

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204308Orig1s000

OTHER REVIEW(S)

Project Manager Overview
NDA 204308
Epaned (enalapril maleate) Powder for oral solution 1 mg/ 1ml

Background:

On August 10, 2012, NDA 204308 was submitted by Silvergate Pharmaceuticals, Inc pursuant to Section 505(b)(2) of the FD&C Act for enalapril maleate, USP Powder for Oral Solution for the treatment of hypertension in pediatric patients [REDACTED]^{(b)(4)}. This 505(b)(2) application relies upon the FDA's finding of safety and efficacy for the listed drug VASOTEC (enalapril maleate), NDA 18998. The review priority for this application was determined to be STANDARD and a PDUFA goal date of June 10, 2013 was assigned. The Division issued a Complete Response on June 7, 2013 because agreement on labeling could not be reached. The Division asserted that the Applicant's proposal to restrict product labeling to a pediatric population was artificial and should be expanded to include adults. The Applicant resubmitted the NDA on June 14, 2013, the Division considered this a Class 1 resubmission and assigned an August 14, 2013 PDUFA goal date.

At the time of initial submission the applicant had a pending Orphan Drug Designation Request. On January 30, 2013 the Office of Orphan Products Development (OOPD) granted an orphan-drug designation for *treatment of hypertension in pediatric patients*.

Because of its orphan designation, this application did not trigger PREA and was not reviewed by the Pediatric Review Committee (PeRC); further, the product is appropriately labeled for use in all relevant pediatric populations.

This NDA was the subject of a Pre-IND meeting under PIND 109473 on October 1, 2010.

This Application received an Overall Acceptable recommendation in EES on July 19, 2013.

This Application was reviewed and cleared for action by the 505(b)(2) committee on July 8, 2013.

NDA Reviews and Memos

Division Director's Memo

Dr. Norman Stockbridge; August 13, 2013, June 6, 2013

The Summary memo of August 13, 2013, outlines that the labeling issues which led to a Complete Response in the first cycle have been resolved and that the application can be approved. In his memo of June 6, 2013, Dr. Stockbridge summarizes that the only open issue responsible for a Complete Response action is agreement on labeling. Dr. Stockbridge describes that the proposed formulation seemed suitable for use in adults and that the restriction to use in children was artificial.

CDTL Memo

Dr. Rajinkanth Madabushi; August 13, 2013; June 5, 2013

Recommended Action: Approval

In his memo of June 5, 2013, Dr. Madabushi summarizes that this application should be approved for the treatment of hypertension in adults and pediatrics (1 month to 16 years of age).

Clinical Review

Dr. Khin U; May 31, 2013; December 5, 2012

Recommended Action: Approval

Please see December 5, 2012 review for details on Dr. U's approval recommendation. Dr. U's memo of May 31, 2013 is in response to an Office of Orphan Drug Products request for the Division to opine on the clinical superiority of the proposed drug product compared to VASOTEC. Dr. U concludes that there is no data to support a superiority claim of Epaned over Vasotec for the indication: "treatment of hypertension in pediatric patients 1 month to 16 years of age."

Clinical Pharmacology

Dr. Martina Sahre; December 14, 2012

Recommended Action: Approval

Please see review for details.

Chemistry Review

Dr. Sherita McLamore-Hines; December 6, 2012; May 10, 2013, July 24, 2013

Recommended Action: Approval

In her review of July 24, 2013, Dr. McLamore-Hines reports that the application can be approved from a CMC perspective.

Consult/Other Reviews:

OPDP

2013-05-15 – Labeling Review

DMEPA

2013-02-19 – Trade Name Review

2013-04-12 – Labeling Review

2013-06-07 – Trade Name Review

2013-07-03 – Trade Name Review

2013-07-10 – Labeling Review

2013-07-18 – Labeling Review

SEALD

2013-08-08 – SRPI Review

Action Items:

An Approval letter will be drafted for Dr. Stockbridge's signature.

