CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208686Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3.5.2 Patent Certification

Certification of No Relevant Patents

Pursuant to 21 USC § 355(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50(i)(1)(ii), in the opinion of and to the best knowledge of Silvergate Pharmaceuticals, Inc., there are no patents that claim the drug, Vasotec® tablets (NDA 018998), on which investigations that are relied upon in this application were conducted or that claim a use of such drug.

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

11/3/15
Date

Department of Health and Human Services
Food and Drug Administration

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

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

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

NDA NUMBER
208686

NAME OF APPLICANT/NDA HOLDER
Silvergate Pharmaceuticals, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)
Epaned® (b) (4)

ACTIVE INGREDIENT(S)	STRENGTH(S)
enalapril maleate	1 mg/mL

DOSAGE FORM
Oral solution

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

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

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

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

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

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

PSC Publishing Services (301) 443-6740 EF

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

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

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Michael C Beckloff	11/24/2015

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

Check applicable box and provide information below.

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

Name Michael C. Beckloff	
Address 7300 W 110th St, Ste 950	City/State Overland Park, KS
ZIP Code 66210	Telephone Number 913.707.3955
FAX Number *(if available)* 913.871.0168	E-Mail Address *(if available)* michael.beckloff@silvergatepharma.com

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

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

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

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

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

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

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

First Section

Complete all items in this section.

1. General Section

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

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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

2. Drug Substance (Active Ingredient)

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

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

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

4.2a) Identify the precise words of the approvel labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

EXCLUSIVITY SUMMARY

NDA # 208686 SUPPL # -- HFD # 110

Trade Name Epaned

Generic Name Enalapril maleate

Applicant Name Silvergate Pharmaceuticals, Inc.

Approval Date, If Known September 20, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

The application relied on the Agency's previous finding of safety and effectiveness for the reference listed drug, Vasotec® (enalapril maleate) tablets (NDA 018998, approved December 24, 1985), distributed by Valeant Pharmaceuticals North America, LLC.
In support of this application, the applicant submitted a report for a study (SG04-01) that investigated the relative bioavailability of 10 mg Epaned (b) (4), 1 mg/mL, vs. 10 mg Epaned Powder for Oral Solution (Reconstituted), 1 mg/mL, under fasted conditions in healthy adults.

If it is a supplement requiring the review of clinical data but it is not an effectiveness

supplement, describe the change or claim that is supported by the clinical data:

--

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

Of note, the applicant requested 7 years of exclusivity at the time of NDA submission as Epaned was granted orphan designation for the treatment of hypertension in pediatric patients 0 to 16 years of age in 2013. During the review cycle, orphan designation was revoked on April 28, 2016, as the prevalence of pediatric hypertension was found to exceed the statutory threshold of 200, 000 persons.

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

YES ☐ NO ☒

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

--

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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

NDA# 018998 Vasotec®

NDA# 204308 Epaned (Powder for Oral Solution)

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of

new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

Investigation #2 !
!
IND # YES ☐ ! NO ☐

! Explain:

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Sabry Soukehal
Title: Regulatory Project Manager
Date: August 24, 2016

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

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

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

/s/

SABRY SOUKEHAL
09/20/2016

NORMAN L STOCKBRIDGE
09/20/2016

1.3.3 Debarment Certification

Silvergate Pharmaceuticals, Inc. (Silvergate), hereby certifies that it did not, and will not, use, in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act (the Act) in connection with this application.

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

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

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

11/3/15
Date

Bui Nguyen, Tri

From: Bui Nguyen, Tri
Sent: Friday, January 15, 2016 1:36 PM
To: michael.beckloff@silvergatepharma.com
Cc: susan.prather@silvergatepharma.com; Flowers, Louis; Bui Nguyen, Tri
Subject: FW: Clarification from Sponsor Regarding Proposed Proprietary Name for NDA 208686

Importance: High

Dear Ms. Prather:

To aid us in completing this review, we requested you clarify what is the proposed name, "Epaned" versus (b) (4)

Given our review timelines please submit an amendment for documentation no later than the close of business **Wednesday, January 20, 2016.**

Include the statement "**AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below).

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

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

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

Best Regards,

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov
Office: (240) 402-3726

From: Susan Prather [mailto:susan.prather@silvergatepharma.com]
Sent: Thursday, January 14, 2016 12:33 PM
To: Flowers, Louis; Michael Beckloff
Cc: Bui Nguyen, Tri
Subject: Re: Clarification from Sponsor Regarding Proposed Proprietary Name for NDA 208686

Good morning Dr. Flowers,

This is to confirm receipt of your request and also in follow-up to my phone message.
I would like some clarification on your request and would appreciate discussing it with you.
I can be reached at 913-871-1230 or (b) (6) (cell).
Thank you and I look forward to speaking with you.

Best regards,
Susan

Susan J. Prather
Director Regulatory Affairs
Silvergate Pharmaceuticals, Inc.
7300 W. 110th Street, Suite 950
Overland Park, KS 66210
913.871.1230
(b) (6)
susan.prather@silvergatepharma.com

From: Flowers, Louis <Louis.Flowers@fda.hhs.gov>
Sent: Thursday, January 14, 2016 9:57 AM
To: Michael Beckloff
Cc: Bui Nguyen, Tri; Susan Prather
Subject: Clarification from Sponsor Regarding Proposed Proprietary Name for NDA 208686

Dear Mr. Beckloff:

Please refer to your NDA 208686 for Enalapril maleate Oral Solution, 1 mg/mL.

We also refer to your correspondence, dated and received December 18, 2015, requesting review of your proposed proprietary name, Epaned (enalapril maleate) Oral Solution, 1mg/ml.

Your submission listed the proposed name in two different ways: “Epaned” on the cover letter versus (b) (4) in the submission.

In looking at the container label below, it appears the name you want would be “Epaned”. Would you please clarify, what is the proposed name?

-Per Cover Letter document:

Dear Dr Stockbridge:

Reference is made to the original NDA for Epaned® (enalapril maleate) Oral Solution, 1 mg/mL, submitted by Silvergate Pharmaceuticals, Inc. (Silvergate) on November 24, 2015, for the treatment of hypertension in adult patients and children older than 1 month, the treatment of symptomatic heart failure, and the treatment of asymptomatic left ventricular dysfunction, to decrease the rate of development of overt heart failure and reduce hospitalization for heart failure.

