CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208686Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	September 16, 2016
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Review
NDA#	208686
Applicant	Silvergate Pharmaceuticals, Inc.
Date of Submission	November 24, 2015
PDUFA Goal Date	September 24, 2016
Proprietary Name / Established (USAN) names	Epaned / Enalapril Maleate
Dosage forms / Strength	Oral Solution / 1 mg/mL
Proposed Indication(s)	1. treatment of hypertension, to lower blood pressure in adults and children older than one month 2. treatment of symptomatic heart failure, usually in combination with diuretics and digitalis. In these patients, EPANED increases survival and decreases the frequency of hospitalization 3. In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤35 percent), EPANED decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure
Recommended:	*Approval*

This secondary review is based on the following reviews:

Material Reviewed/Consulted	
Quality Assessment (8/5/16)	Haripada Sarker, Sherita McLamore-Hines, Sung Kim, Dan Berger, Stephanie Emory, Denise Miller, Cassandra Abellard, Zhuojun Joan Zhao, Dahlia Woody, Wendy Wilson-Lee
CMC Statistical Review (7/5/16)	Malick Mbodj
Pharmacology Toxicology Review (7/21/16)	Muriel Saulnier, Albert DeFelice
Clinical Pharmacology Review (8/17/16 and 9/1/16)	Lars Johannesen, Martina Sahre, Sudharshan Hariharan
Division of Medication Error Prevention and Analysis Review (3/3/16)	Sarah Thomas, Chi-Ming (Alice) Tu
Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance Review (3/7/16)	Shila Nkah
Regulatory Project Manager Memo (8/24/16)	Sabry Soukehal
Office of Prescription Drug Promotion Review (8/28/16)	Zarna Patel

1. Introduction

On November 24, 2015, Silvergate Pharmaceuticals, Inc. submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epaned (enalapril maleate) Oral Solution 1 mg/mL for the following proposed indications:

1) for the treatment of hypertension, to lower blood pressure in adults and children older than one month
2) for the treatment of symptomatic heart failure, usually in combination with diuretics and digitalis. In these patients, EPANED increases survival and decreases the frequency of hospitalization
3) In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤35 percent), EPANED decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, Vasotec® (enalapril maleate) tablets (NDA 018998), distributed by Valeant Pharmaceuticals North America, LLC. The application also cross-references the applicant's NDA for Epaned (enalapril maleate) Powder for Oral Solution (NDA 204308).

The members of the review team are in agreement that the application can be approved and there are no outstanding issues from a labeling perspective. Internal discussion of the application focused on the limitations of the data supporting enalapril maleate's indication for the treatment of hypertension in pediatric patients less than 6 years of age; an issue that is discussed in various places in my review.

2. Background

Enalapril maleate is an angiotensin-converting enzyme (ACE) inhibitor. The reference listed drug, Vasotec® (enalapril maleate) tablets (NDA 018998), was initially approved on December 24, 1985. Epaned (enalapril maleate) Powder for Oral Solution was approved on August 13, 2013 and is available as a kit that includes 1 bottle containing 150 mg enalapril maleate in a powder blend and 1 bottle containing 150 mL Ora-Sweet® SF provided as the diluent for reconstitution. Both Vasotec® (enalapril maleate) tablets and Epaned (enalapril maleate) Powder for Oral Solution are approved and marketed for the indications described in Section 1. The subject of this review is a "ready-to-use" oral liquid formulation of enalapril maleate.

In April 2015, a meeting was held between representatives of Silvergate and the Agency to discuss the approval pathway and requirements for the development of Epaned (b) (4).[1] At that meeting, Silvergate sought confirmation from the Agency that a bioavailability study would not be required, arguing that there were no significant differences between their powder for oral solution and the proposed product that would significantly affect absorption. In its preliminary response, the Agency did not agree that a biowaiver request was appropriate,

[1] See meeting minutes under PIND 125621.

citing concerns that differences in some specific excipients could affect bioavailability. The Agency indicated that a bioequivalence study would be needed, but also indicated Silvergate could "make their case for requesting a biowaiver" and submit the supportive information for review under the NDA. The minutes also indicate that there was discussion of a bioequivalence study, comparing the proposed product and "listed drug products" (not otherwise specified).

