987 approval letter: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2003/19558se5-043ltr.pdf (accessed March 4, 2016)

[2] Orange Book: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm?firstRec=101 (accessed March 4, 2016)

[3] Orphan Designation Search Page (search term: lisinopril; application number 12-3655): http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=365512 (accessed March 4, 2016)

[4] June 11, 2015 Review of a Request for Orphan Drug Designation

[5] Orphan Designation Search Page (search term: Lisinopril): http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=481915 (accessed March 4, 2016)

no FDA-approved ready-to-use liquid formulation of lisinopril for use by pediatric patients who have difficulty swallowing or cannot consume tablets.

II. Prevalence of Pediatric Hypertension

A. Diagnostic Considerations

Prevalence estimates of hypertension in the U.S. pediatric population should ideally be based on how hypertension is defined in the 2004 National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents consensus-based guidelines.[6] These guidelines have been endorsed by the American Academy of Pediatrics and by the American Heart Association. The NHBPEP guidelines recommend interpretation and categorization of systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements in children 3 years to 18 years of age based on the child's age, height, and sex in order to classify BP according to body size (see Table 1). Importantly, the NHBPEP's definition of pediatric hypertension is based on mean SBP and DBP measured on at least three separate occasions to allow for a more precise characterization of the blood pressure (BP) level.

Table 1. Definition of Pediatric Hypertension according to the NHBPEP Guidelines

BP Category	BP Percentile for Sex, Age, Height
Normal	SBP and DBP < 90th
Pre-Hypertension	Mean SBP or DBP: > 90th but ≤ 95th; OR BP > 120/80 mmHg but < 95th in adolescents
Hypertension	Mean SBP or DBP > 95th on at least 3 separate occasions
Stage 1	Mean SBP or DBP: > 95th but ≤ 99th plus 5 mmHg
Stage 2	Mean SBP or DBP: > 99th plus 5 mmHg

(Source: created by this reviewer from [6])

Depending on a child's age, up to 85% of confirmed pediatric hypertension can be due to a secondary cause. See Table 2.

Table 2. Reported Proportions of Confirmed Pediatric Hypertension that is Secondary with the Most Common Underlying Etiologies

[6] The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 114 (Suppl 4th Report): 555-576, 2004.

Pediatric Age Group	Proportion of Secondary Hypertension	Most Common Etiologies[7] (Listed in Order of Frequency)
Birth to < 6 years	70%-85%[8]	Renal Parenchymal Disease Renovascular Disease Endocrine Disease Cardiac/Pulmonary/CNS disease Iatrogenic Genitourinary
6 years to < 12 years	70%-85%[8]	
12 years to 18 years	5%-15%[8]	

(Source: adapted by this reviewer from[7, 8]); CNS: central nervous system

Prevalence estimates of pediatric hypertension based on large community-based screening studies published before the 2004 NHBPEP guidelines have limited relevance for the following reasons: (1) inconsistent definitions of hypertension that relied on a single set of BP measurements; (2) narrow pediatric age ranges; and (3) limited race distributions. While more recently published studies have captured a broader pediatric age range and racial distribution that are potentially more representative of the U.S. pediatric population, these studies also have limited utility because they used claims-based[9,10] approaches or survey data based on a single set of BP measurements[11,12] to define pediatric hypertension rather than the more rigorous diagnostic approach recommended by the NHBPEP.

B. Pharmacologic Treatment Considerations

Prevalence estimates of hypertension in the U.S. pediatric population should capture all patients for whom pharmacologic treatment would be recommended. The NHBPEP guidelines recommend initiating pharmacologic therapy in pediatric patients with the following:[6]

- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite non-pharmacologic measures

[7] Brady TM and Feld LG. Pediatric Approach to Hypertension. Seminars in Nephrology 29: 379-388, 2009.

[8] Flynn JT. Evaluation and Management of Hypertension in Childhood. Progress in Pediatric Cardiology 12: 177-188, 2001.

[9] Dobson CP, Eide M, Nylund CM. Hypertension Prevalence, Cardiac Complications, and Antihypertensive Medication use in Children. Journal of Pediatrics 167: 92-97, 2015.

[10] Welch WP, Yang W, Taylor-Zapata P, et al. Antihypertensive Drug Use by Children: Are the Drugs Labeled and Indicated? The Journal of Clinical Hypertension 14(6): 388-395, 2012.

[11] Kit BK, Kuklina E, Carroll MD, et al. Prevalence of and Trends in Dyslipidemia and Blood Pressure Among US Children and Adolescents, 1999-2012. JAMA Pediatrics 169(3): 272-279, 2015.

[12] Din-Dzietham R, Liu Y, Bielo M, et al. High Blood Pressure Trends in Children and Adolescents in National Surveys, 1963 to 2002. Circulation 116: 1488-1496, 2007.

DPMH Comments: In their amended prevalence estimates, the sponsor failed to specifically address each of these pediatric hypertensive sub-populations for whom pharmacologic therapy would be appropriate. Rather, the sponsor's calculations included only the following three sub-populations in need of pharmacologic intervention:

- *Stage 1 primary hypertension associated with left ventricular hypertrophy (LVH) (This approach does not capture all pediatric patients with primary hypertension who did not have LVH but who would still be candidates for pharmacologic intervention if they failed dietary and lifestyle modifications).*
- *All patients with stage 2 primary hypertension (These patients will likely overlap with those in the secondary hypertension group since Stage 2 hypertension in the majority of pediatric patients is less likely to be primary and most likely to be due to an underlying cause).*
- *All patients with secondary hypertension*

C. Available Prevalence Data on Pediatric Hypertension

According to a 2013 U.S. Preventive Services Task Force (USPSTF) publication, the prevalence of pediatric hypertension in the United States has been reported to range from 1% to 5% and the prevalence of hypertension among obese U.S. children and adolescents is estimated at 11%.[13] Since the USPSTF's prevalence estimates[14,15,16] did not appear to be entirely based on pediatric hypertension diagnosed using the 2004 NHBPEP guidelines, DPMH searched the PubMed database for studies published since the 2004 NHBPEP guidelines that have reported the prevalence of pediatric hypertension using the NHBPEP's definition of hypertension (based on three sets of elevated BP measurements). DPMH's search retrieved four publications reporting prevalence estimates consistent with those reported in the 2013 USPSTF publication. These three studies reported prevalence rates of 2.5% among high school students,[17] 3.2% among 11-17 year olds,[18] 4.5% among 10-19 year olds,[19] and 3.6% among 3-18 years olds.[20] These four studies are briefly summarized in this section.

