CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208686Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

NDA: 208686

Drug: Epaned (enalapril maleate) Oral Solution

Class: Angiotensin-Converting Enzyme (ACE) Inhibitor

Applicant: Silvergate Pharmaceuticals, Inc.

Proposed Indications:

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.

Date of submission: November 24, 2015

PDUFA date: September 24, 2016

Target Action date: September 23, 2016

II. REVIEW TEAM

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

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

Office of Pharmaceutical Quality

Drug Product: Sherita McLamore-Hines
Drug Substance: Haripada Sarker
Microbiology: Denise Miller
Process: Sung Kim
Facilities: Cassandra Abellard
Labeling and environmental assessment (EA): Dan Berger, Stephanie Emory
Biopharmaceutics: Zhuojun Joan Zhao

Office of Clinical Pharmacology

Martina Sahre
Lars Johannesen

Office of Surveillance and Epidemiology
DPV: Amy Chen
DMEPA: Sarah Thomas

Office of Prescription Drug Promotion
Zarna Patel

III. BACKGROUND

Epaned (enalapril maleate) Oral Solution is a ready-to-use ACE inhibitor developed by Silvergate Pharmaceuticals, Inc. for the treatment of hypertension in adults and children older than one month, as well as for the treatment of symptomatic heart failure and asymptomatic left ventricular dysfunction in adults only. The proposed dose is 1mg/ml.

This Application followed a 505(b)(2) pathway utilizing Vasotec® (enalapril maleate) tablets (NDA 18998, approved December 24, 1985) as the reference listed drug.

A type B Pre-IND meeting was held on April 16, 2015 (Pre-IND 125621) during which the approval pathway and NDA requirements for the ready-to-use oral solution were discussed.

The applicant conducted a "Randomized, Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover" study (study SG04-01) that assessed the relative bioavailability of Epaned Oral Solution, 1 mg/mL, vs. reconstituted Epaned Powder for Oral Solution, 1 mg/mL, under fasted conditions in healthy adults. This study served as a basis for this NDA submission.

Of note, on January 30, 2013, enalapril maleate powder for oral solution developed by the applicant was granted orphan drug designation (#12-3767) for the *treatment of hypertension in pediatric patients* 0 to 16 years of age. However, at the request of the Division of Cardiovascular and Renal Products, the prevalence estimate of pediatric hypertension requiring pharmacological therapy was assessed by the Division of Pediatric and Maternal Health (DPMH). There was a concern that, at the time of the orphan designation request, the estimated number of pediatric patients with hypertension exceeded the 200,000 threshold.

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

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

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

IV. APPLICATION REVIEW

1. User Fee

The user fee for this application was paid in full on November 13, 2015 (User Fee ID 3015533).

2. Pediatric Review Committee (PeRC)

At the time of NDA submission, the applicant submitted a request for a full waiver for the heart failure and asymptomatic left ventricular dysfunction indications only as PREA didn't apply to the hypertension indication because of the orphan drug designation.

Following NDA submission, the orphan drug designation for pediatric hypertension was revoked. As a result, the applicant submitted a partial waiver request for pediatric hypertension in patients 1 month of age and younger.

A PeRC meeting was held on August 17, 2016, to discuss the applicant's waiver requests. The committee agreed to the plan to grant 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 to conduct. The committee also agreed to the partial waiver request for the treatment of hypertension in patients less than 1 month old because the product would be unsafe for this patient population.

3. Advisory Committee

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

4. Trade name

The applicant originally submitted the proposed name [redacted] (b) (4) to NDA 208686 on December 18, 2015. Following discussions with the Division of Medication Error Prevention and Analysis, the applicant submitted the proposed name Epaned on February 26, 2016. This name was considered conditionally acceptable. A grant letter was issued on March 07, 2016.