The purpose of this submission is to request a proprietary name review of the primary proposed proprietary name, Epaned (enalapril maleate) Oral Solution, 1 mg/mL

-Per Request for Proprietary Name Review document:

1.1.1 Names for Proprietary Name Review

Proposed primary proprietary name: EPANED (b) (4)

-Per Container Label:

(b) (4)

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

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

/s/

TRI M BUI NGUYEN
01/15/2016

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

Application: NDA 208686

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Epaned (b) (4) (enalapril maleate) 1mg/mL

Applicant: Silvergate Pharmaceuticals, Inc.

Receipt Date: November 24, 2015

Goal Date: September 24, 2016

1. Regulatory History and Applicant's Main Proposals

A pre-IND (PIND 125621) meeting was requested by the Applicant in February 2015 and held on April 2015, to discuss the approval pathway and requirements for the development of the ready-to-use Epaned (b) (4) 1mg/mL for the treatment of hypertension in adults and children older than 1 month and for symptomatic heart failure and asymptomatic left ventricular dysfunction in adults.

The Applicant intends to follow a 505(b)(2) pathway using Vasotec® tablets as the reference listed drug (NDA 18998). The Applicant is also cross-referencing NDA 204308 for Epaned Powder for Oral Solution.

Clinically, the Applicant relies on data from study SG04-01, conducted as a randomized, single-dose, 2-way crossover study in 32 healthy adults. The objective of the study was to assess the bioavailability of single-dose administration of Epaned (b) (4) to Epaned Powder for Oral Solution reconstituted, under fasted conditions.

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

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), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

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 for HL format.

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. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

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

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment: *The first item in HL does not fully match the text in section 4. "A history of angioedema" was omitted from the text in HL.*

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. 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 (or will have)** 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 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. 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 26. The same title 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 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. 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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**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 32. 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)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"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 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

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

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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
01/27/2016

1.3.2 Field Copy Certification

In accordance with FDA *Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (May 2015), Silvergate Pharmaceuticals, Inc., asks that the Electronic Document Room forward an electronic copy of this submission to:

Denver District
Food and Drug Administration
6th Ave and Kipling St
Bldg 20
Denver Federal Center
Denver, CO 80225

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

/s/

JONATHAN T DOW
10/14/2016

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2015. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm

1. APPLICANT'S NAME AND ADDRESS

SILVERGATE PHARMACEUTICALS INC
Wayne Vallee
6251 Greenwood Plaza Blvd.
Suite 101
Greenwood Villiage
CO 80111
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

208-686

2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE

913-661-3813

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[ ] YES [X] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

Epaned (Enalapril Maleate Oral Solution)

6. USER FEE I.D. NUMBER

PD3015533

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? [ ] YES [X] NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food,Drug, and Cosmetic Act

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

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

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

Privacy Act Notice:

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

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information,

including suggestions for reducing this burden to:

Department of Health and Human Services **Food and Drug Administration** **Center for Biologics Evaluation and Research** **Office of Information Management (HFA-710)** **8455 Colesville Road, COLE-14-14253** **Silver Spring, MD 20993-0002**	**Department of Health and Human Services** **Food and Drug Administration** **Center for Drug Evaluation and Research** **Office of Information Management (HFA-710)** **8455 Colesville Road, COLE-14-14253** **Silver Spring, MD 20993-0002**	**An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.**

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Mark C Benkoff	Chief Development officer	11/3/15

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$1,187,100.00

Form FDA 3397 (08/13)

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

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

NOTE: Form FDA 3397 need not be submitted for:

CDER

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

CBER

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

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

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

	pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	WAIVER: Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.

Form FDA 3397 (08/13) (BACK)

Close Print Cover sheet

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208686

NDA ACKNOWLEDGMENT

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

Dear Mr. Beckloff:

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

Name of Drug Product: Epaned® (Enalapril maleate, USP) (b) (4), 1mg/mL

Date of Application: November 24, 2015

Date of Receipt: November 24, 2015

Our Reference Number: NDA 208686

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 23, 2016, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
12/03/2015

Bui Nguyen, Tri

From: Bui Nguyen, Tri
Sent: Tuesday, December 08, 2015 9:55 AM
To: michael.beckloff@silvergatepharma.com
Cc: Soukehal, Sabry; Bui Nguyen, Tri
Subject: NDA 208686 PNR request

Importance: High

Dear Mr. Beckloff:

Please refer to your NDA 208686 for Enalapril maleate (b) (4), 1 mg/mL.

We also refer to your correspondence, dated and received November 24, 2015, requesting review of your original NDA. Your cover letter stated that the labeling relies on the approved labeling for Epaned Powder for Oral Solution (NDA 204308). You can cross reference the other application, NDA 204308, in your submission. However, if you want a Proprietary Name for this application, NDA 208686, you will need to treat this as a new name request per the guidance below.

If you intend to have a proprietary name for the above-referenced product, you should submit a request for proprietary name review, all labels and labeling (please refer to the complete submission guidance link below) within 14 days of this communication.

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

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

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

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

Best Regards,

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov

Office: (240) 402-3726

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/s/

TRI M BUI NGUYEN
12/08/2015

Bui Nguyen, Tri

From: Bui Nguyen, Tri
Sent: Monday, February 01, 2016 3:40 PM
To: Susan Prather; Flowers, Louis
Cc: Michael Beckloff; Soukehal, Sabry; Bui Nguyen, Tri
Subject: RE: NDA 208686, SN0003 Response to request for clarification of the proprietary name.

Importance: High

Dear Ms. Prather:

The review team notes that your Request for Proprietary Name Review for NDA 208686 Enalapril maleate oral solution, 1mg/mL, indicates [redacted] (b) (4) " as the proposed proprietary name. The proposed name contains [redacted] (b) (4)

To aid us in completing the review, please let us know by COB February 5, 2016 if you would like to amend your proposed proprietary name to "Epaned" [redacted] (b) (4)

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

Best Regards,

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov
Office: (240) 402-3726

From: Susan Prather [mailto:susan.prather@silvergatepharma.com]
Sent: Monday, January 18, 2016 3:43 PM
To: Flowers, Louis; Bui Nguyen, Tri
Cc: Michael Beckloff; Soukehal, Sabry
Subject: NDA 208686, SN0003 Response to request for clarification of the proprietary name.

Dear Dr. Flowers and Dr. Bui-Nguyen,

Attached is a copy of Silvergate's response to Dr. Flowers' request for clarification of the proprietary name for Epaned [redacted] (b) (4), and Dr. Bui-Nguyen's follow up email requesting a response by January 20, 2016. The

proprietary name requested is [redacted] (b) (4) I have attached a copy of the Amendment to the Request for Review of Proprietary name which will be submitted electronically to the NDA on January 26, 2016.
The additional time is necessary for linking and the publishing processes.