[13] Moyer VA. U.S. Preventive Services Task Force. Screening for Primary Hypertension in Children and Adolescents. U.S. Preventive Task Force Recommendation Statement. Annals of Internal Medicine 159: 613-619, 2013.

[14] Lurbe E, Alvarez J, Redon J. Diagnosis and Treatment of Hypertension in Children. Current Hypertension Rep 12: 480-486, 2010.

[15] Obarzanek E, Wu CO, Cutler JA, et al. Prevalence and Incidence of Hypertension in Adolescent Girls. Journal of Pediatrics. 157(3): 461-467, 2010.

[16] Flynn JT and Falkner BE. The Importance of Blood Pressure Screening in Children. Journal of Pediatrics 155(2): 299-300, 2009.

[17] Acosta AA, Samuels JA, Portman RJ, et al. Prevalence of Persistent Prehypertension in Adolescents. The Journal of Pediatrics 160:757-761, 2012.

One study by Hansen et al. was previously used to support the orphan designation request for lisinopril.[20] This was a retrospective cohort study to determine the prevalence of pre-hypertension and hypertension, on the basis of International Classification of Diseases Ninth Revision (ICD-9) codes, among 14,187 children and adolescents 3 years to 18 years of age from a large academic urban medical system in northeast Ohio who received well-child care from June 1999 to September 2006. The authors identified 507 children and adolescents (3.6%) who met the NHBPEP's criteria for hypertension.

DPMH Comments: Demographic characteristics were not clearly described to determine if the study population was fully representative of the U.S. pediatric population. However, this was the only study identified by DPMH that used the NHBPEP guidelines and included younger pediatric patients less than 10 years of age.

The other three studies were school-based screenings conducted to determine the prevalence of pre-hypertension and hypertension, based on the NHBPEP guidelines, among children and adolescents from Houston area schools who were 10 years of age and older.[17,18,19]

- Acosta et al screened 1,020 students from a Houston area high school in 2007 and identified 2.5% with hypertension.[17] The study population was 49.2% Hispanic, 25.2% Caucasian, and 16.1% African-American.
- McNiece et al[18] screened 6,790 adolescents 11 years to 17 years of age from nine Houston area schools from 2003 to 2005 and identified 3.2% with hypertension. The study population was 37% Caucasian, 28% African-American, 8% Asian, and 27% Hispanic. A greater proportion of the study population was African-American compared to the total U.S. population (28% vs. 14.3%[8]).
- Sorof et al[19] screened 5,102 school-aged children 10 years to 19 years of age from eight Houston area schools from May 2002 to November 2002 and identified 4.5% with hypertension. The overall prevalence of overweight (body mass index [BMI] $\geq 95^{th}$ percentile) was 20%. The study population was 44% Caucasian, 22% African-American, 7% Asian, 2% other, and 25% Hispanic. A greater proportion of the study population was African-American compared to the total U.S. population (22% vs. 14.3%). The higher prevalence of pediatric hypertension in this study appeared to be strongly determined by the high proportion of the study population that had BMIs greater than normal. The prevalence of hypertension in this study among students with a normal BMI ($< 85^{th}$ percentile) was 2.6% compared to 10.7% in those with obesity (BMI $\geq 95^{th}$ percentile).

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[18] McNiece KL, Poffenbarger TS, Turner JL, et al. Prevalence of Hypertension and Pre-Hypertension among Adolescents. Journal of Pediatrics 150: 640-644, 2007.

[19] Sorof JM, Lai D, Turner J, et al. Overweight, Ethnicity, and the Prevalence of Hypertension in School-Aged Children. Pediatrics 113(3): 475-482, 2004.

[20] Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of Hypertension in Children and Adolescents. JAMA 298(8): 874-879, 2007.

DPMH Comments: Although the racial distributions of the study populations in these three studies were representative of the 2000 Houston census, they may not be fully representative of the general U.S. pediatric population (see Section II.D.). Additionally, the authors in these studies appeared to include Hispanic as a race rather than as an ethnicity, so comparisons with 2014 U.S. census data could not be made to determine if Hispanics were disproportionately represented in the study populations.

D. U.S. Pediatric Population Data

In 2014, the total U.S. population was estimated to be 318,907,401 including 73.6 million (23.1%) children and adolescents from birth to 17 years of age.[21] Among the estimated 73.6 million U.S. youth in 2014, 25.0 million were adolescents 12 years to 17 years of age, 24.7 million were children 6 years to 11 years of age, and 23.9 million were children 0 to 5 years of age.[22] In 2014, 52% of U.S. youth were White, non-Hispanic; 24% were Hispanic; 14% were Black, non-Hispanic; 5% were Asian, non-Hispanic; and 5% were non-Hispanic "all other races".[23]

DPMH Comments: These 2014 U.S. census data were issued March 2015 and were, therefore, publicly available to the sponsor for inclusion in their prevalence calculations prior to their May 5, 2015 re-submission for orphan drug designation.