5. Facilities Inspections

The Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance recommended accepting the data without an on-site inspection because the clinical and analytical sites (Worldwide Clinical Trials Early Phase Services LLC, San Antonio, Texas and [redacted] (b) (4)) were recently inspected and the inspection was classified as No Action Indicated.

6. Regulatory Timeline

Pre-NDA Meeting: April 16, 2015
NDA Receipt Date: November 24, 2015
Filing Day 60: January 23, 2016
Filing 74-Day Letter: February 03, 2016
Advisory Committee: N/A
PDUFA Date: September 24, 2016

7. Reviews

Below are the conclusions reached by the Epaned team members.

a) Divisional Memorandum – September 19, 2016

Dr. Stockbridge's memo documented his concurrence with the review team's recommendation to approve this new drug application. He summarized the bridging performed by the applicant but recommended a more formal approach to chains of bioequivalence studies. Please refer to his memo for further details.

b) Cross-Discipline Team Leader Review - September 16, 2016

Dr. Thompson recommended approval. Her review summarized each disciplines findings (CMC, nonclinical, and clinical pharmacology). She agreed with the reviewers' assessments and stated that the main issue that arose during the review of this application was the limitations of the data supporting enalapril maleate's indication for the treatment of hypertension in pediatric patients less than 6 years of age.
Her review noted that the applicant's search of the published literature and the FAERS database did not raise new safety concerns. She discussed the Agency's decision to fully waive pediatric studies requirements for patients with symptomatic heart failure or asymptomatic left ventricular dysfunction aged birth to 16 years of age, and partially waive pediatric studies requirements for patients 1 month of age and younger with hypertension. Please see her review for further details.

c) Clinical Pharmacology Review – August 17, 2016, September 01, 2016

Drs. Sahre and Johannesen provided an abridged version of a question-based review as the detailed clinical pharmacology review can be located in original NDA 18998. They reviewed the results of study SG04-01 that was conducted to determine if enalapril oral solution was bioequivalent to enalapril powder for oral solution. They concluded that the study showed that the bioequivalence criteria were met for both enalapril and enalaprilat (the active metabolite). This data is supportive of approval. Please see their reviews for details.

d) Pharmacology & Toxicology Review - February 10, 2016

Dr. Saulnier performed a comprehensive review of the published studies in animals receiving enalapril or enalaprilat. She noted that the juvenile toxicity studies conducted at various developmental stages in rats and piglets revealed the susceptibility of the kidney to enalapril. She however clarified that the doses studied were more than 60 times the recommended clinical doses. She also noted that enalapril administration in weanling rats at dosages close to the recommended dosages in pediatric patients was beneficial in reversing the damage after chronic unilateral ureteral obstruction, a condition observed in the pediatric population. She also clarified that dosages that were nephrotoxic in the post natal period were not nephrotoxic in the adult. She further indicated that use of enalapril and other ACE inhibitors in pregnancy can cause fetal anuria, resulting in oligohydramnios, and also lung hypoplasia, both of which persist in the neonate. Dr. Saulnier recommended approval. Please see her review for details.

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

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

i. *Drug Substance*: Enalapril maleate is described as a white to off-white, crystalline powder. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol. Its molecular weight is 492.52 and its molecular formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$.

ii. *Drug Product*: Epaned (b) (4), 1 mg/mL, is a non-sterile, ready-to-use aqueous formulation. Each 1 mL of solution contains 1 mg of enalapril maleate, USP equivalent to 0.764 mg of enalapril, and the following inactive ingredients: citric acid, mixed berry flavor, purified water, sodium benzoate, sodium citrate, and sucralose. Hydrochloric acid or sodium hydroxide is added for pH adjustment. Epaned (b) (4) will be commercially available in a 150-mL polyethylene bottle.

iii. *Expiration date and storage conditions*: the review noted that a 22-month expiry with a 60 day in-use will be assigned to the drug product. The recommended storage condition is refrigerated (2°C-8°C (36°F-46°F), protected from freezing and excessive heat. The drug product can also be stored at room temperature (25°C/77°F) for up to 60 days.

iv. *Microbiology*: The review indicated that the [redacted] (b) (4) was performed on the stability batches only. The report provided on July 01, 2016, supports the effectiveness [redacted] (b) (4).