By Michael Monteleone

August 13, 2013

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

/s/

MICHAEL V MONTELEONE
08/13/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 204308	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Epaned Established/Proper Name: enalapril maleate Dosage Form: powder for oral solution Strengths: 1 mg/ml after reconstitution		
Applicant: Silvergate Pharmaceuticals		
Date of Receipt: June 14, 2013		
PDUFA Goal Date: August 14, 2013		Action Goal Date (if different):
RPM: Michael Monteleone		
Proposed Indication(s): Proposed: treatment of hypertension in adults and children older than one month, to lower blood pressure		

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)
Vastotec (enalapril) NDA 018998	Full Prescribing Information

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

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA/BE studies (SG01-01, SG01-02 and SG01-03).

The development program was designed to be able to bridge to the efficacy and safety findings of NDA 18-998. To that end, the applicant conducted three relative bioavailability studies.

The key findings were as follows:

- When administered in a fasted state, enalapril maleate pediatric oral solution 10 mL (1 mg/mL) was bioequivalent to Vasotec® 10 mg tablets.
- When enalapril maleate pediatric oral solution was administered in a fed state (after a high fat meal), C_{max}, AUC_{last}, and AUC_{inf} of enalapril and enalaprilat were lower compared to administration of the oral solution in the fasted state. C_{max} decreased by 46 and 36% for enalapril and enalaprilat, respectively. AUC_{last} and AUC_{inf} decreased by approximately 14 and 15% for enalapril and 23 and 20% for enalaprilat, respectively. The observed decrease in C_{max} and AUC is not expected to be clinically significant.

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 without the published literature)?

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

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

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

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

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

YES NO

RELIANCE ON LISTED DRUG(S)

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

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

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

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Vasotec (enalapril)	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 new dosage form, albeit one that can be achieved by following instructions for extemporaneous preparation included in the approved labeling of the listed drug.

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

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

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

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

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

YES NO

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

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

YES NO

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

N/A YES NO

If this application relies only on non product-specific published literature, answer “**N/A**”
If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

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

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

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

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 18998 (Vasotec Tablets); NDA 19221 (Vaseretic Tablets) and generics ANDAs 075486, 075483, 075501, 075479, 075657, 075480, 075472, 075480, 075472, 075178, 76486, 75909, 75624, 75788, 75727

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.*

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

/s/

MICHAEL V MONTELEONE
08/13/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	EPANED (enalapril) Powder for Oral Solution
Applicant	Silvergate Pharmaceuticals
Application/Supplement Number	NDA 204308
Type of Application	Original
Indication(s)	Treatment of hypertension in adults and children older than one month
Established Pharmacologic Class ¹	Angiotensin-converting enzyme inhibitor
Office/Division	ODE I/DCRP
Division Project Manager	Michael Monteleone
Date FDA Received Application	June 14, 2013
Goal Date	August 14, 2013
Date PI Received by SEALD	August 6, 2013
SEALD Review Date	August 8, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

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

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: *There should be white space before the product title line.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The reference in the BW should be only the numerical identifier (5.1); the summarized statement in the first bullet should also have a reference.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

YES

Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

Selected Requirements of Prescribing Information

- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

Selected Requirements of Prescribing Information

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:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“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** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

ELIZABETH A DONOHOE
08/08/2013

LAURIE B BURKE
08/08/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Memo

Date: July 18, 2013

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Epaned (Enalapril Maleate Powder for Oral Solution)
1 mg/mL

Application Type/Number: NDA 204308

Applicant: Silvergate Pharmaceuticals

OSE RCM #: 2013-1449-1

***** This document contains proprietary and confidential information that should not be released to the public.*****

INTRODUCTION

This review evaluates the revised container labels and carton labeling for Epaned (Enalapril Maleate Powder for Oral Solution) received on July 15, 2013 (Appendices A through C). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2012-1914 dated April 12, 2013 and OSE Review # 2013-1449 dated July 10, 2013.

MATERIAL REVIEWED

DMEPA reviewed the revised container labels and carton labeling received on July 15, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review #2012-1914 dated April 12, 2013 and OSE Review #2013-1449 dated July 10, 2013 to ensure all our recommendations were implemented.

CONCLUSIONS AND RECOMMENDATIONS

We find the revised labels and labeling acceptable. We have no additional comments at this time.