The prevalence of obesity among U.S. youth was 17.0% in 2011-2014 and was highest among adolescents 12 years to 19 years of age (20.5%) than among younger children 6 years to 11 years of age (17.5%) and pre-school aged children 2 years to 5 years of age (8.9%).[24]

DPMH Comments: Although the reference supporting these numbers was published in November 2015 (after the sponsor's re-submission), these numbers are relatively consistent with those previously published by the same authors. A 2014 publication[25] from the same authors, analyzing the same database, found the prevalence of obesity in the U.S. youth from 2011-2012 to be 16.9%; the prevalence among children 2 years to 5 years of age was 8.4%, those 6 years to 11 years of age was 17.7%, and for those 12 years to 19 years of age was 20.5%.

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[21] Projections of the Size and Composition of the U.S. Population: 2014 to 2060 by Sandra L. Colby and Jennifer M. Ortman; issued March 2015 and accessed at www.census.gov on March 7, 2016

[22] http://www.childstats.gov/americaschildren/tables/pop1.asp?popup=true; accessed March 7, 2016

[23] http://www.childstats.gov/americaschildren/demo1.asp; accessed March 10, 2016

[24] Ogden CL, Carroll MD, Fryar CD, et al. Prevalence of Obesity Among Adults and Youth: United States, 2011-2014. NCHS Data Brief 219: 1-8, 2015.

[25] Ogden CL, Carroll MD, Kit BK, et al. Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. JAMA 311 (8): 806-814, 2014.

III. DPMH's Prevalence Estimate based on Data Available to the Sponsor at the May 5, 2015 Orphan Designation Request for Lisinopril Oral Solution

See Table 3 for DPMH's calculated prevalence estimate for pediatric hypertension in the United States based on the following information:

- 2014 U.S. census data[21]
- The range of prevalence of pediatric hypertension reported in published studies which followed the NHBPEP guidelines[17,18,19,20]
- The reported proportion of confirmed pediatric hypertension that is secondary[8]
- The estimated prevalence of obesity in U.S. youth based on 2014 published values[25]
- The 11% reported prevalence of hypertension among obese U.S. youth.[13,19]

Table 3. Prevalence Estimate of Pediatric Hypertension in the United States

Description	Percent	Denominator	Total	Source
2014 U.S. Census Population (based on report issued March 2015)				
Total Population	--	--	318,907,401	21
Pediatric Population	23.1%	318,907,401	73,600,000 (approximately)	21
0-5 Years	--	--	23,900,000	22
6 Years-11 Years	--	--	24,700,000	22
12 Years-17 Years	--	--	25,000,000	22
Prevalence of Hypertension in U.S. Youth				
0—5 Years	3.6%	23,900,000	860,400	20
6 Years-11 Years	3.6%	24,700,000	889,200	20
12 Years-17 Years	2.5%-4.5%	25,000,000	625,000-1,125,000	17,18,19,20
Total			2,374,600-2,874,600	
Prevalence of Non-WCH				
0-5 Years	47%-56%	860,400	404,388-481,824	26
6 Years-11 Years	47%-56%	889,200	417,924-497,952	26
12 Years-17 Years	47%-56%	625,000-1,125,000	293,750-630,000	26
Total			1,116,062-1,609,776	
Secondary Hypertension in U.S. Youth				
0-5 Years	70%-85%	404,388-481,824	283,071-409,550	8
6 Years-11 Years	70%-85%	417,924-497,952	292,546-423,259	8
12 Years-17 Years	5%-15%	293,750-630,000	14,687-94,500	8
Total			***590,304-927,309***	
Prevalence of Obese U.S. Youth				
0-5 Years	8.4%	23,900,000	2,007,600	25
6 Years-11 Years	17.7%	24,700,000	4,371,900	25
12-17 Year Olds	20.5%	25,000,000	5,125,000	25
Total			11,504,500	
Prevalence of Hypertension Among Obese U.S. Youth				
0-5 Years	11%	2,007,600	220,836	13,19

6 Years-11 Years	11%	4,371,900	480,909	[13,19]
12 Years-17 Years	11%	5,125,000	563,750	[13,19]
Total			***1,265,495***	

(Source: created by this reviewer)

DPMH's calculated combined prevalence of primary hypertension (1,265,495) and secondary hypertension (590,304-927,309) exceed the maximum of 200,000 required for orphan designation.

DPMH Comments:

If only 15.8% (199,949) of the estimated 1,265,495 obese U.S. children (less than 18 years of age) required pharmacologic intervention, then the number of pediatric patients would exceed the criterion for orphan drug designation. DPMH staff (including this reviewer) has clinical experience in pediatric nephrology and hypertension and note that the actual percentage of obese U.S. youth with primary hypertension needing pharmacologic intervention far exceeds 15.8%.

There are no published reports in the U.S. describing the prevalence of pediatric patients with primary hypertension who require pharmacologic intervention specifically due to failed dietary and lifestyle modifications. The only figure DPMH was able to identify is likely an underestimate because the prevalence was derived from a claims-based, cross-sectional study which relied on ICD-9 codes.[10] *This approach is problematic given the extent of under diagnosis of hypertension on this basis as noted in at least one publication*[20] *widely referenced by the sponsor. The study design and limitations of the claims-based study are described elsewhere in this document (see Section IV, DPMH Comment 4), but results showed a prevalence of primary hypertension of 0.18%; antihypertensive drug use among these pediatric patients was 34.1%. The reasons for why these patients required antihypertensive drug therapy (LVH, failed dietary and lifestyle modifications, both) were not captured in the study.*

Therefore, based solely on the likelihood that the number of primary hypertension patients in the U.S. less than 17 years of age who would require treatment is far greater than 200,000,the orphan designation for this product for pediatric hypertension should be removed. Moreover, if the prevalence of secondary hypertension is included in this estimate, the number of pediatric hypertension patients requiring pharmacologic therapy further increases.

IV. DPMH's Re-Examination of Sponsor's Amended Calculations

DPMH re-examined the prevalence estimates provided by the sponsor at the time of their May 5, 2015 re-submission for orphan drug designation. Each of the sponsor's assertions is reviewed with DPMH comments in Table 4 below.