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

8. Consults

a) Office of Surveillance and Epidemiology – Division of Medication Error Prevention and Analysis – April 20, 2016, and June 27, 2016

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

Full details on DMEPA's recommendations can be found in the reviews. DMEPA's comments were sent to the applicant who made the requested revisions. Final agreed-upon carton labels were received July 08, 2016 and final container labels were received July 19, 2016.

b) Office of Prescription Drug Promotion - August 28, 2016

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

9. Labeling

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

V. CONCLUSION

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

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/s/

SABRY SOUKEHAL
09/20/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 208686	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Epaned Established/Proper Name: Enalapril maleate Dosage Form: Solution Strengths: 1mg/mL		
Applicant: Silvergate Pharmaceuticals, Inc.		
Date of Receipt: November 24, 2015		
PDUFA Goal Date: September 24, 2016	Action Goal Date (if different): September 23, 2016	
RPM: Sabry Soukehal		
Proposed Indication(s): - Treatment of hypertension in adults and children older than 1 month - Treatment of symptomatic heart failure - Treatment of asymptomatic left ventricular dysfunction		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 018998: Vasotec® (enalapril maleate) tablets	FDA's previous finding of safety and effectiveness and nonclinical toxicology

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

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

The development program consisted of a three-way bridge. Specifically, this application relied on bridging to the Reference Listed Drug (RLD) Vasotec® (enalapril maleate) tablets (NDA 18,998) by showing that the oral solution was bioequivalent to the powder for oral solution (Epaned (enalapril maleate) NDA 204,308) which was previously shown to be bioequivalent to the RLD.
To support the bridge to the powder for oral solution, the applicant conducted a relative bioavailability study (SG04-01), which showed that the proposed oral solution is bioequivalent to Epaned powder for oral solution for both enalapril (prodrug) and enalaprilat (active metabolite) in terms of AUC and Cmax.

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON PUBLISHED LITERATURE

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*
Vasotec (enalapril maleate) tablets

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

YES ☒ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

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

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

YES ☒ NO ☐

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

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Vasotec® (enalapril maleate) tablets	018998	Yes

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☒

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

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

b) Approved by the DESI process?

YES ☐ NO ☒

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

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

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

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

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

d) Discontinued from marketing?

YES ☐ NO ☒

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

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

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

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

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

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

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

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

YES ☐ NO ☒

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

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

YES ☐ NO ☐

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

N/A ☐ YES ☐ NO ☐

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

Pharmaceutical equivalent(s):

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

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

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

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

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

YES ☒ NO ☐

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

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*
Pharmaceutical alternative(s): Vasotec® (enalapril maleate) tablets – NDA 18998.

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

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

YES ☐ NO ☐

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

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

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

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

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

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

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

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

Date(s):

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

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

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

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

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/s/

SABRY SOUKEHAL
09/14/2016

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

Memorandum

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

Date: August 28, 2016

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

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

Subject: **Epaned (enalapril maleate) Oral Solution**
NDA: 208686
Comments on draft product labeling

In response to your consult dated December 7, 2015, OPDP has reviewed the draft prescribing information (PI) and the proposed Carton and Container labeling for Epaned (enalapril maleate) Oral Solution. We have reviewed the attached substantially complete version of the draft PI emailed to us on August 18, 2016 as well as the proposed Carton and Container Labeling submitted by the sponsor on July 19, 2016. We do not have any comments on the draft PI or the proposed Carton and Container labeling at this time.