Please copy the division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

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/s/

KIMBERLY A DE FRONZO
07/18/2013

IRENE Z CHAN
07/18/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Memo

Date: July 10, 2013

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Epaned (Enalapril Maleate Powder for Oral Solution)
1 mg/mL

Application Type/Number: NDA 204308

Applicant: Silvergate Pharmaceuticals

OSE RCM #: 2012-1914

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1. INTRODUCTON

This review evaluates the revised container label, carton, and insert labeling for Epaned (NDA 204308) submitted in response to the Division of Medication Error Prevention and Analysis' (DMEPA) comments and the Complete Response (CR).

2. REGULATORY HISTORY

On June 5, 2013, the Applicant submitted revised container label and carton labeling in response to DMEPA's comments in OSE Review 2013-694 dated April 12, 2013.

On June 7, 2013, a CR letter was issued to the Applicant citing labeling deficiencies relating to the proposed indications. On June 14, 2013, the Applicant submitted a Resubmission-SN0020 in response to the CR. However, on June 20, 2013, the Applicant submitted a labeling amendment (SN0021) which provides for a revised package insert to remove the heart failure and asymptomatic left ventricular dysfunction indications from the proposed package insert submitted on June 14, 2013.

The proposed proprietary name for this product, Epaned, was found to be acceptable under the Final Proprietary Name Review OSE RCM#2013-1488 dated July 3, 2013.

3. METHODS AND MATERIALS REVIEWED

3.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels for Epaned and Ora-Sweet SF Diluent submitted June 5, 2013 (Appendices A and B)
- Carton Labeling submitted June 5, 2013 (Appendix C)
- Insert Labeling submitted June 20, 2013 (no image)

3.2 PREVIOUSLY COMPLETED REVIEWS

We evaluated our recommendations made in OSE Review# 2012-1914 (dated April 12, 2013) to assess whether our recommendations were implemented and to ensure the revisions adequately address our concerns from a medication error perspective.

4. DISCUSSION

We noted the Applicant incorporated recommendations forwarded by the review division from DMEPA's review OSE RCM #2012-1914. However, the Applicant incorporated additional revisions to the labels and labeling that were not recommended nor reviewed by DMEPA.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

A review of the revised container labels and carton labeling have identified concerns with the presentation of the proprietary name and graphic art work that negatively affect the readability of the proprietary name. Also, further clarification can be made to the recording of the discard date in the mixing instructions as well as the principal display panel of the container label. In addition, upon consultation with the ONDQA Reviewer, it was confirmed that the drug substance is highly soluble requiring a very low amount of the Ora-Sweet diluent to render the product to a solution and avoiding the potential for caking. Therefore, the proposed mixing instructions appear adequate. We will provide recommendations in section 5.1 to improve the readability of the labels and labeling to promote the safe use of the product.

5. CONCLUSION AND RECOMMENDATION

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and minimize distraction of important information on the labels and labeling to promote the safe use of the product. Therefore, DMEPA recommends the following be forwarded to the Applicant for implementation prior to approval of this NDA:

5.1 COMMENTS TO THE APPLICANT

A. *Epaned Container, Ora-Sweet SF Container, Epaned Carton*

1. Revise the proprietary name to appear in title case (i.e., revise ‘epaned’ to ‘Epaned’) to enhance the readability of the proprietary name.
2. Delete or minimize the prominence of the graphic art work (to the left of the proprietary name) by decreasing the size and relocating the graphic away from the proprietary name to increase the readability of the proprietary name.

B. *Ora-Sweet SF Container*

1. Increase the prominence of the word “Diluent” through the use of red color font, boxing, increased font size, or other means, in order to help further differentiate the diluent bottle from the drug substance bottle and mitigate confusion between these two similar looking bottles. Consider a format similar to:

Diluent
for
Epaned

C. *Epaned Container*

1. Replace the statement [REDACTED] (b) (4) on the principal display panel with the statement “Discard unused portion after: _____” to avoid confusion [REDACTED] (b) (4) discard date. Also, revise the following statement to read “Discard 60 days after reconstitution”. Ensure there is sufficient space for the pharmacist to enter the discard date.