Table 4. DPMH Comments about Sponsor's Population Estimate Strategy

Sponsor's Approach	DPMH Comments
U.S. Pediatric Population based on 2010 U.S. Census	2014 U.S. census data should have been used; see Table 3.

Prevalence of Hypertension (3 years-18 years) based on 3.6%[20] prevalence in the U.S. pediatric population	3.6%[20] is appropriate to use for U.S. youth 0-11 years of age but the reported prevalence ranges from 2.5%-4.5%[17,18,19,20] in older U.S. youth 12-17 years of age; see Table 3.
Non-WCH estimate based on 54%[26] prevalence	Using the reported range of prevalence estimates for WCH from all available published studies – rather than a single published estimate - may have been more appropriate. See DPMH comment 2 in Section IV. See Table 3.
Non-obese hypertension estimate based on prevalence of 49%[27]	Both values do not help inform the number of pediatric patients in whom pharmacologic therapy would be needed since these categories do not distinguish between primary vs. secondary hypertension See DPMH comment 3 in Section IV about limitations in the referenced study.[27]
Prevalence of stage 1 hypertension[20]	
Prevalence of Primary Hypertension[10]	See DPMH comment 4 in Section IV about limitations in the referenced study that should preclude use of these study data for the estimate calculation.
Prevalence of LVH in Stage 1 Primary Hypertension[27]	This number may overlap with prevalence estimates for primary and/or secondary hypertension.
Prevalence of Secondary Hypertension[10]	See DPMH comment 4 in Section IV about limitations in the referenced study that should preclude use of these study data for the estimate calculation.
Prevalence of Stage 2 Hypertension[20]	This number may overlap with prevalence estimates for primary and/or secondary hypertension.

(Source: created by this reviewer) WCH: white coat hypertension

DPMH Comments: DPMH notes that verifying the accuracy of the sponsor's calculations is difficult because the different categories delineated by the sponsor are not necessarily mutually exclusive with other categories. For instance, non-obese hypertension is presumably all secondary but can also be classified as stage 1 or stage 2 hypertension. Therefore, the sequential calculation approach used by the sponsor to derive a final prevalence estimate is flawed and would likely underestimate the total number of pediatric hypertension patients who would require pharmacologic treatment.

DPMH independently reviewed the publications referenced by the sponsor in support of their calculations and has the following comments:

DPMH Comment 1:

The sponsor considered the prevalence estimate of 3.6% reported by Hansen and colleagues in 2007[20] to be the high-end of the pediatric hypertension prevalence spectrum.

DPMH agrees with reliance on this estimate.

DPMH Comment 2:

The sponsor referenced a retrospective chart review[26] to determine the prevalence of non-white coat hypertension (WCH). This study identified 267 pediatric patients, ages 1 month to 20 years, who were referred to a pediatric hypertension sub-specialty clinic for initial evaluation of elevated BP. Results showed that, among the 128 patients who underwent ambulatory BP monitoring (ABPM), 46% had white coat hypertension (WCH), 49% had stage 1 hypertension, and 5% had stage 2 hypertension. The sponsor combined the percentage of patients with stage 1 and 2 hypertension (54% of the study population) in their prevalence estimate, but a range from other available studies may be more appropriate. The authors of this publication noted that the prevalence of WCH noted in their study was consistent with previously published ranges for the prevalence of WCH (44%-53%). If 44%-53% of prevalent pediatric hypertension is WCH, then the remaining percentage (47%-56%) should be considered non-white coat hypertension.

DPMH disagrees with use of a single estimate of 54% and suggests that the range of published values (47%-56%) be used instead. DPMH notes that the racial distribution of the study population (43% white, 34% black, 22% Hispanic, 1% Asian) was representative of the Houston metropolitan area but is not fully representative of the U.S. pediatric population. Blacks were overrepresented in the study population compared to the U.S. pediatric population (34% vs. 14%) and Asians were underrepresented in the study population compared to the U.S. pediatric population (1% vs. 5%)

DPMH Comment 3:

The sponsor estimated the prevalence of non-obese hypertension (49%) from a retrospective cohort study which found a 0.3% prevalence of hypertension among pediatric patients 3 years to 17 years of age receiving well-child care in community-based practices and having 1 or more outpatient visits between July 1, 2007 and December 31, 2009 with an initial (index) BP measurement.[27] Follow-up BP measurements obtained in the index cases at subsequent outpatient visits were used to classify hypertension per the NHBPEP guidelines over a total follow-up period of 3.5 years. The authors found the prevalence of patients with normal BPs,

[26] Swartz SJ, Srivaths PR, Croix B, et al. Cost-Effectiveness of Ambulatory Blood Pressure Monitoring in the Initial Evaluation of Hypertension in Children. Pediatrics 122: 1177-1181, 2008.

[27] Lo JC, Sinaiko A, Chandra M, et al. Prehypertension and Hypertension in Community-Based Pediatric Practice. Pediatrics 131: e415-e424, 2013.

pre-hypertension, and hypertension to be 83.4%, 12.0%, and 0.3% (257/85,780), respectively. The sponsor's prevalence estimate for non-obese hypertension of 49% (127/257) reflects the proportion of the study population who met the criteria for hypertension and had a BMI percentile < 85th for sex and age. Although the remaining 51% of hypertensive patients were obese, this publication did not specify if or how primary versus secondary causes of hypertension were distinguished among the hypertensive cohort. The data source for this study appropriately included large urban and suburban community populations from Northern California, Colorado, and Minnesota. However, 37.9% (4,109) of pediatric patients with a BP reading ≥ 95th percentile for sex, age, and height at the index visit did not have subsequent BP measurements taken during the follow-up period and were, therefore, not included in the prevalence estimate; 65% of these patients were less than 12 years of age. Compared with patients with follow-up measurements, a slightly greater proportion of those without follow-up BP were overweight or obese (52.3% vs 48.5%, P < 0.01).