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

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

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/s/

ZARNA PATEL
08/28/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	June 27, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 208686
Product Name and Strength:	Epaned (Enalapril maleate) oral solution, 1 mg/mL
Submission Dates:	June 20, 2016
Applicant/Sponsor Name:	Silvergate Pharmaceuticals, Inc.
OSE RCM #:	2015-2624-1
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling submitted on June 20, 2016 (Appendix A) for Epaned to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

Upon review of the revised container label and carton labeling, we conclude that Silvergate Pharmaceuticals, Inc. incorporated our recommendations from the previous review, and for the most part, the proposed container label and carton labeling are acceptable from a medication safety perspective. However, we note that the dosage form is now missing on the top flap of the carton labeling, and that the NDC number contiguous with the barcode on the container label is not consistent with the NDC number presented on the principal display panel (PDP). The NDC number contiguous with the barcode and the NDC number presented on the PDP match on the carton labeling. Therefore, we provide associated recommendations in section 3.

3 RECOMMENDATIONS FOR SILVERGATE PHARMACEUTICALS, INC.

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

A. Container Label
    1. 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 Labeling
    1. Revise the presentation of the proprietary name and established name on the top flap of the carton labeling to include the dosage form, as follows: "Epaned (enalapril maleate) Oral Solution."[2]

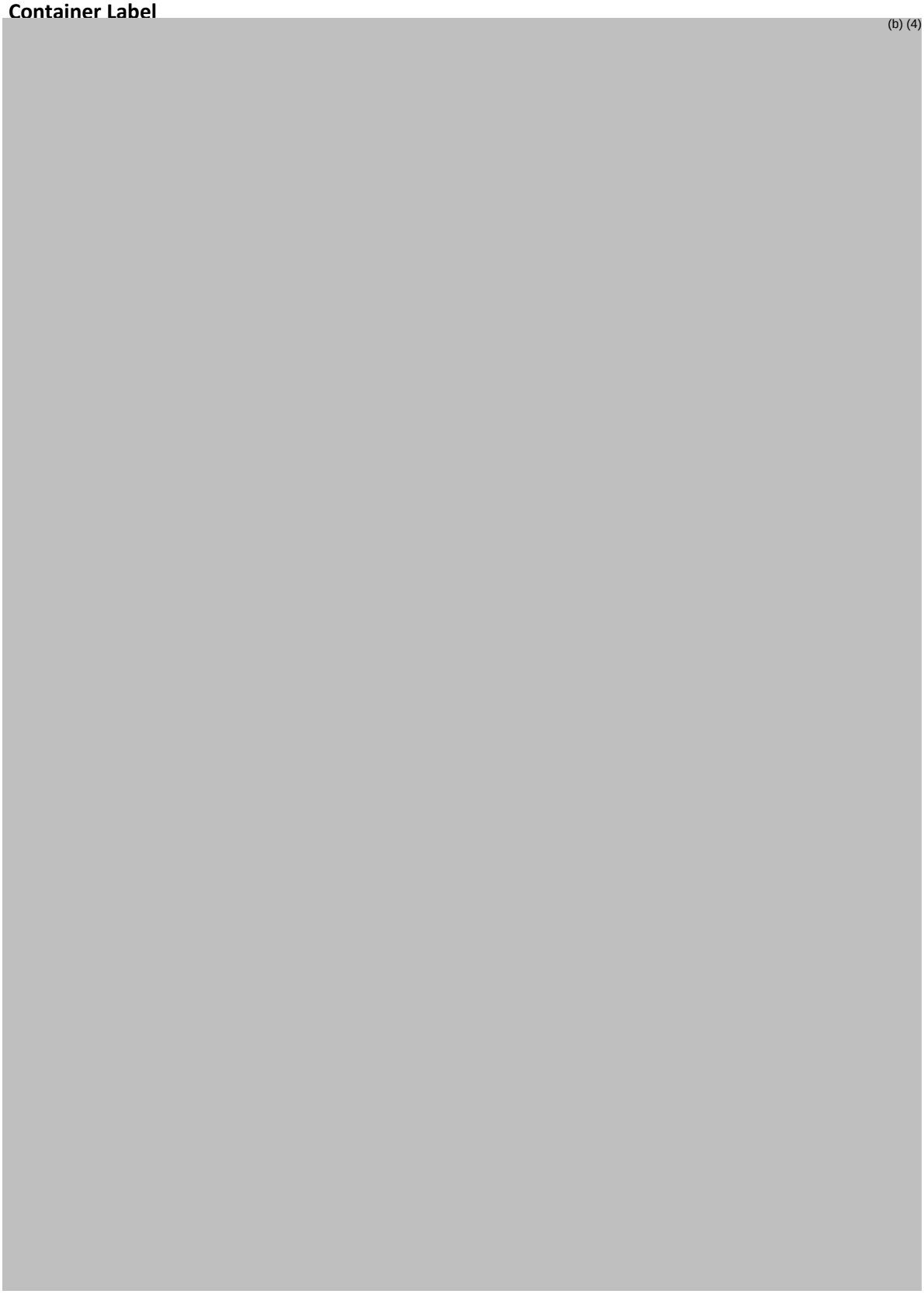
[1] Thomas S. Label and Labeling Review for Epaned (NDA 208686). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APRIL 19. 17 p. OSE RCM No.: 2015-2624.