2. Consider relocating the “Rx Only” statement to the bottom right hand corner of the principal display panel if additional white space is needed to accommodate the discard date entry.
3. In order to align with the above recommendation, revise Step 6 of the “(b)(4)” to read “Calculate 60 days from the date of reconstitution. Write this date as the discard date on the front label.” and delete the sentence “Record reconstitution date on front label”. Please ensure this revision is appropriately reflected in the insert labeling under section 2.6 “Preparation of Epaned”.
4. Include the last instruction that starts with “Tear off these mixing instructions...” as a step of the “(b)(4)” to prevent this information from being missed. Thus, the last step should appear as: “8. Tear off these mixing instructions prior to dispensing.”

Please copy the division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

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/s/

KIMBERLY A DE FRONZO
07/10/2013

SCOTT M DALLAS
07/10/2013

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

Memorandum

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

Date: May 15, 2013

To: Michael Monteleone
Regulatory Project Manager
Division of Cardiovascular and Renal Products

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

Subject: **Enalapril Maleate Powder for Oral Suspension**
NDA: 204308
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on May 3, 2013, for Enalapril Maleate, Powder for Oral Suspension. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI. Our comments are based on the proposed labeling emailed to us on May 1, 2013.

Carton and Container Label

OPDP notes that the carton packaging includes information regarding recommended starting dose for the product but omits important material information from section 2 of the PI. For example, the carton packaging includes the recommended daily dose of the drug, but fails to include important contextual information regarding the maximum daily dose in pediatric patients. The PI states, "Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients."

Furthermore, OPDP notes that the graphic presented in conjunction with the tradename makes representation of the product's approved indication. Specifically, the graphic is representative of the heart, thereby rendering it promotional. OPDP recommends deleting the graphic.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the PPI, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
05/15/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: April 12, 2013

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: (b) (4) (Enalapril Maleate Powder for Oral Solution)
1 mg/mL

Application Type/Number: NDA 204308

Applicant: Silvergate Pharmaceuticals

OSE RCM #: 2012-1914

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for (b) (4) NDA 204308 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On August 10, 2012, Silvergate submitted this 505(b)(2) application under NDA 204308 citing Vasotec® (Enalapril maleate) tablets under NDA 018998 by Valeant Pharmaceuticals as the Reference List Drug (RLD). The labeling for (b) (4) is proposed to be similar to the Vasotec tablets labeling (which was revised on September 13, 2012 under Supplement 77). The main difference to the Vasotec labeling is that (b) (4) is not indicated for heart failure or asymptomatic left ventricular dysfunction. Therefore, information regarding those two indications has not been included in the proposed (b) (4) label. Other differences consist of the inclusion of pharmacokinetic data for (b) (4) as well as corresponding changes to the description, manufacturer, distributor, and proprietary name.

Vasotec tablets were approved on December 24, 1985 and are currently available in 2.5 mg, 5 mg, 10 mg, and 20 mg strengths. Enalapril maleate tablets are also available generically through a number of generic manufacturers with the first ANDA 075048 by Sandoz approved on August 22, 2000. There is currently no powder for oral solution dosage formulation of Enalapril available. If approved, this will be the first oral solution Enalapril product on the market. However, the currently approved insert labeling for Vasotec tablets provides instructions for the preparation of an oral suspension formulation using Vasotec tablets with Ora-Sweet SF™ diluent to achieve the same 1 mg/mL concentration as the proposed product.

On October 19, 2012, the Applicant submitted a revised package insert and pediatric plan addressing patients (b) (4) to 16 years of age as per the Filing Communication letter issued on October 2, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the revised insert labeling submitted on October 19, 2012.

- Active Ingredient: Enalapril Maleate, USP
- Indication of Use: Hypertension treatment in pediatric patients (b) (4)
- Route of Administration: Oral
- Dosage Form: Powder for Oral Solution
- Strength: 1 mg/mL
- Dose and Frequency: The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be 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. Reconstitution with 150 mL of the provided Ora-Sweet® SF results in a 1 mg/mL (b) (4) oral solution.