As discussed during my conversation with Dr. Flowers, we have revised the carton and bottle label to more clearly distinguish the proprietary name and the registered name. Please note that other labeling changes were made based upon comments received on another Silvergate product, Qbrelis, NDA 208401, also under current FDA review, (e.g., more white space to primary panel, representative bar code for spacing purposes, etc.).

If you have any questions or need any additional information, please contact me or Michael Beckloff.
Thank you,

Best regards,
Susan

Susan J. Prather
Director Regulatory Affairs
Silvergate Pharmaceuticals, Inc.
7300 W. 110th Street, Suite 950
Overland Park, KS 66210
913.871.1230
[redacted] (b) (6)
susan.prather@silvergatepharma.com

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/s/

TRI M BUI NGUYEN
02/01/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208686	NDA Supplement # --	If NDA, Efficacy Supplement Type: -- *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Epaned Established/Proper Name: Enalapril Maleate Dosage Form: Solution		Applicant: Silvergate Pharmaceuticals, Inc. Agent for Applicant (if applicable): Michael C. Beckloff
RPM: Sabry Soukehal		Division: Cardiovascular and Renal Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☒ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: August 15, 2016

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 24, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5 (new formulation)
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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

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

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

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval, September 20, 2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	• Letter: 03/07/16 • Review: 03/03/16
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 01/27/16 DMEPA: 04/20/16, 06/27/16 DMPP/PLT (DRISK): ☒ None OPDP: 8/28/16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM reviews: 1/22/16, 9/20/16 505 (b)(2): 9/14/16
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 08/17/16 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	12/03/15, 12/08/15, 1/15/16, 2/01/16, 2/04/16 (two), 2/12/16, 3/31/16, 6/08/16, 6/29/16, and 8/17/16.
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	8/24/16
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	4/16/15
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	9/19/16
Cross-Discipline Team Leader Review *(indicate date for each review)*	9/16/16
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	N/A
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	In CDTL memo dated 9/16/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	8/17/16, 9/01/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	7/21/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	8/05/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	7/05/16 (stats)
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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

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/s/

SABRY SOUKEHAL
09/20/2016

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCT

NDA 208686 Memorandum

Date: August 24, 2016

On April 28, 2016, the Office of Orphan Products Development (OOPD) informed Silvergate Pharmaceuticals Inc. (the Applicant) that their orphan drug designation for the "treatment of hypertension in pediatric patients" (# 12-3767) granted on January 30, 2013 was revoked.

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

Attached are copies of the following:

- The letter dated January 30, 2013 granting the Applicant orphan designation.
- The letter dated April 08, 2016 informing the Applicant of OOPD's intent to revoke the orphan designation.
- The letter dated April 28, 2016 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
Building 32, Room 5271
10903 New Hampshire Avenue
Silver Spring, MD 20993

JAN 3 0 2013

Cardinal Health Specialty Solutions
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Attention: Todd Phillips, PharmD, RAC
US Resident Agent

Re: Designation request # 12-3767
Amendment dated: December 19, 2012
Amendment received: December 20, 2012

Dear Dr. Phillips:

Reference is made to your request submitted on behalf of Silvergate Pharmaceuticals, Inc. for orphan-drug designation of enalapril maleate for the "treatment of hypertension in pediatric patients under 12 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 ***enalapril maleate (powder for oral solution)*** is granted for the *treatment of hypertension in pediatric patients.* Please note that FDA defines pediatrics as children age 0 to 16 years of age. Please note that 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 C.F.R. 316.3(b)(3) & (13) (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 the already approved drug

Please note that if the above 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 final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please 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 (*see* 21 C.F.R. 316.30).

If you have questions regarding the development of your designated product, please feel free to contact Francesca Joseph, MD at 301-796-6805. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

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

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 # 12-3767

Dear Ms. Prather:

[redacted] (b) (4) for the use of enalapril for the treatment of hypertension in pediatric patients (enalapril's designation). Reference is also made to our designation letter dated January 30, 2013, and our letter of intent to revoke orphan designation dated April 8, 2016.

Our letter dated April 8, 2016, stated that upon reconsideration of enalapril'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, enalapril 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 enalapril'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 enalapril's designation for treatment of hypertension in pediatric patients, which was granted on January 30, 2013. Because enalapril 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 Rao

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

cc:

OOPD/File 12-3767
OOPD/Chron

History:
J. Fritsch 4/28/16
H. Startzman
G. Rao

REVOCATION

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/s/

SABRY SOUKEHAL
08/24/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208686

LABELING PMR/PMC DISCUSSION COMMENTS

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

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated November 24, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Epaned (b) (4) (Enalapril maleate), 1 mg/mL.

We also refer to our February 03, 2016, letter in which we notified you of our target date of August 17, 2016 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On July 19, 2016, we received your July 19, 2016, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by **August 24, 2016**. The resubmitted labeling will be used for further labeling discussions.

In addition we have the following comment:

CMC

Please update the SPL product description element to include mixed berry as the flavor in the product characteristics section.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE: Epaned (b) (4) Prescribing Information

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

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/s/

SABRY SOUKEHAL
08/17/2016

PeRC Meeting Minutes
August 17, 2016

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Meshaun Payne
Jackie Yancy
Robert "Skip" Nelson
Barbara Buch
Wiley Chambers
Thomas Smith
Yeruk Mulugeta
Freda Cooner
Gilbert Burkhart
Gerri Baer
Shrikant Pagay
Greg Reaman
Dianne Murphy
Raquel Tapia
Adrienne Hornatko-Munoz
Maura O'Leary
Rosemary Addy
Non Responsive (Ciprofloxacin and Enalapril only)
Lisa Faulcon

Agenda

9:00	Non Responsive				
9:20					
10:00					
10:20					
10:40					
11:00					
11:20	NDA 208686	Epaned (enalapril) Partial and Full Waiver	DCRP	Sabry Soukehal	1. Treatment of hypertension in adults and children older than one month, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. 2. Treatment of symptomatic heart failure. 3. Treatment of asymptomatic left ventricular dysfunction, to decrease the rate of development of overt heart failure and reduce hospitalization for heart failure.
11:35	Non Responsive				
11:35					
11:35					