This study may underestimate the true prevalence of pediatric hypertension in this population, particularly among younger pediatric patients because more than 1/3 of patients with an elevated BP at the index visit were excluded from the final analysis due to the lack of repeated BP measurements in the follow-up period.

DPMH Comment 4:

The sponsor estimated the prevalence of primary hypertension as 89% from a claims-based analysis of pediatric use of antihypertensive drugs in 2008 using data from a national commercial insurer.[10] Using de-identified inpatient, outpatient, physician, and pharmacy claims data from Ingenix's UnitedHealth Group Analytics Platform database, the authors identified 1.45 million children less than 18 years of age in the database who had had continuous coverage for both medical and pharmacy benefits for the entire year. The authors included pediatric patients whose hypertension episode started prior to or in 2008 and analyzed their drug utilization in 2008 only. The authors used ICD-9 codes for primary hypertension to define patients with primary hypertension and considered all other hypertensive pediatric patients to have secondary hypertension. With their approach, the authors found that the prevalence of primary and secondary hypertension was 0.18% (2607/1.4 million) and 0.02% (308/1.4 million), respectively. The combined prevalence rate was 0.20%. Results showed the percentage of all pediatric patients with hypertension who used an antihypertensive drug was highest in those 0 to less than 6 years of age (44.3%), followed by those 12 years to less than 18 years of age (38.1%), and then by those 6 years to less than 12 years of age (30.9%). Angiotensin-converting enzyme inhibitors (ACEi) were the most commonly used antihypertensive drug class in all pediatric age groups, and lisinopril was the most commonly used ACEi.

This study's strength appears to be the ability of the claims-based data to allow a more precise collection of the specific antihypertensive drug prescribed, the drug dosage, and the prescription date in to inform detailed analyses of antihypertensive drug utilization patterns in the study cohort. However, the prevalence estimates for pediatric hypertension in this study are likely an underestimate for several reasons. First, the study's reliance on ICD-9 codes for diagnoses of primary hypertension, rather than through direct BP measurements, is problematic given the

extent of under diagnosis of hypertension on this basis as noted in at least one publication widely referenced by the sponsor.[20] *Second, the authors used a less rigorous definition for hypertension, including for primary and secondary hypertension, than that recommended by the NHBPEP. Third, the results may not adequately represent the U.S. pediatric population demographically and socioeconomically since the study population was limited to those with private health insurance provided by a single national commercial insurer. Since the data were derived from health insurance claims, data on race and ethnicity were not included for analyses.*

V. Conclusions

DPMH has reviewed the sponsor's amended estimates for the prevalence of pediatric hypertension and disagrees with the sponsor's conclusion that the estimate of the prevalence is less than 200,000.

Based on an independent review of available published and other publicly available data, DPMH's calculated combined prevalence of primary pediatric hypertension (1,265,495) and secondary pediatric hypertension (590,304-927,309) exceed the maximum of 200,000 required for orphan designation. These estimates are based on 2014 U.S. census data and peer-reviewed published data that were available to the sponsor prior to their May 5, 2015 re-submission.

VI. Recommendations

DPMH recommends the following:

1. Removal of the orphan designation granted to Silvergate Pharmaceutical's lisinopril oral solution. DPMH further recommends that orphan designation for this product should be removed prior to the PDUFA date of April 30, 2016.

2. Removal of any existing orphan designations for therapies intended to treat pediatric hypertension granted for pediatric hypertension after February 2014 based on availability of published prevalence data of childhood obesity in the United States at that time.

3. Future requests for orphan designation of therapies intended for treatment of pediatric hypertension should be declined unless additional data are shared providing conclusive evidence that the prevalence of pediatric hypertension is less than 200,000.

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/s/

MONA K KHURANA
03/24/2016

LYNNE P YAO
03/24/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 2, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 208401
Product Name and Strength:	Qbrelis (Lisinopril) Oral Solution, 1 mg/mL
Submission Date:	January 19, 2016
Applicant/Sponsor Name:	Silvergate Pharmaceuticals, Inc.
OSE RCM #:	2015-1748-2
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Qbrelis submitted on January 19, 2016 for the risk of medication error (Appendix A). The revisions are in response to our previous review of the labels and labeling for the proposed Qbrelis (Lisinopril) oral solution (See DARRTS Labeling Reviews dated 10/9/2015 and and 12/7/2015).[1,2]

[1] Gao, Tingting. Label and Labeling Review for (b) (4) (Lisinopril) oral solution (NDA 208401). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 9. RCM No.: 2015-1748.

[2] Thomas, Sarah. Label and Labeling Review for Qbrelis (Lisinopril) oral solution (NDA 208401). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 7. RCM No.: 2015-1748-1.

2 CONCLUSION

Silvergate Pharmaceuticals, Inc. incorporated the majority of our recommendations from the previous reviews, with the exception of not removing the statement "Ready to Use". Silvergate stated they would like to retain this statement to clarify that no additional manipulation of the product is required and to distinguish this product from another Silvergate marketed product Epaned (enalapril maleate) Powder for oral solution. Upon discussion with the Review Division, we find Silvergate's rationale acceptable.

Additionally, Silvergate Pharmaceuticals, Inc. made further formatting changes to the container label and our review identified one additional area for improvement. Therefore, we provide the recommendation in Section 3 to Silvergate Pharmaceuticals, Inc.