A number of other issues were also discussed at the April meeting, including the CMC and preclinical data that would be submitted in support of the application, literature searches that would be performed, the appropriateness of the proposed approval pathway, PDUFA fees, PREA and orphan drug exclusivity.[2]

3. CMC/Device

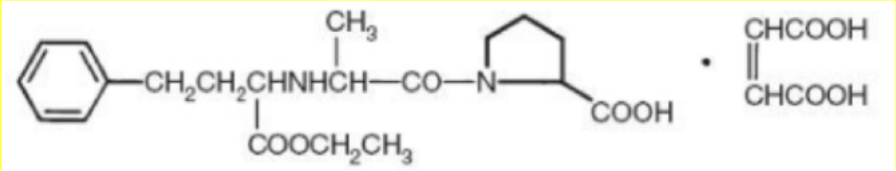
OPQ recommends approval of the application from a quality perspective. There are no unresolved issues at this time and no phase 4 commitments are needed.

Drug Substance: Epaned (enalapril maleate) Oral Solution is the maleate salt of enalapril, the ethyl ester prodrug of a long-acting angiotensin-converting enzyme inhibitor, enalaprilat. Chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1), enalapril maleate is a white to off-white, crystalline powder that is sparingly soluble in water, freely soluble in methanol, and soluble in ethanol. Its molecular weight, molecular formula and structural formula are shown below.

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

Molecular weight: 492.52

Structural formula:



Drug Product: The drug product is a ready-to-use oral formulation. Each 1 mL of the solution contains 1 mg of enalapril maleate, equivalent to 0.764 mg of enalapril. The product, which will be packaged in 150 mL high-density polyethylene bottles, is clear and colorless with a mixed berry flavor. Inactive ingredients include: citric acid, mixed berry flavor, purified water, sodium

[2] As discussed in Sabry Soukehal's memo dated August 24, 2016, Silvergate received Orphan Drug Designation for enalapril maleate for the treatment of hypertension in pediatric patients 0 to 16 years on January 30, 2013. This designation was revoked in April 2016 because the Agency determined that, at the time the request was filed, the prevalence of hypertension in the pediatric population that was amenable to treatment with pharmacology agents exceeded the statutory threshold of 200,000 persons in the United States.

benzoate, sodium citrate, and sucralose, and either hydrochloric acid or sodium hydroxide (added for pH adjustment).

Expiration Date and Storage Conditions: The sponsor proposed a shelf life of (b) (4) months; however, the OPQ review team is recommending a 22 month expiry period when stored refrigerated in the commercial packaging and a 60 day in-use period, after dispensing, when stored at room temperature in the commercial packaging.

According to the CMC statistical review, (b) (4) [3]

FDA's proposed 22-month expiry period is based on the shortest time at which the 95% confidence limits of the mean value intercept with the acceptance criteria for each attribute separately.

4. Nonclinical Pharmacology/Toxicology

The application may be approved from a nonclinical perspective. The application relies on the nonclinical sections of the package insert for Vasotec® (enalapril maleate) tablets. In addition, the applicant conducted a literature search for new nonclinical safety findings, as well as a focused search on the effects and safety of enalapril in growing animals. Dr. Saulnier's review focused on the latter search given the limitations of the clinical database supporting safety in neonates and young children and since juvenile animal studies were not required at the time the reference listed drug was approved for the treatment of hypertension children.

According to Dr. Saulnier, daily oral administration of enalapril or enalaprilat to rat pups and piglets during the neonatal period resulted in irreversible kidney abnormalities. These findings were seen at $\geq$ 10 times the maximum recommended pediatric dose on a mg/M^2 basis; lower doses were not tested. In contrast, renal toxicity was not seen when enalapril was administered to rats with more mature kidneys (i.e., when treatment was initiated after nephrogenesis is thought to be complete in these animals).

In two studies, abnormal heart and lung development was seen in rat pups that received enalapril daily for 7 to 9 days immediately after birth at a dosage 10 times the highest recommended pediatric oral dosage. What to make of these findings is unclear given the lack of a clinical signal to date suggesting that ACE inhibitors cause cardiac and pulmonary toxicity when administered to infants or children.

