

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

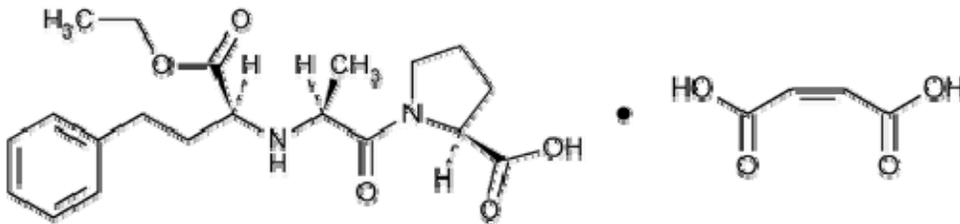
*APPLICATION NUMBER:*

**204308Orig1s000**

**CHEMISTRY REVIEW(S)**

Initial Quality Assessment  
Branch I

**OND Division:** Division of Cardiovascular and Renal Products  
**NDA:** 204-308  
**Applicant:** Silvergate Pharmaceuticals  
**Letter Date:** Aug 10, 2012  
**Stamp Date:** Aug 10, 2012  
**PDUFA Date:** Jun 10, 2013  
**Tradename:** (b) (4)  
**Established Name:** Enalapril maleate  
**Dosage Form:** Powder for oral solution, 1mg/mL after reconstitution  
**Route of Administration:** Oral  
**Indication:** Treatment of hypertension in pediatric patients (b) (4)  
(b) (4) of age  
  
**Assessed by:** Kasturi Srinivasachar  
**ONDQA Fileability:** Yes



## Summary

This is an e-CTD 505(b)(2) NDA application for (b)(4) (enalapril maleate) powder for oral solution. The reference listed drug is Vasotec (enalapril maleate) tablets (NDA 18-998), an ACE inhibitor, approved in 1985. The preparation of a suspension of 1mg/mL of enalapril maleate for pediatric use is described in the Vasotec package insert. This NDA claims a superior formulation which is easier to use and allows for more accurate dosing for the pediatric population. A pivotal bioavailability study comparing the powder for oral solution with Vasotec tablets in healthy volunteers has been carried out in support of this formulation. Only one meeting, a multi-disciplinary pre-IND meeting, was held with the Applicant in Oct. 2010. CMC issues discussed related to the adequacy of drug substance and drug product specifications and the amount of stability data that would be available at the time the NDA is submitted. The Applicant was told that their ID test in the drug product specification based solely on HPLC retention time was not adequate and a more specific test needed to be developed. They were also informed that the drug product specification should include content uniformity as per USP <905>, appearance of the reconstituted solution and reconstitution time. Regarding stability data, it was recommended that 12 months of long term and 6 months of accelerated data be available by the mid-point of the review cycle.

## Drug Substance

Enalapril maleate is a white to off-white crystalline powder with a melting point of (b)(4) °C. It has a water solubility of (b)(4). It is a synthetic compound with (b)(4). All CMC information for this drug substance is contained in DMF (b)(4) and a LOA has been provided. This DMF has been reviewed numerous times and the most recent review on Aug 5, 2010 concludes that it is adequate to support a Vasotec supplement. There are two annual reports and an amendment listed in DARRTS since that date. USP has a monograph for enalapril maleate.

## Drug Product

(b)(4) is a direct blend of (b)(4) w/w of enalapril maleate and (b)(4) of mannitol with an additional (b)(4) w/w of colloidal silicon dioxide. The powder blend is filled into white, 150 (b)(4) HDPE bottles to provide 150 mg of enalapril maleate per bottle. This powder blend is intended to be reconstituted with 150 mL of Ora-Sweet SF at the pharmacy and dispensed as a 1mg/mL solution. Each bottle of (b)(4) is co-packaged with a bottle containing 150 mL of Ora-Sweet SF manufactured by (b)(4). Reference is made to Type 4 DMF (b)(4) for complete information on Ora-Sweet SF. This DMF was last reviewed in 2008 and found to be adequate for (b)(4) which is a mixture of Ora-Sweet SF (b)(4). There have been several amendments submitted to the DMF since 2008.

Both excipients, mannitol and colloidal silicon dioxide are compendial grade. Mannitol functions (b)(4) and colloidal silicon dioxide is used (b)(4). The commercial pediatric formulation proposed in this NDA is based on a formulation developed by the (b)(4). The goal was to develop a formulation that would be stable for a few months after reconstitution when stored at ambient conditions. It is stated that the drug product in powder form is compatible with the container closure system as demonstrated by the primary stability data. In-use stability studies have also established the compatibility of the

reconstituted solution with the diluent, Ora-Sweet SF, in the original container closure over a period of <sup>(b) (4)</sup> conditions.