3 RECOMMENDATIONS FOR SILVERGATE PHARMACEUTICALS, INC.

We recommend the following be implemented for the container label prior to approval of this NDA:

A. 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.[3]

[3] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

APPENDIX A. LABEL AND LABELING SUBMITTED ON JANUARY 19, 2016

Container Label

Carton Labeling

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

/s/

SARAH E THOMAS
02/02/2016

CHI-MING TU
02/02/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 7, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 208401
Product Name and Strength:	Qbrelis (Lisinopril) Oral Solution, 1 mg/mL
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Silvergate Pharmaceuticals, Inc.
Submission Date:	September 30, 2015, and October 16, 2015
OSE RCM #:	2015-1748-1
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

We previously reviewed labels and labeling for the proposed Lisinopril oral solution, 1 mg/mL, product and provided comments on container label, carton labeling, and prescribing information (See DARRTS Labeling Review dated 10/9/2015)[1]. Because the Applicant submitted updated container label and carton labeling with the newly proposed name Qbrelis on October 16, 2015, this review evaluates the proposed updated Qbrelis container label and carton labeling submitted on October 16, 2015, and re-reviewed prescribing information submitted on September 30, 2015 for risk of medication error.

This NDA is a 505(b)(2) application and the reference listed drug is Zestril tablets (NDA 019777).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other – Literature	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Lisinopril is currently available as oral tablets with the following strengths: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg. Silvergate Pharmaceuticals is proposing a lisinopril oral solution, a new dosage form, with a proposed strength of 1 mg/mL. We find the proposed concentration 1 mg/mL in a 150 mL bottle acceptable from a medication error perspective based on the following reasons:

1. A 150 mL bottle will provide a 30 day supply based on the labeled dose of 0.07 mg per kg once daily (up to 5 mg total) [and then dose is adjusted according to blood pressure response up to a maximum of 0.61 mg per kg (up to 40 mg) once daily] for pediatric patients 6 years of age and older with hypertension and GFR> 30 mL/min/1.73 m^2.
2. The proposed concentration of 1 mg/mL is consistent with the 1 mg/mL concentration of existing compounded Lisinopril oral liquids that pharmacies would make from approved tablets for young patients who cannot swallow tablets.[2]

[1] Gao, Tingting. Label and Labeling Review fo (b) (4) (Lisinopril) oral solution. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 9. RCM No.: 2015-1748.

[2] Strickley RG et al. Pediatric drugs--a review of commercially available oral formulations. J Pharm Sci. 2008 May;97(5):1731-74.

We reviewed the proposed prescribing information and believe that it can be improved to promote the safe use of the product. For example, the frequency of administration is not provided for some of the dosing regimens and the route of administration is not specifically stated in the Highlights section of the PI or the full PI, potentially causing confusion related to appropriate dosing. Next, the error-prone symbol "<" is present in the dosage and administration section of the full PI, and this symbol is at risk of misinterpretation as the opposite meaning of its intended meaning.[3,4] In addition, a description of the oral solution is lacking in sections 3 and 16.

In the full PI, the error-prone symbol (b) (4) is present in section 16, which is listed on the ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations as an abbreviation that is frequently misinterpreted and involved in harmful medication errors.[3,4] Also, there is lack of consistency in storage information provided on the container label/carton labeling compared to what is provided in section 16 of the full PI. In addition, non-affirmative language is used in one statement in section 17, which may potentiate inappropriate use if the word (b) (4)" is missed while the end-user is reading the patient counseling information.[3]

Our review of the updated Qbrelis container label and carton labeling found that they can also be improved to promote the safe use of the product. We note the statement "Ready to use" on the container label and carton labeling, which appears promotional in nature and does not add to the usage instruction for this product. Also, we note the statement "Dispense in its original container with the child-resistant closure" on the container label and carton labeling. We clarified with the Product Quality Reviewer to confirm if this statement is accurate. The Product Quality Reviewer responded and explained that the container closure system appears to be a HDPE bottle with a child-resistant cap with a foam liner and lift and peel induction seal. The Product Quality Reviewer believes that the intent of the statement "Dispense in its original container with the child-resistant closure" is for keeping the product in its original packaging to ensure it retains the child-resistant feature. However, since the labeled dose for pediatric patients 6 years of age and older with hypertension and GFR> 30 mL/min/1.73 m^2 is 0.07 mg per kg once daily (up to 5 mg total) [and then dose is adjusted according to blood pressure response up to a maximum of 0.61 mg per kg (up to 40 mg) once daily], it is possible that the pediatric patients may not need the full 150 mL bottle for the prescribed quantity. Since pharmacies may dispense the prescribed amount in a smaller container with a child-resistant cap, the statement "Dispense in its original container with the child-resistant closure" is not necessary and we recommend removing this statement from the container label and carton labeling.

In terms of the container label specifically, the principal display panel (PDP) is too crowded and lacks white space, thus decreasing readability of important information on the PDP.[3] In addition, the statement (b) (4) " is misleading as the (b) (4)" section in the proposed prescribing information does not communicate complete directions for use. In terms of the carton labeling specifically, the word (b) (4)" is not necessarily needed to identify the (b) (4) Also, non-affirmative language is used in one statement found on the carton labeling, which may potentiate inappropriate use if the word "not" is missed while the end-user is reading the labeling.[3]

[3] 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.

[4] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Nov 12]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling for Qbrelis may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Container Label and Carton Labeling
    1. We defer to the Review Team on removing 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. See Appendix H for our recommendations in tracked changes for Prescribing Information (PI)

4.2 RECOMMENDATIONS FOR SILVERGATE PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. General Recommendations for Container label and Carton labeling:
    1. As currently presented in the proposed Prescribing Information section 16, the storage information provides that the product should be stored at "controlled room temperature 20°C-25°C (68°F-77°F) [see USP]…," versus stored at (b) (4) on the container label and carton labeling. We recommend providing clarification and revision of the storage information provided in section 16 and on the container label and carton labeling to ensure consistency of this information across labeling.
    2. Ensure the actual barcode is provided in the indicated place-holder on the container label and carton labeling.
    3. Since the proposed pediatric dosing 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) so that pharmacies may dispense the prescribed amount in a smaller container, which is usually capped with a child-resistant closure.
B. Container label
    1. As currently presented, the principal display panel (PDP) is too crowded and lacks white space, thus decreasing readability for important information on the PDP. [3] 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.
    2. The statement (b) (4) is misleading as the (b) (4)" section in the proposed prescribing information does not communicate complete directions for use. Revise this statement so it's not misleading, or remove this statement from the side panel.
C. Carton labeling
    1. Remove the word (b) (4) KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN."
    2. Non-affirmative language is used in the following statement present on the carton labeling: (b) (4) Therefore, we recommend changing

the phrase to an affirmative statement as follows: “Ensure seal is present and intact before using.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Qbrelis contained in the prescribing information that Silvergate Pharmaceuticals submitted on September 30, 2015, as well as product information for Zestril, the listed drug (LD).