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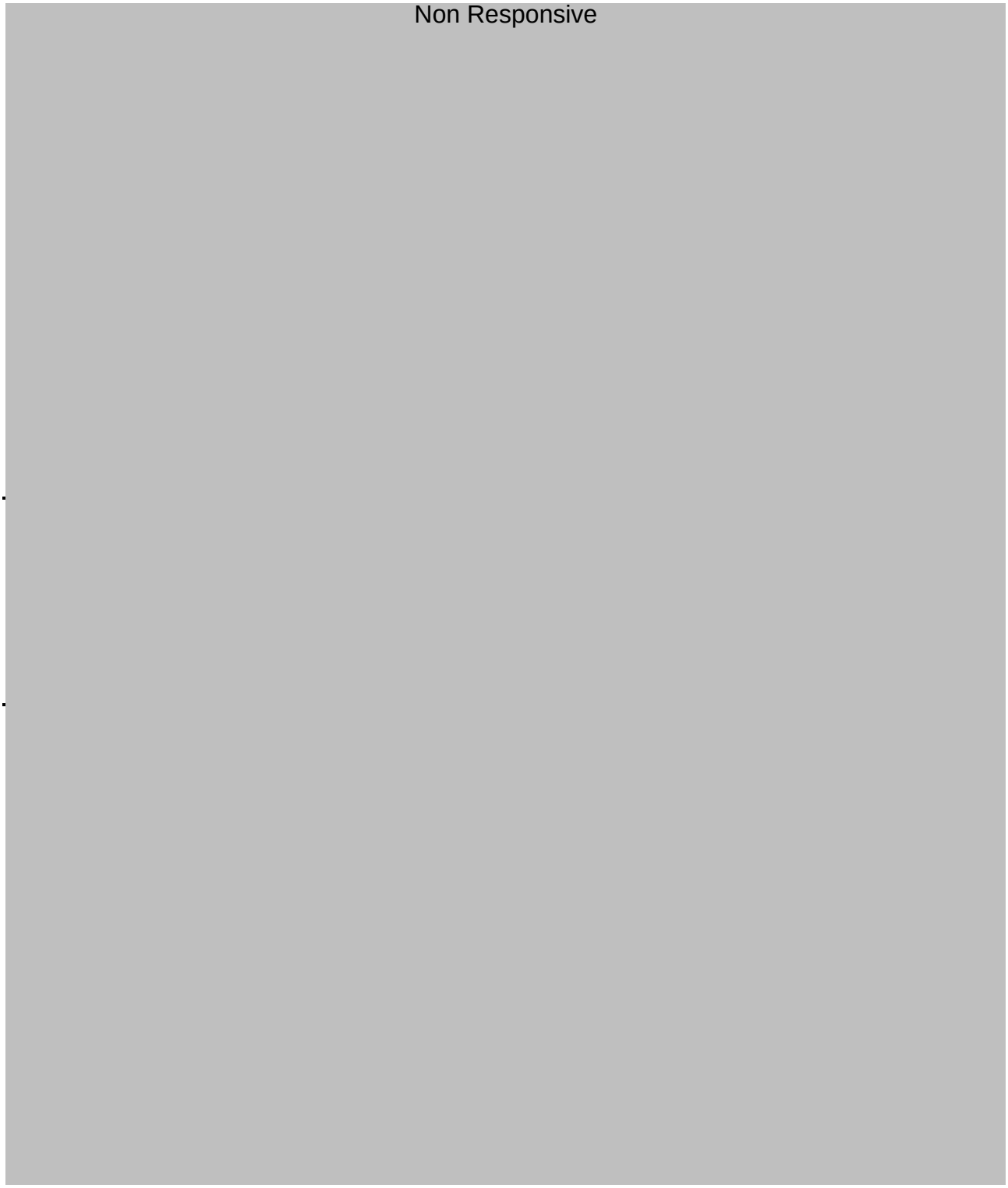

Epaned (enalapril) Partial and Full Waiver

- Proposed Indication: (1) Treatment of hypertension in adults and children older than one month, to lower blood pressure (2) Treatment of symptomatic heart failure (3) Treatment of asymptomatic left ventricular dysfunction

- This product triggers PREA as a new dosage form and has a PDUFA goal date of September 24, 2015.
- The PeRC asked whether we would consider issuing a WR for the sponsor to study in left ventricular dysfunction. The division noted that the data from the NIH study concluded that there was no benefit; however, this product and other ACE inhibitors are used commonly for pediatric heart failure. The PeRC acknowledged that it would be difficult to require this sponsor to study pediatric heart failure when there is already a failed study and it is not clear that pediatric heart failure studies are feasible. However, the PeRC continues to question which products should be studied and whether studies are feasible. The division recommended PeRC consider convening a workshop to address feasibility of pediatric heart failure studies as well as priorities for product development for this indication.
- The division clarified that the solution was bioequivalent to the reference product and that the excipients were reviewed and noted to be present in safe amounts.
- The division noted that labeling of the reference product is not consistent with other ACE inhibitors because the reference product includes an indication down to 1 month of age. Other ACE inhibitors have not been approved down to1 month of age because of the concern regarding effects of ACE inhibition on the renovascular development. The PeRC agreed with the division that the labeling for this product should reflect that this product is not recommended less than 1-2 years of age because of this concern. The PeRC also recommended consulting DPMH for labeling assistance if desired.
- *PeRC Recommendations*:
  - The PeRC agreed to the plan for a full waiver in pediatric patients 0 to <17 years of age for the treatment of symptomatic heart failure and asymptomatic left ventricular dysfunction because studies are impossible and highly impractical (see discussion above).
  - The PeRC agreed to a partial waiver in patients < 1 month of age for the treatment of hypertension but that labeling could include statements to avoid use less than 1-2 years of age (see discussion above).
  - Post PeRC Addendum (9/6/2016): The division contacted PeRC to inform that the recommendation for labeling by the PeRC was not consistent with their conclusion from the meeting. The division stated the following:
    We would like to clarify that section 8.4 of the label describes our concern with the use of ACE inhibitors in pediatric patients 1 month old or younger "It is unknown whether post-natal use of ACE inhibitors such as enalapril before maturation of renal function is complete has long-term deleterious effects on the kidney. In humans, nephrogenesis is thought to be complete around birth; however maturation of other aspects of kidney function (such as glomerular filtration and tubular function) may continue until approximately 2 years of age [see Nonclinical Pharmacology (13.2)]."

    The division does not intend to propose language not recommending the use of Epaned (b) (4) in pediatrics less than 1-2 years of age as indicated in the minutes.

    We note the divisions updated statement to the label to omit the specific recommendations as offered by the PeRC and nothing further is needed.