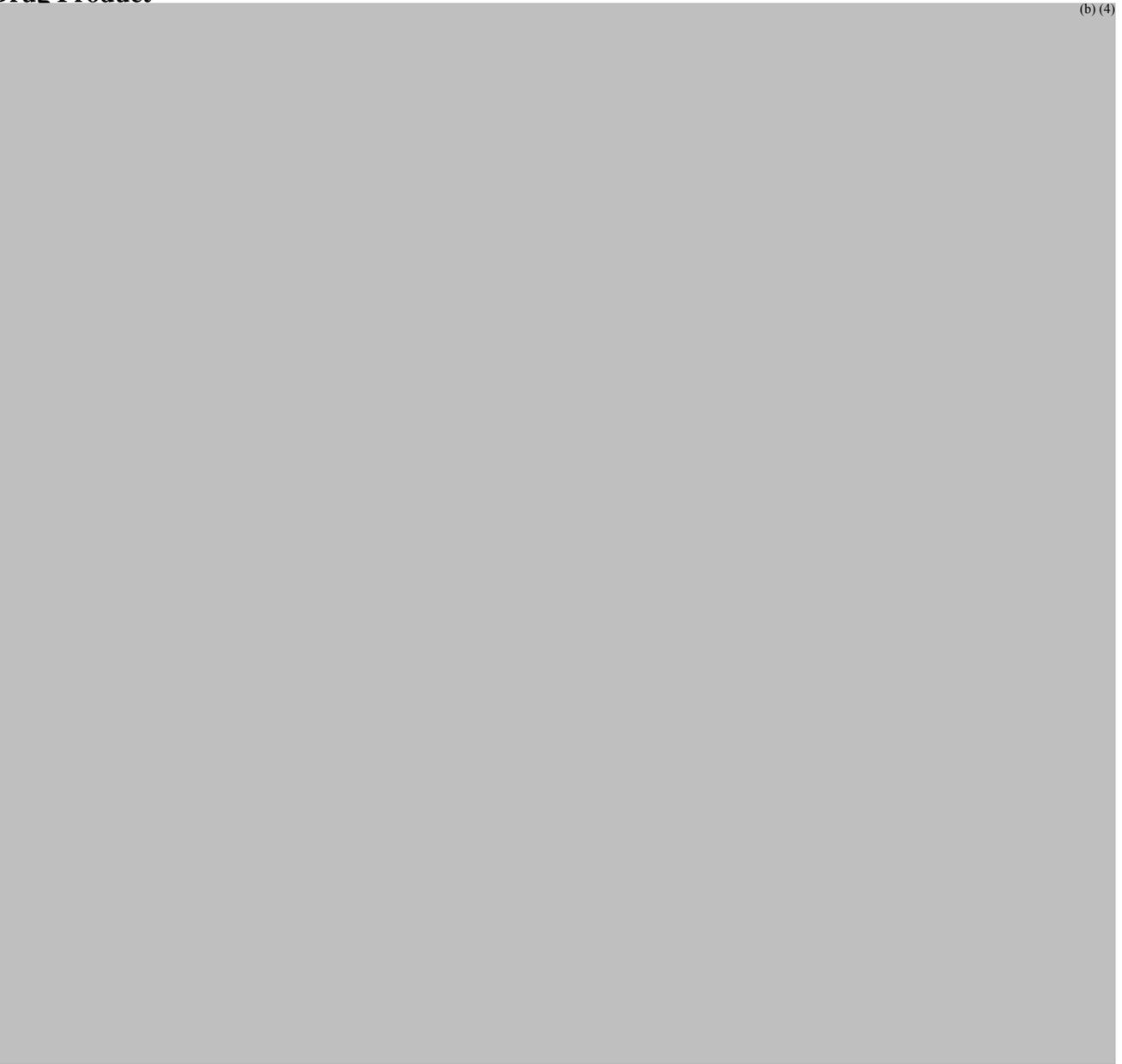
(b) (4)

## Critical Review Issues

### Drug Substance

- Any quality information submitted to DMF (b)(4) since the last review should be evaluated.
- The specifications in the NDA conform to USP but are not in the ICH Q3A format for impurities. Is this acceptable? Similarly, shouldn't the specific (b)(4) be listed?

### Drug Product



**Labeling**

- The package insert does not mention how individual doses should be measured for oral administration nor is there a measuring device, e.g. oral syringe, in the product kit. Is a specific device needed for this pediatric formulation or can this be left to the dispensing pharmacist's discretion?
- The following statement in the How Supplied section of the PI is misleading and should be changed or deleted—" (b) (4) ".
- The ingredients in Ora-Sweet SF should also be listed in the Description section of the PI.

**Comments and Recommendations**

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES; the reviewer should confirm the completeness and accuracy of the entries. Methods Validation by DPA is not deemed necessary based on a preliminary review since the 7 criteria in IQP 5105 are not met; however, the reviewer may choose to initiate MV if the in-depth review reveals concerns with any of the analytical methods. A categorical exclusion from environmental assessment has been requested. A single CMC reviewer is recommended since this is a very simple formulation and the submission has no QbD elements.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead

Aug. 20, 2012  
Date

Ramesh Sood  
Branch Chief

Aug. 20, 2012  
Date

**PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS  
FILING REVIEW FOR NDA**

**NDA Number:** 204-308      **NDA Type:** 3      **Established/Proper Name:** Enalapril maleate/ (b) (4)

**Applicant:** Silvergate Pharmaceuticals, inc      **Letter Date:** Aug 10, 2012      **PDUFA Goal:** June 10, 2013  
(standard review)

**Stamp Date:** Aug 10, 2012

**CMC Reviewer:** Sherita McLamore

**Biopharmaceutics Reviewer:** Akm Khairuzzaman

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		

6.	<p>For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b></p>			NA
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Information in DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Information in DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Information in DMF (b) (4)
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		Information in DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	N/A
23.	Have any Comparability Protocols been requested?	X		Container Closure
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		DMF (b) (4) for drug substance DMF (b) (4) for Ora-Sweet SF