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

Appendix A. Label and Labeling Submitted on June 20, 2016

Container Label

(b) (4)



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

/s/

SARAH E THOMAS
06/27/2016

CHI-MING TU
06/27/2016

LABEL AND LABELING REVIEW

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

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

Date of This Review:	April 19, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 208686
Product Name and Strength:	EPANED (Enalapril maleate) oral solution, 1 mg/mL
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Silvergate Pharmaceuticals, Inc.
Submission Date:	February 26, 2016 and February 29, 2016
OSE RCM #:	2015-2624
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the proposed EPANED container label and carton labeling submitted on February 26, 2016 and the prescribing information (PI) submitted on February 29, 2016 for risk of medication error.

This NDA is a 505(b)(2) application and the listed drug is Vasotec tablets (NDA 18998).

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Epaned Powder for Oral Solution is currently marketed by Silvergate Pharmaceuticals. Epaned powder for oral solution requires reconstitution with the accompanying diluent Ora-Sweet SF by a pharmacist to a 1 mg/mL concentration prior to dispensing to the patient. The proposed product, EPANED, is already a ready-to-use 1 mg/mL oral solution (b) (4). The only usage difference in the proposed product, EPANED, is the elimination of reconstitution.

We reviewed the proposed PI and found absence of the route of administration information, error-prone symbols ">" and "cc"[1,2], unspecified creatinine clearance calculation method, and use of non-affirmative language. Thus, the proposed PI can be improved to promote the safe use of the product.

Our review of the proposed EPANED container label and carton labeling found that they can also be improved to promote the safe use of the product. We note the presence of an equivalency statement indicating the strength in terms of the active moiety on the container label, but not on the carton labeling and the PI. We defer to OPQ for the labeling of the equivalency statement on the container label, carton labeling, and the PI.[3]

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[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.

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

[3] Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. Food and Drug Administration. 2015. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf

Additionally, the equivalency statement contains a trailing zero on the container label, and therefore requires revision to prevent a ten-fold misinterpretation.[2] In terms of the container label specifically, among other formatting improvements noted, the principal display panel (PDP) is too crowded and lacks white space, thus decreasing readability of important information on the PDP.[1] In terms of the carton labeling specifically, the established name and strength lack prominence, and the graphic competes in size with the proprietary name.