- How Supplied: product is supplied as a kit:
 1. One 150 mL bottle contains 150 mg of Enalapril maleate powder for oral solution in an HDPE bottle with child-resistant cap
 2. One 150 mL bottle of Ora-Sweet SF
- Storage: at 25°C (77°F); excursions permitted to 15°C -30°C (59°F -86°F) [see USP Controlled Room Temperature].
- Container and Closure Systems: (as provided by ONDQA)

<i>Container</i>	<i>Closure</i>
White (opaque) 150 (b) (4) HDPE, round bottle, Drug (b) (4)	White (opaque) (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS and ISMP databases for Enalapril or Vasotec medication error reports. We also reviewed the (b) (4) labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	December 31, 2012 (search conducted without time limit)
Drug Names	(Enalapril as active ingredient) (Vasotec as trade name) (Vasotec* as verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database searches identified 246 cases. Each case was reviewed for relevancy and duplication. After individual review, 232 cases were not included in the final analysis for the following reasons:

1. Suicide attempt or intentional overdose (n=41)

2. Accidental exposure (child inadvertently ingested medication or drug was given to wrong patient (n=11)
3. Medication error did not involve Enalapril or Vasotec (n=4)
4. Adverse events reported without a medication error (n=16)
5. Adverse events reported with use of generic Enalapril (n=43)
6. Lack of efficacy/drug ineffectiveness with generic Enalapril (n=28)
7. Product substitution issue (dispensed generic Enalapril instead of Vasotec) (n=9)
8. Missed dose/medication not administered as scheduled/poor compliance (n=11)
9. Monitoring error (was not aware patient already received Capoten when administered Vasotec) (n=1)
10. Transcribing error due to use of symbols not understood by nurse (physician used '\$' as abbreviation for 'd/c' to discontinue an order (n=1)
11. Entry error by technician resulting in overdose (decimal point was omitted so order for '2.5 mg' was read as '25 mg') (n=1)
12. Product quality issue (tablets were crumbly/crushed/"soft", or bottle contained mixture of multiple strengths). These reports have been forwarded to DQRS for their attention (n=4)
13. Use of expired medication (n=1)
14. Foreign cases (excluded because uncertain if the product marketed in these countries is in same packaging configuration or if the product has the same dosing as in United States) (n=61)

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on December 31, 2012 for additional cases and actions concerning Enalapril or Vasotec. The PubMed search conducted using the terms medication error and Vasotec did not identify any reference. Therefore, the same search was reran using the generic name Enalapril (instead of Vasotec) and one reference was identified discussing "taking the side-effects of drugs into account" but it did not discuss a medication error.

Similarly, the ISMP database search conducted using only the brand name Vasotec did not identify any reference. Therefore, a second search using the generic name Enalapril (instead of Vasotec) was performed which yielded one citation. The citation reported "Enalapril 2.5 mg IV was administered to a patient after transfer from a critical care unit to a medical unit. The drug had been discontinued upon transfer, but the orders had not yet been transcribed." Since this is a transcription error, no action is warranted.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label for Enalapril submitted on August 10, 2012 (Appendix B)
- Carton Labeling for Enalapril submitted on August 10, 2012 (Appendix C)
- Container Labels for Ora-Sweet SF diluent submitted on August 10, 2012 (Appendix D)
- Insert Labeling submitted on October 19, 2012 (no image)

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had not conducted any previous review for Enalapril or Vasotec.

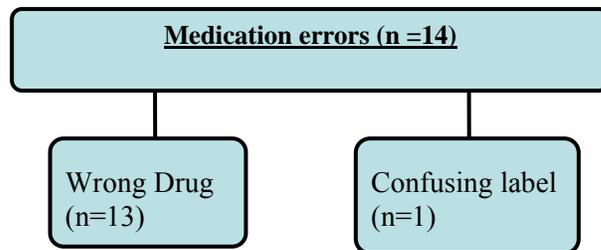
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the (b)(4) product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, only fourteen (b)(4) medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of medication error cases included in the review by type of error.