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	X		Fileable for Product Quality. A separate filing review will be submitted for Biopharmaceutics by Akm Khairuzzaman
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			See Biopharmaceutics Filing Review

37.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X	Request in-use study with primary stability batches at 12 month time point subject to further evaluation by reviewer
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KASTURI SRINIVASACHAR  
08/27/2012

RAMESH K SOOD  
08/28/2012

## **NDA 204-308**

### **Enalapril Maleate Powder for Oral Solution, 1mg/mL after reconstitution**

**Silvergate Pharmaceuticals**

**Sherita D. McLamore-Hines, Ph.D.**

Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment

# Table of Contents

<b>Table of Contents</b> .....	Error! Bookmark not defined.
<b>Chemistry Review Data Sheet</b> .....	Error! Bookmark not defined.
<b>The Executive Summary</b> .....	Error! Bookmark not defined.
I. Recommendations .....	
A. Recommendation and Conclusion on Approvability.....	<b>Error! Bookmark not defined.</b>
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....	<b>Error! Bookmark not defined.</b>
II. Summary of Chemistry Assessments .....	<b>Error! Bookmark not defined.</b>
A. Description of the Drug Product(s) and Drug Substance(s).....	
B. Description of How the Drug Product is Intended to be Used .....	<b>Error! Bookmark not defined.</b>
C. Basis for Approvability or Not-Approval Recommendation.....	<b>Error! Bookmark not defined.</b>
III. Administrative .....	<b>Error! Bookmark not defined.</b>
A. Reviewer's Signature .....	<b>Error! Bookmark not defined.</b>
B. Endorsement Block .....	<b>Error! Bookmark not defined.</b>
C. CC Block .....	<b>Error! Bookmark not defined.</b>
<b>Chemistry Assessment</b> .....	Error! Bookmark not defined.
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....	
S DRUG SUBSTANCE.....	
P DRUG PRODUCT .....	
A APPENDICES .....	
R REGIONAL INFORMATION.....	
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	
A. Labeling & Package Insert .....	
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	
III. List Of Deficiencies To Be Communicated.....	

# Chemistry Review Data Sheet

1. NDA: 204-308
2. REVIEW: #3
3. REVIEW DATE: July 23, 2013
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Original Submission  
Amendment  
Amendment  
Amendment  
Amendment  
Amendment

August 10, 2012  
January 10, 2013  
March 5, 2013  
March 18, 2013  
April 19, 2013  
May 9, 201

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Amendment

June 14, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Silvergate Pharmaceutical, Inc  
Address: 5371 Gordon Way  
Dublin, OH 43017



## Chemistry Review Data Sheet

Representative: Beckloff Associates, Inc.  
7400 West 110th Street, Suite 300,  
Overland Park, KS 66210  
Telephone: 913-451-3955

Telephone: 614-783-2497

### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
  - b) Non-Proprietary Name (USAN): Enalapril Maleate
  - c) Code Name/# (ONDC only): n/a
  - d) Chem. Type/Submission
- Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of Hypertension in Pediatric Patients

11. DOSAGE FORM: Oral Powder for Solution

12. STRENGTH/POTENCY: 1 mg/mL after Reconstitution

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

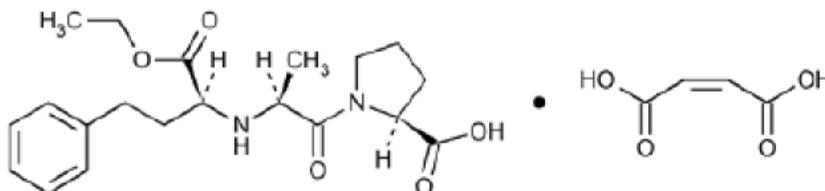
### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: L-Proline-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-, (Z)-2-butenedioate (1:1)

Molecular Formula:  $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$

## Chemistry Review Data Sheet

Molecular Weight: 492.52



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance	1	Adequate	12/06/2012	N/A
	II		(b) (4)	1	Adequate	1/26/2013	N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-998	NDA for the reference listed drug (Vasotec Tablets)

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	4/3/2013	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	Acceptable	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Categorical Exclusion 21 CFR 25 31(b) <i>Acceptable</i>	12/1/2012	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	

# The Chemistry Review for NDA 204-308

## The Executive Summary

### A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is approved. The applicant has demonstrated the capacity to manufacture drug product with adequate quality and stability.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase 4 activity recommendations.

## II. Summary of Chemistry Assessments

Enalapril maleate has been identified as the active pharmaceutical ingredient in this application. Enalapril maleate is manufactured by (b) (4). The drug substance is a pro-drug which undergoes hydrolysis to enalaprilat following oral administration. Enalapril maleate has a USP monograph and is an established active pharmaceutical ingredient that is approved for use under NDA 18-998. The drug substance is described as a white to off white crystalline powder with a molecular weight of 492.52 and a melting point of (b) (4) °C. Enalapril maleate drug substance has been fully characterized. The applicant references DMF (b) (4) for a complete description of the manufacturing process and all relevant characterization data pertaining to Enalapril maleate. DMF (b) (4) has been reviewed and is adequate to support this application.