Table 2. Relevant Product Information for Qbrelis and the Listed Drug		
Product Name	**Qbrelis**	**Zestril (NDA 019777)**
Initial Approval Date	N/A	May 19, 1988
Active Ingredient	Lisinopril	
Indication	• Treatment of hypertension in adults and pediatric patients 6 years of age and older • Adjunct therapy for heart failure • Reduction of mortality in acute myocardial infarction	
Route of Administration	Oral	
Dosage Form	Oral solution	Tablets
Strength	1 mg/mL	2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg
Dose and Frequency	**Hypertension:** Initial adult dose is 10 mg once daily, and then adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose, with doses of up to 80 mg used but do not appear to give greater effect. Initiate patients on diuretics at 5 mg once daily. Pediatric patients 6 years of age and older with glomerular filtration rate >30 mL/min/1.73m^2: Initial dose is 0.07 mg per kg once daily (up to 5 mg total), and then adjusted according to blood pressure response up to a maximum of 0.61 mg per kg (up to 40 mg) once daily. **Heart Failure:** Initiate with 5 mg once daily when used with diuretics and (usually) digitalis as adjunctive therapy, and increase as tolerated to a maximum dose of 40 mg once daily. The recommended starting dose for these patients with hyponatremia (serum sodium <130 mEq/L) is 2.5 mg daily. **Acute Myocardial Infarction (MI):** Give 5 mg in hemodynamically stable patients within 24 hours of MI, followed by 5 mg after 24 hours, then 10 mg after 48 hours and then 10 mg once daily; Initiate therapy with 2.5 mg in patients with a low systolic blood pressure (≤ 120 mmHg and > 100 mm Hg) during the first 3 days after the infarct. If hypotension occurs (systolic blood pressure ≤ 100 mmHg), a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure < 90 mmHg for more than 1 hour) Qbrelis & Zestril should be withdrawn. **Renal Impairment:** For patients with creatinine clearance ≥ 10 mL/min and ≤30 mL/min, reduce the initial dose to half of the usual recommended dose- i.e., hypertension, 5 mg; systolic heart failure, 2.5	

	mg and acute MI, 2.5 mg. Up titrate as tolerated to a maximum of 40 mg daily. For patients with creatinine clearance < 10 mL/min or on hemodialysis, the recommended initial dose is 2.5 mg once daily.	
How Supplied	150 mL high-density polyethylene (HPDE) bottle with a child-resistant cap	Bottles of 90 and 100 count
Storage	Per section 16, the storage information provides that the product should be stored at "controlled room temperature 20°C-25°C (68°F-77°F) [see USP]…," (b) (4) on the container label and carton labeling. Protect from freezing and excessive heat.	20-25°C (68-77°F) [see USP]. Protect from moisture, freezing and excessive heat. Dispense in a tight container.
Container Closure	High-density polyethylene (HPDE) bottle with a child-resistant cap.	Bottle

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 17, 2015, we searched the L:drive and AIMS using the term, Lisinopril, to identify reviews previously performed by DMEPA.

B.2 Results

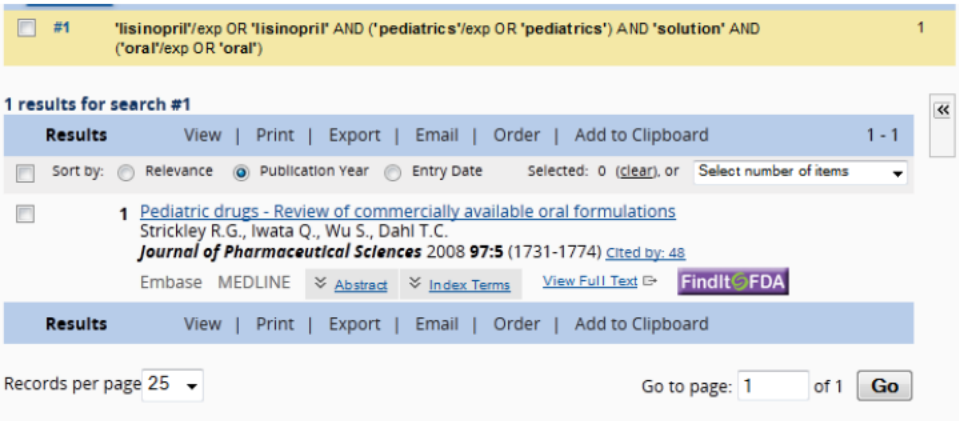
Our search identified one relevant previous review[5], and we evaluated this previous review for applicable recommendations that should be included in this current review.

[5] Gao, Tingting. Label and Labeling Review for (b) (4) (Lisinopril) oral solution. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 9. RCM No.: 2015-1748.

APPENDIX F. Literature

F.1 Methods

We searched the Embase on August 26, 2015 using the criteria listed in yellow highlighted row below:



F.2 Results

This search retrieved one article[6]. We evaluated this article in detail and pulled the following relevant information that may inform our review.

Table 3. (*Continued*)

Drug Name/Marketed Name	Marketed Formulation/Storage	Active in Formulation	Dose	Inactive in Formulation (as Listed in Package Insert or PDR)	Manipulation	Company/Indication

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Lisinopril is available in 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg strength tablets. Lisinopril has been studied in patients greater than 6 years of age at dose of 0.1–0.2 mg/kg, and the recommended starting dose is 0.07 mg/kg once daily up to 5 mg total daily. (b) (4)

(b) (4)

[6] Strickley RG et al. Pediatric drugs--a review of commercially available oral formulations. J Pharm Sci. 2008 May;97(5):1731-74.