Figure 1: Vasotec (Enalapril) medication errors categorized by type of error



¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² 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>. Accessed June 1, 2011.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The confusing label complaint (case #5760804v.1) received by the Agency on 1/22/1993 involved an order for Vasotec IV 1.25 mg q 6h. The pharmacy sent 4 vials to cover a 24 hour period. However, two days later, the dose was increased to Vasotec IV 2.5 mg q6h. The Pharmacist then sent an extra 4 vials/day (for a total of 8 vials per day). The nurse used 2 vials to make each dose of 2.5 mg thinking it was 1.25 mg PER VIAL instead of 1.25 mg/mL (2 mL = 2.5 mg /vial). It was reported the error occurred since the 1.25 mg designation was the most prominent information on the label. While this issue is concerning, no action is warranted at this time since the Vasotec injectable product (approved on 2/9/1988 under NDA 019309) was discontinued from the market on 8/20/2010 and no Enalapril product is currently available in an injectable formulation.

The most common type of medication error that occurred with Vasotec and Enalapril involved confusion with other products on the market due to similarities in the names and/or product characteristics. Products that were confused with Vasotec or Enalapril included: Zestril (case #3832885v.2), Metformin (case #3916341v.2), Zocor (case #3985929v.1 and #4051778v.1), Synthroid (case #3987108v.1), Furosemide (case #3991407v.1), Toprol XL (case #3999870v.1), Lisinopril (case #4025808v.1 and #6203310v.1), Anafranil (case #5668626v.1), Coumadin (case #6026395v.1), Vesicare (case #6506194v.1), and with “other” drugs that were unspecified (case #3875998v.1). Since the product confusion reported occurred with multiple products from multiple suppliers, affecting labeling changes to one of these products may in turn result in confusion with another unsuspecting product on the market leading to new errors amongst products previously not deemed problematic. Therefore, no labeling revision is recommended at this time for these cases, because no two products appear to be at an increased risk of error or harm.

It should be noted that the currently approved Vasotec Tablets insert labeling already contains the following instructions for the preparation of an oral suspension to result in a 1 mg/mL final concentration.

Add 50 mL of Bicitra® to a polyethylene terephthalate (PET) bottle containing ten 20 mg tablets of VASOTEC and shake for at least 2 minutes. Let concentrate stand for 60 minutes. Following the 60-minute hold time, shake the concentrate for an additional minute. Add 150 mL of Ora-Sweet SF™ to the concentrate in the PET bottle and shake the suspension to disperse the ingredients. The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 30 days. Shake the suspension before each use.

The compounded oral suspension and the proposed oral solution share similarities in the final concentration (1 mg/mL) and the same diluent (Ora-Sweet SF). However, there are distinct differences in the preparation process (shake for 2 minutes then hold for 60 minutes vs. 30 seconds and no hold time), storage conditions (refrigeration vs. room temperature), and stability (30 days vs. 60 days). Due to the similarities, we considered the potential errors that may exist from confirmation bias where the proposed oral solution may be presumed to be the same as the compounded oral suspension product leading to wrong storage and/or discard date. The first scenario to

be considered is when the patient may confuse the proposed product for the old compounded product but this risk poses little or no clinical consequence to the patient since the proposed product has a longer stability and a more convenient storage condition compared to the compounded product. We feel the potential for product confusion will further be minimized due to the fact that the practice of manually compounding by crushing the tablets will eventually become obsolete upon the introduction of a more convenient, commercially available oral solution. In addition, we feel medication errors may further be mitigated through labels and labeling revisions as recommended in section 4.

It was unclear in the submission whether this product will need to be shaken prior to each use (after reconstitution) since it is an oral solution and not an oral suspension formulation. Therefore, we consulted with ONDQA who confirmed via verbal and written communication that shaking would only be required at the time of reconstitution of the product by the pharmacist. However, after the product is given to the patient, it should be in the form of a homogeneous solution and as such, a “shake well” statement would not be required.

Due to the opaque color of the drug bottle, we considered the risk of “caking” of the powder that may not be evident to the preparer prior to reconstitution. We consulted with ONDQA regarding the need for additional instructions to ensure proper mixing of the powder prior to reconstitution to avoid inconsistent dosing in the event of “caking”. However, ONDQA confirmed that due to the high solubility of the drug substance, the risk of under/overdosing due to “caking” is unlikely as solubility is almost instantaneous upon direct contact with the diluent.