The drug product, (b) (4) Powder for Oral Solution, is being developed for the treatment of hypertension in pediatric patients (b) (4). Enalapril maleate is currently approved in a tablet form under the brand name Vasotec® in NDA 18-998. Vasotec® was indicated in adults and in pediatric patients between 1 month and 16 years of age; however, the pediatric formulation did not exist. Thus, subsequent to the approval of NDA 18-998, to fill this void and circumvent the obvious problems associated with infants and young children ingesting tablets, the agency approved a package insert for Vasotec® Tablets which provided directions for preparing an oral suspension from the tablets. The drug product is presented as Powder for Oral Solution containing 150 mg of enalapril maleate per bottle. Each bottle of the Powder for Oral Solution will be co-packaged with a bottle of Ora-Sweet® SF. Ora-Sweet SF is commercially available, manufactured by (b) (4) and is pre-packaged in 150 (b) (4) HDPE bottles. Reconstitution of the Powder for Oral Solution with 150 mL of Ora-Sweet® SF should be executed by the pharmacist prior to dispensing to patients and will result in a 1 mg/mL solution of enalapril maleate.

The drug product is a direct blend formulation consisting of (b) (4) enalapril maleate and (b) (4) mannitol and (b) (4) colloidal silicon dioxide. The drug product is manufactured by (b) (4). The commercial batch size for the drug

## Executive Summary Section

product is (b) (4). The drug product is packaged in 150 mL round, white, HDPE bottle with a (b) (4) child resistant cap with a heat induction foil inner seal. The applicant provided a detailed description of the packaging components and referenced DMFs (b) (4) for a more comprehensive description.

The applicant included six months of long term and accelerated stability data for three registration lots of the drug product in the original application and a 12-month stability update in December 2012. The stability protocol for the Powder for Oral Solution included testing for appearance, identification (release only), content uniformity (release only), assay, related substances and water content. The long term stability data showed very little change and variability over the 12 month period. Under accelerated conditions, there was an observed increasing trend in the related substances (b) (4) and consequently a decreasing trend in the assay observed. Additionally, there was no statistical analysis performed. While the data were within the prescribed specifications limits, the applicant has not provided sufficient amount data to support the request (b) (4) month expiry for the powder for oral solution. Thus, based on ICH Q1E and the data submitted in this application an **18-month expiry** will be assigned to the Powder for Oral Solution.

In addition to the stability for the Powder for Oral Solution, the applicant included stability data for the reconstituted drug product. Regarding the reconstituted drug product, the applicant provided 12 weeks of data for the original in-use study and 8 weeks of data in the extended in-use study. During the review cycle, the applicant was asked to submit in-use stability data for the “aged” drug product. In response, the applicant provided up to 13 weeks of data for samples which had been stored for 12 months under ICH long term conditions and committed to performing annual in-use stability testing at 24 and 36 months. The samples were tested for appearance, assay, related substances, preservative content, microbial limits, pH, and antimicrobial effectiveness. All data were comparable and within the prescribed specifications limits. There was a notable and expected increase in the Enalaprilat content after 13 weeks (which is beyond the requested expiry); however, the reviewer feels that this increase is of no concerns as Enalaprilat is the active moiety of the drug substance. Accordingly, based on the data included in this application an (b) (4) **in-use period** will be assigned to the reconstituted drug product.

**B. Description of How the Drug Product is Intended to be Used**

The drug product, (b) (4) Powder for Oral Solution is being developed for treatment of hypertension in pediatric patients (b) (4). The usual recommended starting dose for the drug product is of 0.08 mg/kg once daily with a maximum daily dose of 40 mg. Each bottle of the Powder for Oral Solution will be co-packaged with a bottle of Ora-Sweet® SF. Ora-Sweet SF is commercially available, manufactured by (b) (4) and is pre-packaged in 150 (b) (4) HDPE bottles. The applicant references DMF (b) (4) for the manufacture and control of Ora-Sweet® SF. Reconstitution of the Powder for Oral Solution with 150 mL of Ora-Sweet® SF should be executed by the pharmacist prior to dispensing to patients and will result in a 1 mg/mL solution of enalapril maleate. The directions for reconstitution of the drug product included on the bottle are add of 75 mL Ora-Sweet® SF and shake well for 30 seconds then add of another 75 mL Ora-Sweet® SF and shake well for additional 30.

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

From a CMC perspective, this application is approved. The drug substance was determined to be safe, effective, and manufactured with inherent quality in DMF (b) (4). The applicant identified CQA and established controls to ensure the quality of the drug product. The batch analysis results confirm adequate quality of the drug product at release. Further, the intended commercial packaging the presentations provide adequate protection of the drug product and ensure drug product quality over the proposed shelf-life as demonstrated by the primary and in-use stability data

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date

RSood

**C. Block**

Orig. NDA 204308

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/s/  
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SHERITA D MCLAMORE  
07/23/2013