[3] Under accelerated storage conditions, significant changes were observed at six months for enalapril (b) (4), enalaprilat, and total related substances (other than (b) (4)).

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology recommends approval of the application from a clinical pharmacology perspective. The applicant used a three-way bridge to bridge to the reference listed drug. In brief, Silvergate (1) established a bridge between Vasotec 10 mg tablets and Epaned (enalapril maleate) Powder for Oral Solution (Study SG01-03, submitted to NDA 204308) and (2) established a bridge between Epaned (enalapril maleate) Oral Solution and Epaned (enalapril maleate) Powder for Oral Solution (Study SG04-01, submitted in the current application).

The results of these bridging studies are shown below. As shown in the table, bioequivalence criteria were met for both the prodrug (enalapril) and its active metabolite (enalaprilat) in the comparison of (1) the reference listed drug and powder and (2) the powder and solution. Although the upper-boundary of the 90% CI for the geometric mean ratio of the Cmax for the solution relative to the powder almost exceeds the permissible upper boundary (125), as noted in the Clinical Pharmacology Review, enalapril is a prodrug that is rapidly converted to the active moiety, enalaprilat and the boundaries of the 90% CI for enalaprilat were well within the boundaries for bioequivalence. As also noted in the Clinical Pharmacology Review, the geometric ratio for the Cmax for the powder as compared to the tablet was less than unity (both the point estimate as well as the upper bound of the 90% CI).

Table 1: Comparison of AUC0-inf and Cmax in SG01-03 (powder/tablet comparison) and SG04-01 (powder to solution comparison). The top number for each study provides the results for enalapril; the bottom number provides the results for enalaprilat.

	C_{max}		**$AUC_{0\text{-}inf}$**	
	C_{max} (ng/mL)	Geometric mean ratio (% [90% CI])	AUC (ng*h/mL)	Geometric mean ratio (% [90% CI])
SG 01-03				
Powder	55.2		100.7	
	37.5	92.4 [87.5 to 97.7]	428.3	96.5 [92.2 to 101]
Tablet	59.7	91 [84.1 to 98.3]	104.4	96.6 [92.8 to 100.4]
	41.3		443.6	
SG 04-01				
Solution	72.4		116	
	40	115 [106.3 to 124.5]	412.2	110 [104 to 116.4]
Powder	63	108.9 [101.4 to 117]	105.4	104.9 [99.9 to 110.1]
	36.7		393	

Source: Table 1, Clinical Pharmacology Review dated September 1, 2016

A time-course comparison of the geometric mean concentration of enalapril and enalaprilat in these studies is shown below. Bearing in mind the considerations noted above, these profiles can also be viewed as supportive of bioequivalence.