We also evaluated the directions for reconstitution for clarity and ease of performance and noted that the directions for reconstitution states to “add *approximately* one-half (75 mL) of the Ora-Sweet SF bottle to the powder bottle”. Although we recognize the recommendation is requiring only an estimation of the amount of the diluent to be added to the drug bottle, it may be difficult for the preparer to conduct this estimation without any form of measuring mechanism, especially considering that the bottle is opaque and may be difficult to determine the half-way point. Therefore, we recommend revising the directions to include the use of a suitable measuring device for measuring out the diluent quantity for reconstitution (e.g., a graduated cylinder, a beaker, or similar device) that would be readily available at the pharmacy setting where the reconstitution is expected to take place.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of the product.

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA.

Comments to the Division:

A. Insert Labeling

1. Add another sentence in the section entitled “Preparation of (b) (4) in the Dosage and Administration section to instruct the preparer to (b) (4).
(b) (4)
2. Because the symbols $>$, $<$, \leq , \geq appear on the ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations, we recommend using the appropriate terms “greater than, less than”, etc... instead of the symbols as they have been mistaken as the opposite of its intended meaning and practitioners have mistakenly used the incorrect symbol. Specifically, we request the following sections be revised:

The Dosage and Administration, Dosage Adjustment in Hypertensive Patients with Renal Impairment subsection uses the symbols $>$ and \leq . Please revise the symbols to use the appropriate terminology. In addition, we note the paragraph and table use the overlapping number of 30 and 80. The use of overlapping numbers can lead to confusion. Consider if it is appropriate to present the creatinine clearance groups as 81 mL/min or greater, 31 mL/min to 80 mL/min, and 30 mL/min or less.
3. Under the How Supplied section 16, revise the first bullet to read “One bottle containing 150 mg of Enalapril Maleate Powder for Oral Solution in an HDPE bottle with child-resistant cap to provide 1 mg/mL final concentration after reconstitution”.
4. Under the How Supplied section 16, revise the second bullet point to read: “One bottle containing 150 mL of Ora-Sweet SF provided as the diluent for reconstitution.”
5. Revise the storage condition statement to include the units $^{\circ}\text{C}$ or $^{\circ}\text{F}$, respectively, and replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers because a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the statement (b) (4) to read “...excursions permitted to 15°C to 30°C (59°F to 86°F)”.

DMEPA recommends the following be implemented prior to approval of this NDA.

Comments to the Applicant:

A. General Comment:

Add the use of a measuring device to the statement “Add approximately one-half (75 mL) of the Oral-Sweet SF bottle to the (b) (4) Powder for Oral Solution” found under the preparation or mixing instructions in the insert labeling under section 2, and in the (b) (4) drug bottle and Oral-Sweet diluent bottle. Revise this statement to read “Measure approximately 75 mL of the Oral-Sweet SF using a suitable measuring device and add to the (b) (4) Powder for Oral Solution” since it is difficult for the preparer to ascertain the correct volume through an opaque bottle.

B. Container Label:

1. Revise the proprietary name, established name and strength to appear similar to:

(b) (4)

(Enalapril Maleate
Powder for Oral Solution)

1 mg/mL

2. Ensure the established name (which includes the dosage form) is at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features and has prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).
3. Remove or minimize and relocate the graphic art work on the principal display panel above the proprietary name because it is distracting and interferes with the readability of the proprietary name.
4. Remove the (b) (4) r to minimize distraction of important information on the principal display panel.
5. Relocate the “Rx only” statement to the bottom of the principal display panel away from the center to avoid crowding of more important information.
6. Revise the statement (b) (4) on the principal display panel to read: “When reconstituted, each mL contains: Enalapril Maleate 1 mg.”
7. Add a net quantity statement on the principal display panel to read: “150 mL (when reconstituted)”.
8. Add the degree sign and remove the hyphen from the Storage statement. Revise the storage statement (b) (4)

(b) (4) to read "...excursions permitted to 15°C to 30°C (59°F to 86°F)".

9. Revise the top portion of the side panel to appear more consistent with the principal display panel. Consider a format similar to the following:

Mixing Instructions for (b) (4)™
Enalapril Maleate Powder for Oral Solution, 1 mg/mL
(When reconstituted, each mL contains: Enalapril maleate 1 mg)

10. Delete the "(b) (4)" statement on the side panel.
11. Relocate the Quick Code to the retained side panel. Ensure there is adequate white space between the Quick Code and the bar code.
12. To further assist patients with proper usage of the reconstituted oral solution within the 60 days expiration date, consider revising the statement "Discard 60 days after reconstitution" to appear prominently on the retained side panel as (b) (4) then add the statements "Discard 60 days after this date. For example:
(b) (4) Discard 60 days after this date.