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/s/

MESHAUN L PAYNE
09/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208686

GENERAL ADVICE

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

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated November 24, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Epaned [(b) (4)] (Enalapril maleate), 1 mg/mL.
R
We also refer to your June 20, 2016 submission containing revised draft bottle and carton labels.

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

A. Bottle Label:

Revise the NDC number contiguous with the barcode on the side panel (52652[(b) (4)]-1) to match the NDC number presented on the PDP (52652-4001-1).

B. Carton Label:

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: "Epaned (enalapril maleate) Oral Solution."[1]

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

[1]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.

Sincerely,

{See appended electronic signature page}

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

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/s/

NORMAN L STOCKBRIDGE
06/29/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208686

GENERAL ADVICE

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

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated November 24, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Epaned (b) (4) (Enalapril maleate), 1 mg/mL.

We also refer to your February 29, 2016 submission containing revised draft prescribing information.

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

A. General Recommendations for Container label and Carton labeling

1. As currently presented, the storage information is inconsistent as follows:
   a. Prescribing Information section 16: (b) (4)
   b. Container label: "store refrigerated 2-8 °C (36-46 °F). After dispensing, may be stored at (b) (4) room temperature 20-25 °C (68-77 °F) for up to 60 days. Avoid freezing and excessive heat."
   c. Carton labeling: "store refrigerated 2-8 °C (36-46 °F). After dispensing, may be stored at (b) (4) room temperature. 20-25 °C (68-77 °F) Avoid freezing and excessive heat."

   Revise the container label to read "store refrigerated…. Avoid freezing and excessive heat. Keep container tightly closed." Relocate the refrigerated storage statement on the principal display panel (PDP) to the side panel with the remaining storage information on the container label so that the complete storage information is presented together. This will also help to increase white space on the PDP, and increase readability of the important information on the PDP. In addition, revise the carton labeling to read "store refrigerated… room temperature

20-25 °C (68-77 °F) for up to 60 days. Avoid freezing and excessive heat. Keep container tightly closed."

2. As currently presented, the equivalency statement on the container label contains a trailing zero following a decimal point, which is on ISMP's list of error-prone abbreviations, symbols, and dose designations. Remove the trailing zero (e.g. 1.0 mg) to avoid a ten-fold misinterpretation.

B. Container label

1. Consider reorienting the barcode on the container label to a vertical position to improve the ability to scan the barcode. Barcodes placed in a horizontal position on cylindrical medical containers may not scan due to bottle curvature.

C. Carton labeling

1. Per 21 CFR 201.10(g)(2), we recommend printing the established name in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined so that the established name has a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. The strength lacks prominence on the carton labeling. We recommend that you increase the prominence of the strength (e.g., by increasing font size, bolding of font).
3. Decrease the size of the company logo/graphic on the carton labeling, as it competes in size with the proprietary name.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

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

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/s/

NORMAN L STOCKBRIDGE
06/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208686

INFORMATION REQUEST

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

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated November 24, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Epaned (b) (4) (Enalapril maleate), 1mg/mL.

We also refer to the 9 publications that you provided in support of your 505(b)(2) application. These literature articles, published between 1994 and 2013, report findings in the developing brain and kidney after enalapril administration to neonates and young animals.

Although useful, we found other publications, [Angiotensin-converting enzyme inhibition aggravates renal interstitial injury resulting from partial unilateral ureteral obstruction in the neonatal rat. Christina O. Chen, et al. *Am* J Physiol Renal Physiol 292: F946–F955, 2007; Angiotensin converting enzyme inhibition decreases cell turnover in the neonatal rat heart. Choi JH et al. Pediatr Res. 2002 Sep;52(3):325-32; ACE inhibition modulates transforming growth factor-beta receptors in the young rat. Nam Soo Kang, et al. Pediatr Nephrol (2003) 18:865–871; and others] also published in this time frame, that are missing from your list. Please provide a comprehensive review of the literature describing the experience in neonates and young animals receiving enalapril. In particular, we are interested in articles that focus on enalapril's effects on the kidney and the potential effects of enalapril on the growth and development of other organ systems.

For ease of review, please provide a copy of each literature article as well as a written document summarizing the article findings and addressing their relevance to your application.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

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

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/s/

NORMAN L STOCKBRIDGE
03/31/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208686

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Michael C. Beckloff
Chief Development Officer

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated and received November 24, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Enalapril Maleate Oral solution, 1 mg/mL.

We also refer to:

- Your correspondence, dated and received December 18, 2015, requesting review of your proposed proprietary name, Epaned (b) (4)
- Our correspondence, dated January 15, 2016, requesting clarification of your proposed proprietary name
- Your January 25, 2016, amendment, received January 27, 2016, providing clarification of your proposed proprietary name
- Our correspondence , dated February 12, 2016, requesting the submission of an amendment to your request for proprietary name review
- Your amendment, dated and received February 26, 2016, requesting review of your proprietary name, Epaned

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

If any of the proposed product characteristics as stated in above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Tri Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Sabry Soukehal, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
03/07/2016

Bui Nguyen, Tri

From: Bui Nguyen, Tri
Sent: Friday, February 12, 2016 11:03 AM
To: Susan Prather
Cc: Bui Nguyen, Tri
Subject: RE: Epaned (b) (4) NDA 208686

Importance: High

Dear Ms. Prather:

Please refer to your New Drug Application (NDA) 208686. Please refer to communication dated and received February 01, 2016.

We have reviewed the communication and have the following comments:

(b) (4) Therefore, we recommend you amend your Request for Proprietary Name Request to "Epaned" as the proposed proprietary name.

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

Best Regards,

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov
Office: (240) 402-3726

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/s/

TRI M BUI NGUYEN
02/12/2016

Bui Nguyen, Tri

From: Bui Nguyen, Tri
Sent: Thursday, February 04, 2016 3:50 PM
To: Soukehal, Sabry
Cc: Bui Nguyen, Tri
Subject: NDA 208686, SN0003 Response to request for clarification of the proprietary name.

Dear Ms. Prather:

Please refer to your New Drug Application (NDA) 208686. Please refer to communication dated and received February 01, 2016.

We have reviewed the communication and have the following comments:

(b) (4) Therefore, we recommend you amend your Request for Proprietary Name Request to "Epaned" as the proposed proprietary name.

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

Best Regards,

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov
Office: (240) 402-3726

From: Susan Prather [mailto:susan.prather@silvergatepharma.com]
Sent: Monday, February 01, 2016 6:14 PM
To: Bui Nguyen, Tri; Flowers, Louis
Cc: Michael Beckloff; Soukehal, Sabry
Subject: Re: NDA 208686, SN0003 Response to request for clarification of the proprietary name.