RAMESH K SOOD  
07/24/2013

## **NDA 204-308**

### **Enalapril Maleate Powder for Oral Solution, 1mg/mL after reconstitution**

**Silvergate Pharmaceuticals**

**Sherita D. McLamore-Hines, Ph.D.**

Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment

APPEARS THIS WAY ON ORIGINAL

# Table of Contents

<b>Table of Contents</b> .....	Error! Bookmark not defined.
<b>Chemistry Review Data Sheet</b> .....	Error! Bookmark not defined.
<b>The Executive Summary</b> .....	Error! Bookmark not defined.
I. Recommendations .....	
A. Recommendation and Conclusion on Approvability.....	<b>Error! Bookmark not defined.</b>
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....	<b>Error! Bookmark not defined.</b>
II. Summary of Chemistry Assessments .....	<b>Error! Bookmark not defined.</b>
A. Description of the Drug Product(s) and Drug Substance(s).....	
B. Description of How the Drug Product is Intended to be Used .....	<b>Error! Bookmark not defined.</b>
C. Basis for Approvability or Not-Approval Recommendation.....	<b>Error! Bookmark not defined.</b>
III. Administrative .....	<b>Error! Bookmark not defined.</b>
A. Reviewer's Signature .....	<b>Error! Bookmark not defined.</b>
B. Endorsement Block .....	<b>Error! Bookmark not defined.</b>
C. CC Block .....	<b>Error! Bookmark not defined.</b>
<b>Chemistry Assessment</b> .....	Error! Bookmark not defined.
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....	
S DRUG SUBSTANCE.....	
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A APPENDICES .....	
R REGIONAL INFORMATION.....	
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	
A. Labeling & Package Insert .....	
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	
III. List Of Deficiencies To Be Communicated.....	

# Chemistry Review Data Sheet

1. NDA: 204-308
2. REVIEW: #2
3. REVIEW DATE: May 9, 2013
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous Documents

Original Submission

Document Date

August 10, 2012

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment

Amendment

Amendment

Amendment

Amendment

Document Date

January 10, 2013

March 5, 2013

March 18, 2013

April 19, 2013

May 9, 2013

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name:

Silvergate Pharmaceutical, Inc

Address:

5371 Gordon Way  
Dublin, OH 43017

## Chemistry Review Data Sheet

Representative: Beckloff Associates, Inc.  
7400 West 110th Street, Suite 300,  
Overland Park, KS 66210  
Telephone: 913-451-3955

Telephone: 614-783-2497

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
  - b) Non-Proprietary Name (USAN): Enalapril Maleate
  - c) Code Name/# (ONDC only): n/a
  - d) Chem. Type/Submission
- Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of Hypertension in Pediatric Patients

11. DOSAGE FORM: Oral Powder for Solution

12. STRENGTH/POTENCY: 1 mg/mL after Reconstitution

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

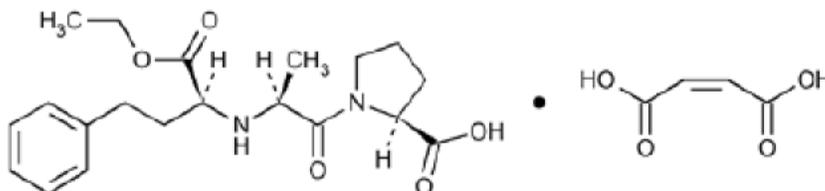
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: L-Proline-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-, (Z)-2-butenedioate (1:1)

Molecular Formula:  $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$

## Chemistry Review Data Sheet

Molecular Weight: 492.52



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance	1	Adequate	12/06/2012	N/A
	II			1	Adequate	1/26/2013	N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-998	NDA for the reference listed drug (Vasotec Tablets)

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	4/3/2013	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	Acceptable	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Categorical Exclusion 21 CFR 25 31(b) <i>Acceptable</i>	12/1/2012	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	

# The Chemistry Review for NDA 204-308

## The Executive Summary

### A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is approved. The applicant has demonstrated the capacity to manufacture drug product with adequate quality and stability. The applicant requested a (b) (4) month expiry for the drug product; however, it was determined that there was insufficient data to support a (b) (4) month expiry. Thus, an 18-month expiry will be assigned for the drug product and an (b) (4) in-use period will be assigned for the reconstituted solution.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase 4 activity recommendations.

## II. Summary of Chemistry Assessments

Enalapril maleate has been identified as the active pharmaceutical ingredient in this application. Enalapril maleate is manufactured by (b) (4). The drug substance is a pro-drug which undergoes hydrolysis to enalaprilat following oral administration. Enalapril maleate has a USP monograph and is an established active pharmaceutical ingredient that is approved for use under NDA 18-998. The drug substance is described as a white to off white crystalline powder with a molecular weight of 492.52 and a melting point of (b) (4) °C. Enalapril maleate drug substance has been fully characterized. The applicant references DMF (b) (4) for a complete description of the manufacturing process and all relevant characterization data pertaining to Enalapril maleate. DMF (b) (4) has been reviewed and is adequate to support this application.

The drug product, (b) (4) Powder for Oral Solution, is being developed for the treatment of hypertension in pediatric patients (b) (4). Enalapril maleate is currently approved in a tablet form under the brand name Vasotec® in NDA 18-998. Vasotec® was indicated in adults and in pediatric patients between 1 month and 16 years of age; however, the pediatric formulation did not exist. Thus, subsequent to the approval of NDA 18-998, to fill this void and circumvent the obvious problems associated with infants and young children ingesting tablets, the agency approved a package insert for Vasotec® Tablets which provided directions for preparing an oral suspension from the tablets. The drug product is presented as Powder for Oral Solution containing 150 mg of enalapril maleate per bottle. Each bottle of the Powder for Oral Solution will be co-packaged with a bottle of Ora-Sweet® SF. Ora-Sweet SF is commercially available, manufactured by (b) (4) and is pre-packaged in 150 (b) (4) HDPE bottles. Reconstitution of the Powder for Oral Solution with 150 mL of Ora-Sweet® SF should be executed by the pharmacist prior to dispensing to patients and will result in a 1 mg/mL solution of enalapril maleate.