4 CONCLUSION & RECOMMENDATIONS

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

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Container Label and Carton Labeling
    1. We note the presence of the equivalency statement indicating the strength in terms of the active moiety on the container label but not on the carton labeling and the PI. We defer to OPQ for the labeling of the equivalency statement on the container label, carton labeling, and the PI.[3]

B. See Appendix H for our recommendations in tracked changes for PI.

4.2 RECOMMENDATIONS FOR SILVERGATE PHARMACEUTICALS

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

A. General Recommendations for Container label and Carton labeling:

1. As currently presented, the storage information is inconsistent as follows:
    i. Prescribing Information section 16: (b) (4)
    ii. 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."
    iii. 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.[1] 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.[2]

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.[4]

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, and so we recommend that you increase the prominence of the strength (e.g., increasing font size, bolding of font, etc.).
    3. Decrease the size of the company logo/graphic on the carton labeling, as it competes in size with the proprietary name.[1]

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for EPANED contained in the prescribing information that Silvergate Pharmaceuticals submitted on February 29, 2016, as well as product information for Vasotec, the listed drug (LD).

Table 2. Relevant Product Information for EPANED and the Listed Drug		
Product Name	EPANED	Vasotec (NDA 18998)
Initial Approval Date	Epaned Kit (NDA 204308): August 13, 2013	December 24, 1985
Active Ingredient	Enalapril Maleate	
Indication	• Angiotension-converting enzyme (ACE) inhibitor indicated for the treatment of: o Hypertension in adult patients and pediatric patients older than one month of age o Symptomatic congestive heart failure o Asymptomatic left ventricular dysfunction, to decrease the rate of development of overt heart failure and reduce hospitalization for heart failure	
Route of Administration	Oral	
Dosage Form	Oral solution	Tablets
Strength	1 mg/mL	2.5 mg, 5 mg, 10 mg, 20 mg
Dose and Frequency	**Hypertension:** • Adult: recommended initial dose is 5 mg once daily. The recommended initial dose is 2.5 mg daily in patients taking diuretics and in those patients with CrCl≤30 mL/min. An initial dose of 2.5 mg may be administered to dialysis patients on dialysis days. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses, and the maximum dose is 40 mg daily. • Pediatrics (children greater than 1 month of age): recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily, with doses adjusted according to blood pressure response. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients. EPANED is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available. **Heart Failure:** Initiate at 2.5 mg twice daily. Titrate up to 20 mg twice daily as tolerated. In patients with hyponatremia (serum sodium less than 130 mEq/L) or serum creatinine greater than 1.6 mg/dL, the recommended initial dose is 2.5 mg once daily. **Asymptomatic Left Ventricular Dysfunction:** Initiate at 2.5 mg twice daily. Titrate up to a maximum of 10 mg twice daily as tolerated.	
How Supplied	150 mL white, round, high-density polyethylene bottle with a white,	• 2.5 mg strength: Bottles of 30 count and unit of use bottles of

	polypropylene, child-resistant cap and tamper-evident seal	90 count • 5 mg, 10 mg, 20 mg strengths: Bottles of 30 count, unit of use bottles of 90 count, and bottles of 1000 count
Storage	Per Section 16 of PI, prior to dispensing to the patient, keep EPANED refrigerated (2-8°C/36-46°F) and avoid freezing and excessive heat. Patients may store EPANED at room temperature (25°C/77°F) for up to 60 days; limited excursions permitted to 15-30°C/59-86°F [see USP controlled room temperature]. Do not freeze. Keep container tightly closed.	Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture. Dispense in a tight container as per USP, if product package is subdivided.
Container Closure	High-density polyethylene (HPDE) bottle with a child-resistant cap and tamper-evident seal.	Tablets are packaged in 30-, 90-, and 100-count HDPE bottles each with a child resistant closure-induction seal liner system containing a desiccant canister and in a 1000-count HDPE bottle with a non-child resistant closure-induction seal liner system containing a desiccant canister.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 21 and 22, 2016, we searched the L:drive and AIMS using the terms, enalapril, Epaned, and NDA application numbers 208686 and 204308 to identify reviews previously performed by DMEPA relevant to the proposed product.