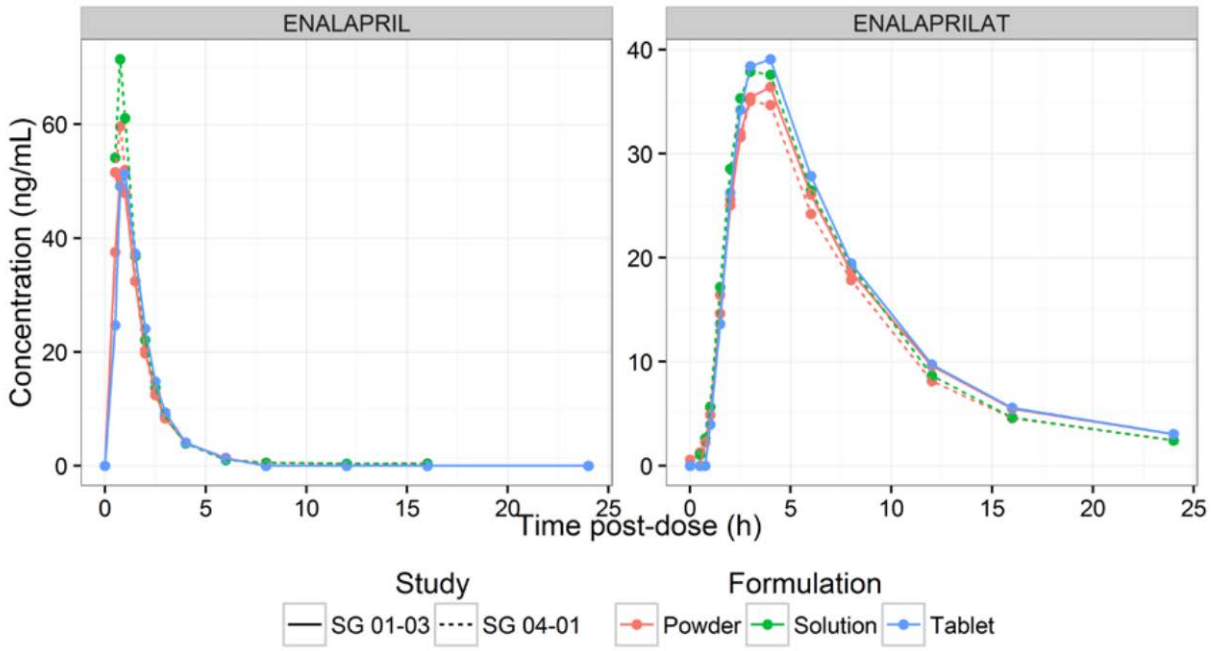


Figure 1: Comparison of the time-course of the geometric mean concentration for enalapril (left) and enalaprilat (right) in study SG01-03 (solid) and SG04-01 (dashed). The different formulations are represented by different colors: powder (red), solution (green) and tablet (blue).
Source: Figure 1, Clinical Pharmacology Review dated September 1, 2016

> Reviewer's Comment: There was internal discussion about whether one needed to use the available data to derive estimates of the geometric mean ratios for the solution vs. the reference listed drug; however, it was felt that the analyses performed to date provide adequate reassurance of bioequivalence.

Labeling: The Office of Clinical Pharmacology is also recommending edits to the label related to findings from a pharmacokinetic study of enalapril in pediatric patients and dosing in patients with renal impairment. These recommended changes have been accepted by the applicant.

6. Clinical Microbiology

According to the Quality Review, there are no quality microbiology concerns.

7. Clinical/Statistical- Efficacy

The application is relying on the Agency's previous finding of safety and effectiveness for Vasotec® (enalapril maleate) tablets. For a discussion of the efficacy data supporting use of the product for the treatment of hypertension in children, see Section 10.

8. Safety

In addition to relying on the Agency's previous finding of safety for the reference listed drug, the application contains information on the safety findings in Study SG04-01, safety findings as reported in the published literature, and the results of a FAERS search. Review of these data did not raise new safety concerns.

Study SG04-01

A total of 32 healthy subjects were exposed to single 10 mg doses of at least one of the following treatments in Study SG04-01: enalapril maleate oral solution and enalapril maleate powder for oral solution. There were no deaths, serious or severe adverse events. The only adverse event reported in more than 2 subjects in either treatment arm was "vessel puncture site pain." One subject experienced an out of range laboratory value thought to be of clinical significance by the investigator (TEAE of neutropenia). The subject had a screening neutrophil count of 2.2 (laboratory reference range of 1.8 to 7.2) on June 29, 2015, a count of 1.0 at the end of study visit on July 30, 2015 and a count of 1.6 at follow-up testing on August 3, 2015.

Literature Search

The applicant conducted a literature search using PUBMed for published reports on the clinical safety experience with enalapril. The search focused on literature published between May 1, 2012, and July 31, 2015, corresponding to the end date for the literature search conducted for NDA 204308 (Epaned Powder for Oral Solution) and the data cutoff date for the current NDA. These published reports did not raise new concerns about the safety of enalapril maleate when used as a treatment for hypertension in children or for its approved indications in adults. Safety findings reported in pediatric patients are discussed below.

Safety Findings in Pediatric Patients

Four clinical studies conducted in pediatric patients, one analysis of unintentional exposures in pediatric patients, and one publication containing two case reports of acute renal failure and hypotension in infants with congestive heart failure treated with enalapril are discussed in the application. Two of the four studies explored efficacy and safety in the treatment of chronic kidney disease. One study, a retrospective chart review, described the impact of ACE inhibitors on the response to intravenous potassium chloride supplementation in pediatric cardiac intensive care patients. The fourth study, also a retrospective study, compared blood pressures in patients with acute kidney injury following initiation of ACE inhibitor therapy with blood pressures in patients who did not experience acute kidney injury after ACE inhibitor therapy.