## Executive Summary Section

The drug product is a direct blend formulation consisting of (b) (4) enalapril maleate and (b) (4) mannitol and (b) (4) colloidal silicon dioxide. The drug product is manufactured by (b) (4). The commercial batch size for the drug product is (b) (4). The drug product is packaged in 150 mL round, white, HDPE bottle with a (b) (4) child resistant cap with a heat induction foil inner seal. The applicant provided a detailed description of the packaging components and referenced DMFs (b) (4) for a more comprehensive description.

The applicant included six months of long term and accelerated stability data for three registration lots of the drug product in the original application and a 12-month stability update in December 2012. The stability protocol for the Powder for Oral Solution included testing for appearance, identification (release only), content uniformity (release only), assay, related substances and water content. The long term stability data showed very little change and variability over the 12 month period. Under accelerated conditions, there was an observed increasing trend in the related substances (b) (4) and consequently a decreasing trend in the assay observed. Additionally, there was no statistical analysis performed. While the data were within the prescribed specifications limits, the applicant has not provided sufficient amount data to support the request (b) (4) month expiry for the powder for oral solution. Thus, based on ICH Q1E and the data submitted in this application an **18-month expiry** will be granted for the Powder for Oral Solution.

In addition to the stability for the Powder for Oral Solution, the applicant included stability data for the reconstituted drug product. Regarding the reconstituted drug product, the applicant provided 12 weeks of data for the original in-use study and 8 weeks of data in the extended in-use study. During the review cycle, the applicant was asked to submit in-use stability data for the “aged” drug product. In response, the applicant provided up to 13 weeks of data for samples which had been stored for 12 months under ICH long term conditions and committed to performing annual in-use stability testing at 24 and 36 months. The samples were tested for appearance, assay, related substances, preservative content, microbial limits, pH, and antimicrobial effectiveness. All data were comparable and within the prescribed specifications limits. There was a notable and expected increase in the Enalaprilat content after 13 weeks (which is beyond the requested expiry); however, the reviewer feels that this increase is of no concerns as Enalaprilat is the active moiety of the drug substance. Accordingly, based on the data included in this application an (b) (4) **in-use period** will be assigned to the reconstituted drug product.

**B. Description of How the Drug Product is Intended to be Used**

The drug product, (b) (4) Powder for Oral Solution is being developed for treatment of hypertension in pediatric patients (b) (4). The usual recommended starting dose for the drug product is of 0.08 mg/kg once daily with a maximum daily dose of 40 mg. Each bottle of the Powder for Oral Solution will be co-packaged with a bottle of Ora-Sweet® SF. Ora-Sweet SF is commercially available, manufactured by (b) (4) and is pre-packaged in 150 (b) (4) HDPE bottles. The applicant references DMF (b) (4) for the manufacture and control of Ora-Sweet® SF. Reconstitution of the Powder for Oral Solution with 150 mL of Ora-Sweet® SF should be executed by the pharmacist prior to dispensing to patients and will result in a 1 mg/mL solution of enalapril maleate. The directions for reconstitution of the drug product included on the bottle are add of 75 mL

## Executive Summary Section

Ora-Sweet<sup>®</sup> SF and shake well for 30 seconds then add of another 75 mL Ora-Sweet<sup>®</sup> SF and shake well for additional 30.

**C. Basis for Approvability or Not-Approval Recommendation**

From a CMC perspective, this application is approved. The drug substance was determined to be safe, effective, and manufactured with inherent quality in DMF (b)(4). The applicant identified CQA and established controls to ensure the quality of the drug product. The batch analysis results confirm adequate quality of the drug product at release. Further, the intended commercial packaging the presentations provide adequate protection of the drug product and ensure drug product quality over the proposed shelf-life as demonstrated by the primary and in-use stability data

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date

RSood

**C. Block**

Orig. NDA 204308

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/s/  
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SHERITA D MCLAMORE  
05/10/2013

RAMESH K SOOD  
05/10/2013

# **NDA 204-308**

## **Enalapril Maleate Powder for Oral Solution, 1mg/mL after reconstitution**

**Silvergate Pharmaceuticals**

**Sherita D. McLamore-Hines, Ph.D.**

Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment

APPEARS THIS WAY ON ORIGINAL

# Table of Contents

<b>Table of Contents .....</b>	<b>3</b>
<b>Chemistry Review Data Sheet.....</b>	<b>4</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations.....	
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s) .....	
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block .....	11
<b>Chemistry Assessment .....</b>	<b>12</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE.....	12
P DRUG PRODUCT .....	22
A APPENDICES .....	47
R REGIONAL INFORMATION .....	47
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	51
A. Labeling & Package Insert .....	51
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	55
III. List Of Deficiencies To Be Communicated.....	<b>Error! Bookmark not defined.</b>

# Chemistry Review Data Sheet

1. NDA: 204-308
2. REVIEW: #1
3. REVIEW DATE: November 15, 2012
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

n/a

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Submission

August 10, 2012

## 7. NAME & ADDRESS OF APPLICANT:

Name:	Silvergate Pharmaceutical, Inc
Address:	5371 Gordon Way Dublin, OH 43017 Beckloff Associates, Inc. 7400 West 110th Street, Suite 300, Overland Park, KS 66210 Telephone: 913-451-3955
Representative:	
Telephone:	614-783-2497