B.2 Results

Our search identified four relevant previous reviews[5,6,7,8], and we evaluated the previous reviews for applicable recommendations that should be included in this current review. Most recommendations were incorporated into subsequent label and labeling revisions by the sponsor. A few recommendations from the April 12, 2013 label and labeling review[5] remain applicable to this review, and these are incorporated in section 4 of this review (e.g., a recommendation against the use of the ">" symbol; increasing the prominence of the established name so that it is at least half of the size of the proprietary name on the carton labeling).

[5] DeFronzo, Kimberly. Label and Labeling Review for Enalaped (Enalapril maleate) powder for oral solution. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 April 12. RCM No.: 2012-1914.

[6] DeFronzo, Kimberly. Label and Labeling Review for Epaned (Enalapril maleate) powder for oral solution. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 July 10. RCM No.: 2013-1449.

[7] DeFronzo, Kimberly. Label and Labeling Memo Review for Epaned (Enalapril maleate) powder for oral solution. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 July 18. RCM No.: 2013-1449-1.

[8] Fava, Walter. Label and Labeling Review for Epaned (Enalapril maleate) powder for oral solution. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 February 27. RCM No.: 2014-284.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On January 22, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Searched the Acute Care, Community, and Nursing Newsletters.
Search Strategy and Terms	Match Any of the Words: enalapril Epaned

D.2 Results:

Our search retrieved thirteen newsletters[9,10,11,12,13,14,15,16,17,18,19,20,21], but none of the newsletters are specifically applicable to Epaned or the associated label and labeling.

[9] Institute of Safe Medication Practices. ISMP Med Saf Alert Acute Care. Safety briefs: Safe ways to restock ADCs. 2013;18(19):2-3.

[10] Institute of Safe Medication Practices. ISMP Med Saf Alert Nurse Advise -ERR. Building a case for medication reconciliation. 2006;4(4):1.

[11] Institute of Safe Medication Practices. ISMP Med Saf Alert Nurse Advise -ERR. Getting to the route of the problem: Oral and IV doses differ. 2007;5(1):1.

[12] Institute of Safe Medication Practices. ISMP Med Saf Alert. Protease inhibitors and renal effects. 1997;2(4):2.

[13] Institute of Safe Medication Practices. ISMP Med Saf Alert. ISMP Quarterly Action Agenda: July- September 2000. Look/sound-alike drug names, ambiguous or look-alike labeling and packaging. 2000;5(20): 2.

[14] Institute of Safe Medication Practices. ISMP Med Saf Alert Acute Care. Table 2. Top 10 drugs associated with severe hypersensitivity by reaction type. 2014;19(9):2-3.

[15] Institute of Safe Medication Practices. ISMP Med Saf Alert. Safety briefs. 1999;4(13): 2.

[16] Institute of Safe Medication Practices. ISMP Med Saf Alert. 2000;5(19).

[17] Institute of Safe Medication Practices. ISMP Med Saf Alert. Safety briefs. 2001;6(11): 2.

[18] Institute of Safe Medication Practices. ISMP Med Saf Alert Acute Care. Abandon use of immediate-release nifedipine for hypertensive crisis. 2004;9(15): 3.

[19] Institute of Safe Medication Practices. ISMP Med Saf Alert Acute Care. Issues related to drug information. 2004;9(21):3.

[20] Institute of Safe Medication Practices. ISMP Med Saf Alert Acute Care. Building a case for medication reconciliation. 2005;10(8):1.

[21] Institute of Safe Medication Practices. ISMP Med Saf Alert Acute Care. Nurse and pharmacist resolve oral-to-IV dosing conflict. 2006;11(1):3.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on December 28, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type of error and the factors contributing to the errors when sufficient information was provided by the reporter. [22]

Table 3: FAERS Search Strategy	
Date Range	**August 13, 2013 to December 1, 2015**
Product	**Enalapril; Enalapril maleate** [Product Active Ingredient] **Epaned** [Product Name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search identified 21 cases, of which none are relevant for this review.