C. Carton Labeling

1. See comments B.1. through B.8..
2. Simplify the "Contains:" statement with the following revised version:
 - i. 1 bottle containing 150 mg Enalapril Maleate Powder for Oral Solution
 - ii. 1 bottle containing 150 mL Ora-Sweet SF provided as a Diluent for reconstitution
3. Increase the prominence of the statement "Discard 60 days after reconstitution" through the use of large font size, bolding, capitalized lettering, red coloring, boxing, or similar means.
4. Delete the trademark statement on the principal display panel below the storage statement to accommodate other important information as this statement is already included on the back panel.
5. Ensure the lot number and expiration date is included on the carton labeling as it currently does not appear to indicate this information.

D. Ora-Sweet SF Container Label

1. See comment B.8.
2. Include the type of flavoring used by revising the statement (b) (4) with the specific flavoring of the vehicle used in Ora-Sweet SF. For example: Revise it to state... "Berry-flavored Sugar-Free Syrup Vehicle" so the flavor information is readily available to the end user.

3. Increase the prominence of the statement “Diluent for (b) (4) TM”. Consider possibly increasing the prominence of the word “Diluent” by increasing the font size, font color, bolding, or some other means such as presenting the statement in a stacked format. For example,

Diluent
for (b) (4) TM

4. Revise the Directions for reconstituting (b) (4) as follows:
 - i. Remove the reference to the volume “150 mL” from step 2 since it is redundant.
 - ii. Replace step 5 with the statement (b) (4)
[Redacted]
 - iii. Replace step 6 with the statement (b) (4)
[Redacted] for Oral Solution bottle”.

If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

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 post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

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

/s/

KIMBERLY A DE FRONZO
04/12/2013

SCOTT M DALLAS
04/12/2013

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 # 204308 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: enalapril maleate Dosage Form: powder for oral solution Strengths: 1 mg/ ml (after reconstitution)		
Applicant: Silvergate Pharmaceuticals, Inc. Agent for Applicant (if applicable): Beckloff Associates, Inc.		
Date of Application: August 10, 2012 Date of Receipt: August 10, 2012 Date clock started after UN: NA		
PDUFA Goal Date: June 10, 2013	Action Goal Date (if different):	
Filing Date: October 9, 2012	Date of Filing Meeting: September 10, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): Treatment of hypertension in pediatric patients (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): PINE 109473				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, 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</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>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.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>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)].</p>		<p>X</p>																		
<p>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)]?</p> <p><i>If you answered yes to any of the above 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</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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 will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>			X	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

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

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>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), 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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
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)?	X			
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)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>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].</i></p> <p><i>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..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>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)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage 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.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):			X	
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 1, 2010	X			Pre-IND/Pre-NDA
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):			X	
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 10, 2012

BLA/NDA/Supp #: 204308

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: enalapril

DOSAGE FORM/STRENGTH: powder for oral solution, 1mg/ml after reconstitution

APPLICANT: Silvergate

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of hypertension in pediatric patients (b) (4).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael Monteleone	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Rajnikanth Madabushi		Y
Clinical	Reviewer:	Khin U	Y
	TL:	Thomas Marciniak	N
Clinical Pharmacology	Reviewer:	Martina Sahre	Y
	TL:	Divya Menon-Andersen	Y
Biostatistics	Reviewer:	Jialu Zhang	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Muriel Saulnier	Y
	TL:	Albert DeFelice	Y

Product Quality (CMC)	Reviewer:	Sherita McLamore-Hines	Y
	TL:	Kasturi Srinivasachar	Y
OSE/DMEPA (proprietary name)	Reviewer:	Kim Defronzo	N
	TL:	Irene Chan	Y

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No clinical studies.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>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</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Review Division	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): Label PLR formatting issues; PREA waiver incomplete <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MICHAEL V MONTELEONE
10/02/2012