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
- b) Non-Proprietary Name (USAN): Enalapril Maleate
- c) Code Name/# (ONDC only): n/a
- d) Chem. Type/Submission
  - Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: Treatment of Hypertension in Pediatric Patients

## 11. DOSAGE FORM: Oral Powder for Solution

## 12. STRENGTH/POTENCY: 1 mg/mL after Reconstitution

## 13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

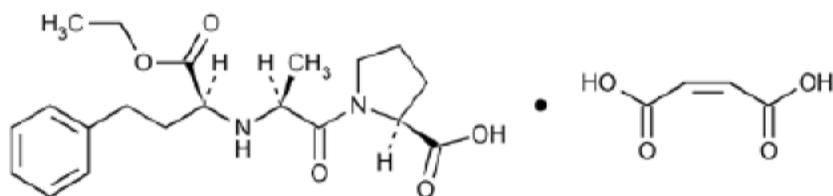
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: L-Proline-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-, (Z)-2-butenedioate (1:1)

Molecular Formula:  $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$

Molecular Weight: 492.52

## Chemistry Review Data Sheet



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance	1	Adequate	12/06/2012	N/A
	II		(b) (4)	1	Pending	Pending	N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Data Sheet

6 – DMF not available  
 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-998	NDA for the reference listed drug (Vasotec Tablets)

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	Acceptable	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Categorical Exclusion 21 CFR 25 31(b) <i>Acceptable</i>	12/1/12	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	

# The Chemistry Review for NDA 204-308

## The Executive Summary

### A. Recommendation and Conclusion on Approvability

At this time a recommendation for the Chemistry, Manufacturing, and Controls (CMC) section of NDA 204-308 is pending. The approval from a CMC standpoint is contingent on an acceptable recommendation from the Office of Compliance and an adequate response to the CMC deficiencies outlined below:

1. Provide the full specification that you will use to release drug substance batches.
2. Provide tests and acceptance criteria used to accept Ora-Sweet<sup>®</sup> SF from the manufacturer.
3. Provide details of process parameters for the blending operation [REDACTED] (b) (4) and the data to support the proposed process parameters.
4. Content uniformity for the drug product is accomplished by UV; however, it is not clear if the impurities contribute to the assay at the prescribed wavelength. Please clarify
5. The known impurities in the drug substance and drug product should be reported in weight percent and not area percent.
6. The proposed acceptance criterion for [REDACTED] (b) (4) in the drug product specification is "calculate results". This is not acceptable. Propose acceptance criteria that are based on data generated from batches of the drug product manufactured by the proposed commercial process and on the available stability data.
7. As per ICH Q3B(R), the proposed acceptance criterion for the individual unidentified related substance in the drug product is above the identification threshold and therefore not acceptable. Revise the acceptance criterion for the individual unidentified related substance in the drug product to NMT [REDACTED] (b) (4) %.
8. The acceptance criterion for the reconstitution time in the drug product specification is overly broad. Revise this specification to be consistent with the reconstitution instruction on the label.
9. Evaluate the limit for water content in the drug product and propose a limit based on your available data.
10. The assay data for the reconstituted drug product demonstrates a decreasing trend over time. It is not clear if product that is reconstituted from Powder for Oral Solution with an assay closer to [REDACTED] (b) (4) % will remain within the specification for the proposed in-use shelf life. Propose an assay release specification for the drug product that will accommodate a loss of [REDACTED] (b) (4) % in the reconstituted solution.
11. "Report Results" is not an acceptable acceptance criterion for the preservative content in the reconstituted drug product. Propose acceptance criteria for methyparaben, propylparaben and potassium sorbate based on the available data.
12. Provide updated stability data for the Powder for Oral Solution.
13. Provide updated in-use stability data for the aged drug (i.e. stored at least 12 months).
14. Revise the stability protocol to include in-use stability testing at the last timepoint.
15. Update the post-approval stability commitment to include storage under accelerated conditions for the first three commercial batches as per ICH Q1A (R2).
16. Ora-Sweet<sup>®</sup> SF will have an expiry assigned by the manufacture. The Powder for Oral Solution will have an expiry assigned based on the available stability data. Please clearly delineate how the differences in these expiration dates will be addressed.

## Executive Summary Section

17. The molecular weight for Enalapril Maleate listed in the description section of the package insert is (b) (4). The molecular weight for Enalapril Maleate as indicated in the USP is 492.52. Update the package insert to be reflective and consistent with the information in the USP.
18. Revise the storage statement and the “How Supplied Section” to include a statement that is specific for the powder and a statement that is specific for the oral solution (b) (4). Do not freeze.” (b) (4)
19. The following statement in the How Supplied section of the package insert is misleading and should be changed or deleted: “(b) (4),”
20. Update the Description section of the package insert to include the components of the diluent, Ora-Sweet® SF.