[22] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[23] along with postmarket medication error data, we reviewed the following EPANED label and labeling submitted by Silvergate Pharmaceuticals on February 26, 2016 and February 29, 2016.

- Container label submitted February 26, 2016
- Carton labeling submitted February 26, 2016
- Prescribing Information submitted February 29, 2016

G.2 Label and Labeling Images

Container Label

[23] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/s/

SARAH E THOMAS
04/19/2016

CHI-MING TU
04/20/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 208686	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Epaned (b) (4) (proposed) Established/Proper Name: Enalapril Maleate Dosage Form: Solution Strengths: 1mg/mL		
Applicant: Silvergate Pharmaceuticals, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: November 24, 2015 Date of Receipt: November 24, 2015 Date clock started after UN: n/a		
PDUFA Goal Date: September 24, 2016	Action Goal Date (if different): n/a	
Filing Date: January 23, 2016	Date of Filing Meeting: January 11, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s): - Treatment of hypertension in adults and children older than 1 month - Treatment of symptomatic heart failure - Treatment of asymptomatic left ventricular dysfunction		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

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

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): PIND 125621	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☐	☒		Request sent to CDER-DRTL on 1/5/16 and 1/22/16

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

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

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

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

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

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

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

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

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

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

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

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☐	☒		Enalapril maleate received an orphan drug designation (12-3767) on January 30, 2013

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

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

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

[4]

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

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

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

If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	A link to the labeling was included in the consult.
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** April 16, 2015 (PIND 125621) ***If yes, distribute minutes before filing meeting***	☒	☐		The minutes were included in the applicant's submission.
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 11, 2016

BACKGROUND:

Epaned (Enalapril maleate) is an angiotensin-converting enzyme (ACE) inhibitor indicated for the treatment of hypertension in patients older than 1 month, the treatment of symptomatic heart failure, and the treatment of asymptomatic left ventricular dysfunction. The effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion.

Silvergate pharmaceuticals developed a read-to-use Oral Solution of enalapril maleate at 1mg/mL and is seeking approval of this new formulation via the 505(b)(2) pathway, using Vasotec® tablets (NDA 18998) as the reference listed drug. They also cross-reference NDA 204308 for enalapril maleate Powder for Oral Solution.

A type B pre-IND meeting was held on April 2015 to discuss the approval pathway and requirements for the development of the ready-to-use Epaned Oral Solution 1mg/mL.

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 Oral Solution to Epaned Powder for Oral Solution reconstituted, under fasted conditions.

REVIEW TEAM:

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

OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Martina Sahre / Lars Johannesen	Y
	TL:	Raj Madabushi	N
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Muriel Saulnier	Y
	TL:	Al Defelice	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Wendy Wilson	N
	RBPM:	Maryam Changi	Y
• Drug Substance	Reviewer:	Hari Sarker	N
• Drug Product	Reviewer:	Sherita McLamore	N
• Process	Reviewer:	Sung Kim	N
• Microbiology	Reviewer:	Denise Miller	N
• Facility	Reviewer:	Cassandra Abellard	Y
• Biopharmaceutics	Reviewer:	Joan Zhao	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Elsbeth Chikhale (Acting Biopharm TL)		N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Zarna Patel	N
	TL:	Amy Toscano	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Sarah Thomas	Y
	TL:	Alice Tu	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other attendees	Stephen Grant		Y
	Michael Monteleone		Y
	Colleen Locicero		Y
	Tri Bui Nguyen		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Norman Stockbridge, MD, PhD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): April 27, 2016 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): Wrap-up: August 8, 2016 Primary review: August 17, 2016 CDTL review: August 31, 2016 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

SABRY SOUKEHAL
01/22/2016