Dear Dr. Bui-Nguyen,

It was nice to speak with you today. Pursuant to our discussion today, please forward this email and attachment to DMEPA for comments/clarification.

Silvergate currently markets Epaned (Enalapril Maleate Powder for Oral Solution). It is a kit that contains 2 bottles, 1 with Epaned Powder and 1 with OraSweet SF Diluent which is added to the Epaned powder by the pharmacist at the time of dispensing.

Epaned (b) (4) is a ready to use solution and it will replace this product.

(b) (4)

.

We are amenable to (b) (4) Epaned as the proprietary name with (enalapril maleate oral solution) beneath it. I have attached a draft bottle label with this change.

Please confirm with DMEPA that Epaned as the proprietary name is acceptable with (enalapril maleate oral solution) beneath it.

Thank you for your assistance and I look forward to hearing from either you or a DMEPA associate soon. If you or DMEPA have any questions, please contact me at either phone number below.

Best regards,
Susan

Susan J. Prather
Director Regulatory Affairs
Silvergate Pharmaceuticals, Inc.
7300 W. 110th Street, Suite 950
Overland Park, KS 66210
913.871.1230
(b) (6)
susan.prather@silvergatepharma.com

From: Bui Nguyen, Tri <Tri.Bui-Nguyen@fda.hhs.gov>
Sent: Monday, February 01, 2016 2:39 PM
To: Susan Prather; Flowers, Louis
Cc: Michael Beckloff; Soukehal, Sabry; Bui Nguyen, Tri
Subject: RE: NDA 208686, SN0003 Response to request for clarification of the proprietary name.

Dear Ms. Prather:

The review team notes that your Request for Proprietary Name Review for NDA 208686 Enalapril maleate oral solution, 1mg/mL, indicates (b) (4) as the proposed proprietary name. The proposed name contain (b) (4)

To aid us in completing the review, please let us know by COB February 5, 2016 if you would like to amend your proposed proprietary name to "Epaned" (b) (4)

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

Best Regards,

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov
Office: (240) 402-3726

From: Susan Prather [mailto:susan.prather@silvergatepharma.com]
Sent: Monday, January 18, 2016 3:43 PM
To: Flowers, Louis; Bui Nguyen, Tri
Cc: Michael Beckloff; Soukehal, Sabry
Subject: NDA 208686, SN0003 Response to request for clarification of the proprietary name.

Dear Dr. Flowers and Dr. Bui-Nguyen,

Attached is a copy of Silvergate's response to Dr. Flowers' request for clarification of the proprietary name for Epaned (b) (4), and Dr. Bui-Nguyen's follow up email requesting a response by January 20, 2016. The proprietary name requested is (b) (4) I have attached a copy of the Amendment to the Request for Review of Proprietary name which will be submitted electronically to the NDA on January 26, 2016.
The additional time is necessary for linking and the publishing processes.

As discussed during my conversation with Dr. Flowers, we have revised the carton and bottle label to more clearly distinguish the proprietary name and the registered name. Please note that other labeling changes were made based upon comments received on another Silvergate product, Qbrelis, NDA 208401, also under current FDA review, (e.g., more white space to primary panel, representative bar code for spacing purposes, etc.).

If you have any questions or need any additional information, please contact me or Michael Beckloff.
Thank you,

Best regards,
Susan

Susan J. Prather
Director Regulatory Affairs
Silvergate Pharmaceuticals, Inc.
7300 W. 110th Street, Suite 950
Overland Park, KS 66210
913.871.1230
(b) (6)
susan.prather@silvergatepharma.com

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/s/

TRI M BUI NGUYEN
02/04/2016

Bui Nguyen, Tri

From: Bui Nguyen, Tri
Sent: Thursday, February 04, 2016 3:48 PM
To: Susan Prather; Michael Beckloff
Cc: Bui Nguyen, Tri; Soukehal, Sabry
Subject: RE: NDA 208686, SN0003 Response to request for clarification of the proprietary name.

Importance: High

Dear Susan;

This correspondence is to notify you that your email address is not secure. Use of secure email allows transparent and complete communication between FDA and sponsors. FDA communication via unsecure email cannot include commercial confidential information (e.g. trade secrets, manufacturing or patient information). Therefore, sponsors should establish secure email with FDA to allow for informal communications that may include commercial confidential information.

Please contact the Office of Information Management (OIM) to for additional information or to request secure email at SecureEmail@fda.hhs.gov.

For additional information, please refer to *Draft Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development. December 2015* and the Electronic Regulatory Submissions and Review Web page.
http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/default.htm

Sincerely,

{See appended electronic signature page}

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov
Office: (240) 402-3726

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/s/

TRI M BUI NGUYEN
02/04/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208686

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

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

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated November 24, 2015, received November 24, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Epaned (b) (4) (Enalapril maleate), 1mg/mL.

We also refer to your amendment dated December 18, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **September 24, 2016**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **August 17, 2016**.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

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

During our preliminary review of your submitted labeling, we found that you did not provide a review and summary of the available information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.
Resubmit the following information **by February 29, 2016**.

- a review and summary of all available published literature regarding enalapril maleate use in pregnant and lactating women,
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

PROMOTIONAL MATERIAL

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the indication *treatment of hypertension in pediatric patients* has orphan drug designation, you are exempt from this requirement.

We acknowledge receipt of your request for a full waiver of pediatric studies for *symptomatic heart failure* and *asymptomatic left ventricular dysfunction* indications. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

NORMAN L STOCKBRIDGE
02/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 125621

MEETING MINUTES

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

Dear Mr. Beckloff:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Epaned® (enalapril maleate) Oral Solution.