The proposed change in the comparability protocol is not acceptable. In addition to the photostability data, you should commit to full testing of the Powder for Oral Solution and for the reconstituted drug product. At the time of submission, you should include a minimum of 3 months of accelerated data for the Powder for Oral Solution and 12 weeks for reconstituted drug product stored in the new container closure system for 3 batches manufactured with the proposed container/closure system together with the appropriate DMF references and corresponding letters of authorization. This information should be submitted to the agency in the form of a CBE-30 supplement.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

N/A

## II. Summary of Chemistry Assessments

Enalapril maleate has been identified as the active pharmaceutical ingredient in this application. Enalapril maleate is manufactured by (b) (4). The drug substance is a pro-drug which undergoes hydrolysis to enalaprilat following oral administration. Enalapril maleate has a USP monograph and is an established active pharmaceutical ingredient that is approved for use under NDA 18-998. The drug substance is described as a white to off white crystalline powder with a molecular weight of 492.52 and a melting point of (b) (4) °C. Enalapril maleate drug substance has been fully characterized. The applicant references DMF (b) (4) for a complete description of the manufacturing process and all relevant characterization data pertaining to Enalapril maleate. DMF (b) (4) has been reviewed and is adequate to support this application.

The drug product, (b) (4) Powder for Oral Solution, is being developed for the treatment of hypertension in pediatric patients (b) (4). Enalapril maleate is currently approved in a tablet form under the brand name Vasotec® in NDA 18-998. Vasotec® was indicated in adults and in pediatric patients between 1 month and 16 years of age; however, the pediatric formulation did not exist. Thus,

## Executive Summary Section

subsequent to the approval of NDA 18-998, to fill this void and circumvent the obvious problems associated with infants and young children ingesting tablets, the agency approved a package insert for Vasotec<sup>®</sup> Tablets which provided directions for preparing an oral suspension from the tablets. The drug product is presented as Powder for Oral Solution containing 150 mg of enalapril maleate per bottle. Each bottle of the Powder for Oral Solution will be co-packaged with a bottle of Ora-Sweet<sup>®</sup> SF. Ora-Sweet SF is commercially available, manufactured by (b) (4) and is pre-packaged in 150 (b) (4) HDPE bottles. Reconstitution of the Powder for Oral Solution with 150 mL of Ora-Sweet<sup>®</sup> SF should be executed by the pharmacist prior to dispensing to patients and will result in a 1 mg/mL solution of enalapril maleate.

The drug product is a direct blend formulation consisting of (b) (4) enalapril maleate and (b) (4) mannitol and (b) (4) colloidal silicon dioxide. The drug product is manufactured by (b) (4). The commercial batch size for the drug product is (b) (4). The drug product is packaged in 150 mL round, white, HDPE bottle with a (b) (4) child resistant cap with a heat induction foil inner seal. The applicant provided a detailed description of the packaging components and referenced DMFs (b) (4) for a more comprehensive description.

The applicant has requested a (b) (4) month expiry for the drug product and an (b) (4) in-use shelf-life. The applicant included six months of long term and accelerated stability data for three registration lots of the drug product. These three batches were manufactured at a scale of (b) (4) which is equivalent to (b) (4) and packaged in the intended commercial container closure system. The applicant also included up to 12 weeks of stability data for the reconstituted drug product. The stability protocol for the Powder for Oral Solution included testing for appearance, identification (release only), content uniformity (release only), assay, related substances and water content. The reconstituted samples were tested for appearance, assay, related substances, preservative content, microbial limits, pH, and antimicrobial effectiveness. For the Powder for Oral Solution, all data were acceptable and within the prescribed acceptance criteria; however, 6 months of data is not sufficient data to support the requested expiry. Regarding the reconstituted drug product, the applicant provided 12 weeks of data for the original in-study and 8 weeks of data in the extended in-use study. While all data were comparable and within the prescribed specifications limits, the applicant has not provided an adequate amount data to support the request expiry for the powder or the constituted solution. The applicant was asked to submit in-use stability data for the "aged" drug product. Additionally, because assay data for the reconstituted drug product demonstrated a decreasing trend over time. The applicant was asked to propose an assay release specification for the drug product that will accommodate a loss of (b) (4) % in the reconstituted solution.

## Executive Summary Section

**B. Description of How the Drug Product is Intended to be Used**

The drug product, (b) (4) Powder for Oral Solution is being developed for treatment of hypertension in pediatric patients (b) (4). The usual recommended starting dose for the drug product is of 0.08 mg/kg once daily with a maximum daily dose of 40 mg. Each bottle of the Powder for Oral Solution will be co-packaged with a bottle of Ora-Sweet® SF. Ora-Sweet SF is commercially available, manufactured by (b) (4) and is pre-packaged in 150 (b) (4) HDPE bottles. The applicant references DMF (b) (4) for the manufacture and control of Ora-Sweet® SF. Reconstitution of the Powder for Oral Solution with 150 mL of Ora-Sweet® SF should be executed by the pharmacist prior to dispensing to patients and will result in a 1 mg/mL solution of enalapril maleate. The directions for reconstitution of the drug product included on the bottle are add of 75 mL Ora-Sweet® SF and shake well for 30 seconds then add of another 75 mL Ora-Sweet® SF and shake well for additional 30.

**C. Basis for Approvability or Not-Approval Recommendation**

A recommendation for the approvability of NDA 204308 from a CMC perspective can not be determined until the concerns related to the manufacture and control of the drug product as outlined in this review have been adequately addressed.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date  
RSood

**C. CC Block**

Orig. NDA 204308

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/s/  
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SHERITA D MCLAMORE  
12/06/2012

KASTURI SRINIVASACHAR  
12/06/2012