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/s/

SARAH E THOMAS
12/07/2015

CHI-MING TU
12/07/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 9, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 208401
Product Name and Strength:	(b) (4) (Lisinopril) Oral Solution, 1 mg/mL
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Silvergate Pharmaceuticals, Inc.
Submission Date:	June 30, 2015 and September 30, 2015
OSE RCM #:	2015-1748
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

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/s/

TINGTING N GAO
10/09/2015

CHI-MING TU
10/09/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: 208401

Application Type: New NDA

Name of Drug/Dosage Form: (b) (4) (Lisinopril) Oral Solution

Applicant: Silvergate Pharmaceuticals, Inc.

Receipt Date: June 30, 2015

Goal Date: April 30, 2016

1. Regulatory History and Applicant's Main Proposals

A pre-IND (PIND 116486) meeting was requested by the Applicant in September 2012 to discuss the development of Lisinopril oral solution for the treatment of hypertension in adults patients and pediatric patients 6 years and older, the (b) (4) signs and symptoms of systolic heart failure, and the reduction of mortality in the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction. After receiving the Division's preliminary comments on November 2012, the Applicant elected to cancel the meeting.
The Applicant intends to follow a 505(b)(2) pathway using Zestril® tablets as the reference listed drug (NDA 19777). Clinically, the Applicant relies on two randomized, open-label, single-dose, 2-period, 2-treatment, 2-way crossover studies conducted under fasted (SG03-01) and fed (SG03-02) conditions to compare the rate of absorption and oral bioavailability of Lisinopril Oral Solution to Zestril® tablet.

2. Review of the Prescribing Information

This review is based on the Applicant's submitted Word format of the prescribing information (PI). The Applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

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.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the Applicant in the 74-day letter. The Applicant will be asked to correct these deficiencies and

resubmit the PI in Word format by October 02, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

NO 12. All text in the BW must be **bolded**.

Comment: *Only the heading was bolded.*

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

NO 14. The BW 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 is aligned to the left and not centered*

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.****"*).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

SABRY SOUKEHAL
09/10/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208401	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: (b) (4) (proposed) Established/Proper Name: Lisinopril Dosage Form: Solution Strengths: 1mg/ml		
Applicant: Silvergate Pharmaceuticals, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: June 30, 2015 Date of Receipt: June 30, 2015 Date clock started after UN: n/a		
PDUFA/BsUFA Goal Date: April 30, 2016	Action Goal Date (if different): n/a	
Filing Date: August 29, 2015	Date of Filing Meeting: August 12. 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): - Treatment of hypertension in adults patients and pediatric patients 6 years and older - (b) (4) heart failure - (b) (4) treatment of (b) (4) acute myocardial infarction		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): PIND 116486	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***		☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☒ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	n/a			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	Although not required because the submission is electronic, a field copy certification was included.
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	An agreed iPSP will be reached under the NDA.
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4]

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☐	☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☒	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 30, 2012 ***If yes, distribute minutes before filing meeting***	☒	☐		Pre-IND 116486 meeting minutes
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 12, 2015

BACKGROUND: Lisinopril Oral Solution is an ACE inhibitor developed by Silvergate Pharmaceuticals, Inc. for the treatment of hypertension in adult patients and pediatric patients 6 years and older to lower blood pressure as well as for the (b) (4) 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.
This Application intends to follow a 505(b)(2) pathway utilizing Zestril® (lisinopril) tablets (NDA 19777) as the reference listed drug.
A type B pre-IND meeting was requested by the Applicant in September 2012 (Pre-IND 116486). The Division provided preliminary responses on November 2012. Because the Division's responses adequately addressed Silvergate's questions, the meeting was subsequently cancelled.
Two randomized, open-label, single-dose, 2-period, 2-treatment, 2-way crossover studies were conducted under fasted (SG03-01) and fed (SG03-02) conditions to compare the rate of absorption and oral bioavailability of Lisinopril Oral Solution to Zestril tablet. Those studies serve as a basis for this NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sabry Soukehal	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Division Director/Deputy	Norman Stockbridge (Director)		Y
Office Director/Deputy			
Clinical	Reviewer:	n/a	
	TL:		
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Peter Hinderling	Y
	TL:	Raj Madabushi	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Ququan Liu	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elizabeth Hausner	Y
	TL:	Thomas Papoian	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Wendy Wilson	Y
	RBPM:	Maryam Changi	Y
• Drug Substance	Reviewer:	Rao Kambhampati	N
• Drug Product	Reviewer:	Rao Kambhampati	N
• Process	Reviewer:	Sung Kim	N
• Microbiology	Reviewer:	Vinayak Pawar	N
• Facility	Reviewer:	Ebern Dobbin	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Zarna Patel	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Tingting Gao	N
	TL:		
OSE/DRISK (REMS)	Reviewer:	Donella Fitzgerald	Y

	TL:	Kimberly Lehrfeld	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
OSE/DPV1	Reviewer:	Amy Chen	Y
	TL:		
Other attendees	Stephen Grant (Deputy Director)		Y
	Alexis Childers (Senior Regulatory Health Project Manager)		Y
	Brian Proctor (Regulatory Health Project Manager)		Y
	Tri Nguyen (OSE Project Manager)		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO The Applicant submitted study reports on the bioequivalence of (b) (4) and Zestril in fasted (study SG03-01) and fed (study SG03-02) healthy adults.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Due to the nature and contents of the submission, the site inspection will be requested by the clinical pharmacology group.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety***	☐ YES Date if known: ☐ ☒ NO ☐ To be determined Reason:

or efficacy issues ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	 ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO

• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Norman Stockbridge, MD, PhD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): around December 3, 2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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
08/29/2015