Spontaneous adverse event reports

The applicant searched the FAERS database for adverse drug experiences involving the use of various enalapril formulations over a 3-year period from April 2012 through June 2015. According to the applicant, there were 30 cases in pediatric patients, 0 to 16 years of age, in which a product containing enalapril or enalaprilat was listed as the primary suspect; however, some of these cases appear to be duplicates. Some reports were consistent with the known adverse event profile of the drug in adults; others were difficult to interpret as isolated reports,

because limited information was provided and/or because confounding factors were also reported.

During the search period, there were 699 cases in patients older than 16 years of age in which a product containing enalapril or enalaprilat was listed as the primary suspect for causing an adverse event. The most frequently reported adverse reactions (angioedema, renal failure acute, hypotension, and hyperkalemia) are known risks of the product.

9. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held.

10. Pediatrics

Data supporting use in children: To date, three ACE inhibitors (enalapril maleate, benazepril, and lisinopril) have been approved for use in pediatric patients with hypertension. Of these agents, only enalapril maleate is approved to treat hypertension in children less than 6 years of age and the data supporting this use have important limitations. In brief, according to the Vasotec® (enalapril maleate) label, data supporting efficacy in the treatment of pediatric hypertension is derived from a trial that limited enrollment to pediatric patients 6 to 16 years of age. In this study, enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. In contrast, dosing recommendations in hypertensive pediatric patients less than 6 years of age appear to be derived from PK data obtained from a multiple-dose pharmacokinetics study of enalapril maleate.

The current submission does not contain a review of the published literature on enalapril's efficacy in treating hypertension in pediatric patients. However, in support of NDA 204308 for Epaned (enalapril maleate) Powder for Oral Solution, Silvergate submitted the results of a review of the published literature on the use of enalapril maleate to treat hypertension in this population. The literature search, which focused on literature published between January 2000 and 30 April 2012, identified two studies supporting efficacy in the treatment of pediatric hypertension.[4,5] One of the studies appears to be the efficacy trial described in labeling; the other study was also conducted in children 6 years of age or older. I did not identify any additional completed trials on enalapril's efficacy in treating pediatric hypertension in my search of the published literature or in published reviews on the treatment of pediatric hypertension.[6,7] As discussed in other sections, the applicant conducted a literature search on

[4] Schaefer F, et al. Efficacy and safety of valsartan compared to enalapril in hypertensive children: a 12-week, randomized, double-blind, parallel-group study. *J Hypertens.* 2011; 29:2484–2490.
[5] *Wells T,* et al. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. *J Clin Pharmacol*. 2002;42(8):870–880.
[6] Meyers R, Sui A. Pharmacotherapy Review of Chronic Pediatric Hypertension. *Clin Ther.* 2011;33:1331–1356.
[7] Portman R et al. Pediatric Hypertension: Diagnosis, Evaluation Management, and Treatment for the Primary Care Physician. *Curr Probl Pediatr Adolesc Health Care*. 2005; 35:262-294.

the safety of enalapril in young animals and in children. The applicant also searched the FAERS database for adverse drug experiences in children.

PREA: No pediatric studies are planned. Silvergate is requesting a full waiver of pediatric study requirements for symptomatic heart failure in patients from birth to 16 years of age and patients with asymptomatic left ventricular dysfunction and a partial waiver for patients 1 month of age and younger with hypertension. The Division and PeRC agree with Silvergate's waiver requests.

- The Agency is waiving the pediatric study requirement for the treatment of (a) symptomatic heart failure and (b) asymptomatic patients with left ventricular dysfunction because necessary studies are impossible or highly impracticable. The causes and mechanisms of heart failure are different in children compared to adults. The form of heart failure seen in adults is rare in children; hence conducting a trial is highly impractical.
- The Agency is waiving the pediatric study requirement for the treatment of hypertension in children less than one month of age because the product would be unsafe in this pediatric group. In humans, nephrogenesis is generally thought to be complete around 1 month of age. In animals and humans, administration of RAAS inhibitors prior to completion of nephrogenesis can have deleterious effects on the kidney.