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2015. The purpose of the meeting was to discuss the appropriate approval pathway and requirements for the ready-to-use Epaned® (b) (4), 1mg/ml formulation.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND
Meeting Date and Time:	16 April 2015, 11:00 a.m. – 12:00 p.m. Eastern Time
Meeting Location:	White Oak, Building 22, Room 1421
Application Number:	PIND 125621
Product Name:	Epaned® (enalapril maleate) Oral Solution
Indication:	Treatment of hypertension in adults and children older than 1 month and for symptomatic heart failure and asymptomatic left ventricular dysfunction in adults
Sponsor/Applicant Name:	Silvergate Pharmaceuticals, Inc.
Meeting Chair:	Norman Stockbridge MD, PhD
Meeting Recorder:	Sabry Soukehal, RQAP-GLP

FDA ATTENDEES

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Mike Monteleone, MS, RAC	Associate Director for Labeling
Shari Targum, MD	Clinical Team Leader
Albert Defelice, PhD	Non-Clinical Team Leader
Muriel Saulnier, DVM, PhD, DABT	Non-Clinical Reviewer
Quynh Nguyen, PharmD, RAC	Regulatory Health Project Manager
Sabry Soukehal, RQAP-GLP	Consumer Safety Officer

*Office of New Drug Quality Assessment

Mohan Sapru, PhD	CMC Lead
Sherita McLamore-Hines, PhD	Regulatory Review Chemist

*Office of Clinical Pharmacology

Sudharshan Hariharan, PhD	Clinical Pharmacology Acting Team Leader
Martina Sahre, PhD	Clinical Pharmacology Reviewer

*Office of Pediatric Therapeutics

Robert "Skip" Nelson MD PhD	Deputy Director

*Division of Biopharmaceutics, OPQ
Angelica Dorantes, PhD — Acting Biopharmaceutics Branch Chief

*Office of Management
Teresa Ramson, PharmD. — PDUFA User Fee Staff

*Office of Orphan Products Development, Orphan Drug Designation Program
Henry H. Startzman III, MD — Director

SPONSOR ATTENDEES

Frank Segrave — Chief Executive Officer
Michael C. Beckloff — Chief Development Officer
Susan J. Prather — Director, Regulatory Affairs

1.0 BACKGROUND

The Sponsor developed a ready-to-use Epaned® [redacted (b) (4)] Currently, Epaned® is mixed with Ora-Sweet® SF Diluent for reconstitution just prior to dispensing. The aim of the new Epaned® Oral Solution is to eliminate the need for reconstitution.

The purpose of the meeting is to discuss the appropriate approval pathway and requirements for the ready-to-use Epaned® [redacted (b) (4)] 1mg/ml formulation.

FDA sent Preliminary Comments to Silvergate Pharmaceuticals, Inc. on April 10, 2015.

2. DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: [redacted (b) (4)] is the approved and qualified supplier of enalapril maleate USP used in the production of Silvergate's marketed product, Epaned® Powder for Oral Solution, 1 mg/mL. [redacted (b) (4)] will be the primary supplier of the API for Epaned® Oral Solution. Since [redacted (b) (4)] is an approved supplier for Epaned® Powder for Oral Solution, Silvergate intends to include both suppliers in the NDA, with a commitment to place the first commercial (post-validation) batch utilizing [redacted (b) (4)] enalapril maleate on routine stability and include this information in an annual report. **Does the Agency agree with this approach since [redacted (b) (4)] is an approved supplier for Silvergate's Epaned® Powder for Oral Solution formulation?**

FDA Preliminary Response to Question 1: The Agency agrees with the proposed approach.

Discussion during the meeting: The Sponsor had no further comments. This question was not discussed during the meeting.

Question 2: The specifications for Epaned® (b) (4) 1 mg/mL, which comply with ICH Q3B, are provided in section 10.1.2.6, table 3. **Does the Agency agree that the current proposed drug product specifications are appropriate for the NDA?**

***FDA Preliminary Response to Question 2*:** The test for the identification is not specific and is therefore not acceptable as standalone identification test (see ICH Q6A). All other tests are acceptable; however, the acceptability of the acceptance criteria is a review issue.

Discussion during the meeting: The Sponsor stated that their HPLC assay is stability-indicating and specific for the drug product. (b) (4) Therefore, the Sponsor asked if they would need to develop a PDA detector. Dr. Sapru responded that if the Sponsor believes that their method is specific for identification, then they should submit the data to make a case for that. If the data are available, the Division does not anticipate issues. The Sponsor asked if the validation data of the HPLC assay were sufficient and Dr. Sapru replied yes.

Question 3: The Epaned® (b) (4) formulation is stored under refrigerated conditions until dispensed by the pharmacist. The proposed stability program consists of refrigerated conditions, to support the shelf-life of the product prior to dispensing, and an in-use study at room-temperature conditions, to support unrefrigerated storage conditions of (b) (4) 60 days once dispensed. **Does the Agency agree that the stability program, as outlined below in section 10.1.2.8, is acceptable?**

***FDA Preliminary Response to Question 3*:** The proposed drug product stability protocol appears reasonable.

Discussion during the meeting: The Sponsor had no further comments. This question was not discussed during the meeting.

Question 4: The current plan is to submit the NDA with (b) (4) months of refrigerated and (b) (4) months of room-temperature stability data on 3 registration batches, in accordance with ICH Guidance Q1A(R2) and Guidance Q1C, and supplementing the stability data during the review process. Data on a development batch of the proposed formulation through 12 months will be available for inclusion in the NDA. An appropriate statistical analysis will be conducted to support the proposed expiration date. In-use study data on the registration batches will also be included in the submission. **Does the Agency agree that this plan is acceptable?**

***FDA Preliminary Response to Question 4*:** It is our expectation that the NDA will include at least twelve (12) months of long-term stability data and at least six (6) months of accelerated stability data at the time of submission. Although not considered a filing issue, we will evaluate the proposed expiration period based on the quantity and quality of the stability data provided in the submission. The proposed expiration period should ensure that the drug product is commercially viable. We would like to remind you that as stated in *Guidance for Industry ICH Q1E Evaluation of Stability Data* "where long-term data are not amenable to statistical analysis, the proposed shelf life can be up to one-and-a-half times as long as, but should not be more than

6 months beyond, the period covered by long-term data," if relevant supporting data are available.

Discussion during the meeting: The Sponsor wanted to confirm if their current plan to submit (b) (4) months of refrigerated and (b) (4) months of room-temperature stability data including statistical analysis on 3 additional batches was acceptable. The Division indicated that 12 months of room-temperature and 6 months of accelerated stability data was acceptable. The Division also mentioned that it could look at the extrapolation and analysis data if they were available.

The Sponsor then asked about the best way to provide stability updates to the Division during the NDA review process. The Division indicated that after providing at least twelve (12) months of long-term stability data and at least six (6) months of accelerated stability data at the time of NDA submission, the Applicant has the option of providing additional stability data, in support of proposed retest and/or expiration period, before the mid-cycle review time.

2.2. Nonclinical

Question 5: In the Epaned® (b) (4) NDA, Silvergate plans to reference the nonclinical section of the Epaned® (enalapril maleate) Powder for Oral Solution label (the reference listed drug) to fulfill the nonclinical requirements for the 505(b)(2) NDA. In addition, a literature search will be conducted to identify new nonclinical and clinical pediatric information. Any significant findings will be included in the NDA. **Please confirm that the nonclinical plan is acceptable and will meet the nonclinical requirements of the NDA.**

FDA Preliminary Response to Question 5: Yes, this is acceptable.

Discussion during the meeting: The Sponsor had no further comments. This question was not discussed during the meeting.

2.3. Clinical

(b) (4)

(b) (4)

(b) (4) A bioequivalence study will be needed to support the approval of your proposed drug product.

Discussion during the meeting: The Sponsor requested further understanding of the Division's preliminary response. Dr. Dorantes indicated that the response was based on the regulations, but (b) (4) their proposed drug product. (b) (4) (b) (4) The Sponsor asked if the Division expects a two-way fasted bioequivalence study, comparing the proposed and listed drug products and the Division said yes. (b) (4) (b) (4) The Sponsor also asked whether a food-effect study would need to be conducted as part of a bioequivalence study; the Division said that was not necessary, since the food effect was already studied for the oral solution.

2.4. Submission Specific Information

Question 7: The application is planned as a 505(b)(2) NDA, referencing Epaned® (enalapril maleate) Powder for Oral Solution as the reference listed drug. **Please confirm the acceptability of the proposed application as a 505(b)(2) NDA and that Epaned® (enalapril maleate) Powder for Oral Solution is the appropriate reference listed drug.**

FDA Preliminary Response to Question 7: You may cross-reference your previously approved 505(b)(2) application (NDA 204308, Epaned Powder for Oral Solution) to support the approval of your proposed product.

If the cross-referenced portions of your previously approved 505(b)(2) NDA involve reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or published literature (as distinguished from any cross-referenced investigations that were conducted by or for you or for which you obtained a right of reference or use), then the application for your proposed product should be submitted pursuant to section 505(b)(2) of the FD&C Act. Your new 505(b)(2) application should identify this/these listed drug(s) as relied upon for your new 505(b)(2) application in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application, including, but not limited to, an appropriate patent certification/statement and notification, apply to each listed drug upon which an applicant relies.

For information on the 505(b)(2) regulatory pathway, please see the section at the end of this document.

Discussion during the meeting: The Sponsor asked is referencing their data was enough and the Division said yes.

Question 8: If no clinical efficacy or safety studies are required for approval, Silvergate believes that the NDA submission will require one-half of the current PDUFA fee at the time of submission. **Please confirm that the PDUFA fee for the planned submission would be one-half of the current PDUFA fee at the time of submission.**

***FDA Preliminary Response to Question 8*:** The amount of user fee required for an application (a full application fee or half of an application fee) depends on whether clinical data are required for the approval of the application. At this time, we anticipate that the data required for your application are not considered clinical data for user fee purposes; therefore, your application would require half of an application user fee. However, the final user fee determination will be based on the actual application submitted to the Agency in its entirety for review at the time of submission.

Discussion during the meeting: The Sponsor had no further comments; however after discussing question 9, the User Fee Staff reiterated that the final user fee determination will be based on the actual application submitted to the Agency in its entirety for review at the time of submission. If it is determined that pediatric data are required to fulfill PREA and if these data are required to be submitted at the time of submission of the NDA, then this application requires the full application fee at the time of submission.

2.5. Pediatric Research Equity Act Question

Question 9: Silvergate received orphan drug designation for Enalapril maleate, USP, Powder for Oral Solution on January 30, 2013 (12-3767), for the treatment of hypertension in pediatric patients. Because the active moiety has orphan drug designation, Silvergate believes that the Epaned® (b) (4) NDA is exempt from the requirements of the Pediatric Research Equity Act regarding pediatric studies. **Please confirm that the Epaned® (b) (4) NDA is exempt from the requirements of the Pediatric Research Equity Act.**

FDA Preliminary Response to Question 9: Yes, it is exempt from the PREA studies.

Discussion during the meeting: The Sponsor asked what was needed from a PSP standpoint. Dr. Nelson clarified that the PREA exemption applies to the hypertension indication only, and not to the symptomatic heart failure and asymptomatic left ventricular dysfunction indications. The Sponsor indicated that the latter two indications apply to adults only as mentioned in the previous approval letter. The Division agreed but wanted to share with the Sponsor its preliminary conclusion that the PREA exemption only applies to one indication (hypertension). Dr. Nelson recommended that the Sponsor work with the Division regarding their pediatric plans for these other two indication, and referred the Sponsor to the draft Guidance for Industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf).

2.6. Orphan Drug Marketing Exclusivity

Question 10: Pursuant to earlier discussions with the Agency regarding clinical superiority of a ready-to-use formulation over both a reconstituted product (e.g., Epaned® Powder for Oral Solution) and an extemporaneous suspension prepared from enalapril maleate tablets and the granted orphan designation, Silvergate believes that orphan marketing exclusivity of 7 years will be granted. **Please confirm that orphan drug marketing exclusivity based on clinical superiority of a ready-to-use solution over a reconstituted product or an extemporaneous compounded suspension is appropriate.**

FDA Preliminary Response to Question 10: Eligibility for marketing exclusivity based on clinical superiority of an orphan designated subject of a marketing application over previously approved "same drugs" for the same designated indication is determined at the time of NDA review and involves discussions between the Office of Orphan Products Development and the appropriate Review Division(s). However, if Epaned (b) (4) were found to be equivalent to enalapril powder for oral solution and the Epaned (b) (4) were a ready-to-use solution that did not require reconstitution, this could form the basis for clinical superiority and could result in the awarding of 7 years of marketing exclusivity for the approved pediatric hypertension indication.

Discussion during the meeting: It is the Sponsor's understanding that with the proposed ready-to-use formulation, which does not require reconstitution, they would be eligible for 7-year marketing exclusivity.

Dr. Startzman stressed that exclusivity is determined at the time of NDA approval. In order for the Sponsor to be granted exclusivity, a safety advantage needs to be demonstrated. Dr. Startzman reiterated that if Epaned (b) (4) were found to be equivalent to enalapril powder for oral solution and the Epaned (b) (4) were a ready-to-use solution that did not require reconstitution, then this could represent a safety advantage and could result in the awarding of 7 years of marketing exclusivity for the approved pediatric hypertension indication.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Please refer to the ***Discussion during the meeting*** for Question 9.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

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/s/

NORMAN L STOCKBRIDGE
05/05/2015