11. Other Relevant Regulatory Issues

Facilities review/inspection: Because the clinical and analytical facilities had been recently inspected and received a classification of No Action Indicated (NAI), the Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance recommended accepting the data without an on-site inspection.

Financial disclosures: The applicant has adequately disclosed financial interests/arrangements with clinical investigators involved in Study SG04-01. The provided information does not raise questions about the integrity of the data. See the Appendix for additional information.

Other: The 505(b)(2) Clearance Committee has cleared the application.

12. Labeling

Proprietary name: According to DMEPA, the proposed proprietary name, Epaned, is acceptable.

Reviewer's comment: Both the powder form of the product and the solution share the same proprietary name. (b) (4)

Physician labeling: The following modifications were made to the label by the review team.

- Revisions were made to address concerns about the limitation of the data supporting use of enalapril for the treatment of hypertension in infants and children < 6 years of age. Text in

Section 8 of the label related to use in pediatric patients with hypertension now reads as shown below; edits were also made to the discussion of PD data in children less than 6 years of age in Section 12 of the label.

"EPANED is not recommended in neonates (i.e., infants 1 month of age or less), preterm infants who have not reached a corrected post-conceptual age of 44 weeks, and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2 *[see Nonclinical Pharmacology (13.2)]*.

Enalapril lowers blood pressure in hypertensive pediatric patients age 6 years to 16 years. Use of enalapril in these age groups is supported by evidence from adequate and well-controlled studies of enalapril in pediatric and adult patients as well as by published literature in pediatric patients *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.1)]*. Clinical efficacy studies of enalapril in pediatric patients with hypertension did not enroll patients less than 6 years of age. In a previous clinical study in pediatric patients between 2 months and 6 years of age, a higher weight-based dose was required to match exposure in children aged 6 to 16 years *[see Clinical Pharmacology (12.3)]*.

It is unknown whether post-natal use of ACE inhibitors such as enalapril before maturation of renal function is complete has long-term deleterious effects on the kidney. In humans, nephrogenesis is thought to be complete around birth; however maturation of other aspects of kidney function (such as glomerular filtration and tubular function) may continue until approximately 2 years of age *[see Nonclinical Pharmacology (13.2)]."*

- Text was added to Section 13 indicating that irreversible renal toxicity was seen in rat pups exposed to daily enalapril during the period of nephrogenesis.
- Text in Section 12.3 of the label was updated to indicate that hypertensive children aged 2 months to 6 years required higher weight-based doses compared to the older age groups to achieve similar steady-state AUC.

The applicant has accepted these edits to the label. Similar revisions should be made to the label for the reference listed drug.

Labeling and Nomenclature: OPQ, in consultation with the Labeling and Nomenclature Committee, DMEPA, and DCRP, is recommending that the Epaned drug product established name retain the drug substance salt, enalapril maleate. Changing to the free base enalapril may cause medication errors as the current product for oral solution is based on the salt form.

Other: Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information and the proposed Carton and Container labeling and does not have any comments.

13. Recommendations/Risk Benefit Assessment

- *Recommended Regulatory Action:* Approval.
- *Risk Benefit Assessment:* The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, Vasotec® (enalapril maleate) tablets (NDA

018998), approved on December 24, 1985. Bioequivalence to the reference listed drug was demonstrated via a three-way bridge. From a CMC, non-clinical pharmacology-toxicology, clinical pharmacology, and clinical safety and efficacy perspective, the application can be approved.

- *Recommendation for Postmarketing Risk Evaluation and Management Strategies:* None.

- *Recommendation for other Postmarketing Requirements and Commitments:* None.

- *Recommended Comments to Applicant:* Per the OPQ Review, the following comment should be included in the approval letter:

  Based on the data submitted and in accordance with ICH Q1E, we grant a 22 month expiry for Epaned (enalapril maleate) Oral Solution when stored refrigerated in the commercial packaging. We grant a 60 day in-use period, after dispensing, when stored at room temperature in the commercial packaging.

Appendix

Clinical Investigator Financial Disclosure
Review Template

Covered Clinical Study (Name and/or Number): SG04-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 7		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

ALIZA M THOMPSON
09/16/2016