# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204308Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

| | |
|---|---|
| NDA Number | 204-308 |
| Submission Date(s) | 8/10/2012 |
| Submission Type; Code | ORIG-1, S0000, S0001, S0005 |
| Sponsor | Silvergate Pharmaceuticals, Inc. |
| Proposed Brand Name | (b) (4) |
| Generic Name | Enalapril maleate pediatric oral solution |
| Relevant IND(s) | 109473 |
| Formulation; Strength(s) | Powder for oral solution; 1 mg/mL |
| Indication | Treatment of hypertension in pediatrics (b) (4) |
| Reference Listed Drug (NDA #) | Vasotec® (18-998) |
| OCP Division | Division of Clinical Pharmacology 1 |
| OND division | Division of Cardiovascular and Renal Products |
| Reviewer | Martina Sahre, PhD |
| Secondary Reviewer | Divya Menon-Andersen, PhD |
| Team Leader | Rajanikanth Madabushi, PhD |

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## 1 Executive Summary

Enalapril maleate (Vasotec®) was approved in 1985 and is currently indicated for the treatment of hypertension in adults and pediatrics (1 month to 16 years of age) and for the treatment of symptomatic congestive heart failure and asymptomatic left ventricular dysfunction in adults. The sponsor of the herein reviewed NDA (NDA 204-308) is seeking an indication for the treatment of hypertension in pediatrics (b) (4)

Enalapril maleate pediatric oral solution will be available as powder (150 mg) for oral solution co-packaged with Ora-Sweet SF[1] (150 mL) for reconstitution. The final product will yield a solution of 1 mg/mL enalapril maleate.

The submission consisted of three relative bioavailability studies, the results of which are used to bridge to the finding of efficacy and safety of the reference listed drug Vasotec®.

### 1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP1) reviewed the original NDA 204-308 and recommends approval from the clinical pharmacology perspective, provided that labeling changes are addressed.

### 1.2 Phase 4 Requirements/Commitments

There are no post-marketing commitments or requirements for this application.

### 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The pharmacokinetic and pharmacodynamic properties of enalapril maleate were reviewed under NDA 18-998 (Vasotec®). Information on pediatric dosing was added to

[1] SF indicates that this Ora-Sweet product is sugar free.

the label in 2001.

The development program for [redacted] was designed to be able to bridge to the efficacy and safety findings of NDA 18-998. To that end, the sponsor conducted three relative bioavailability studies, of which two are reviewed in this document.

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 Cmax and AUC is not expected to be clinically significant.

## 2 Question-Based Review (QBR)

This is an abridged version of a question-based review. For a detailed review, refer to the original NDA 18-998.

### 2.1 General attributes of the drug and drug product

Enalapril maleate pediatric oral solution will be distributed as a powder in a 150 mL bottle, co-packaged with a 150 mL bottle of Ora-Sweet SF. Before dispensation to the patient, the powder will be dissolved in 150 mL Ora-Sweet SF to yield a solution of 1 mg/mL. The final reconstituted product will be a clear light pink to slightly red solution. The brand name has not been finalized and the solution will be referred to as [redacted] or enalapril maleate pediatric oral solution throughout this review.

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The physical and chemical properties of enalapril maleate have been reviewed in NDA 18-998 (Vasotec®).

The inactive ingredients are mannitol powder USP [redacted] and colloidal silicone dioxide NF [redacted]. The final powder will contain [redacted]% enalapril maleate.

#### 2.1.2 Are additional instructions for preparation and dispensation of the final solution required to ensure accurate dosing?

During the first clinical study (SG01-01), it was observed that shaking upon

reconstitution led to entrapped air in the final product, which prompted an amendment to the protocol that instructed the investigational pharmacy to gently swirl and invert the product instead of shaking it. Possibly due to improper wetting and dissolution of the powder particles, the gentle inversion procedure lead to poor bioavailability in the first clinical trial (SG01-01). For the second and third trial (SG01-02 and 03) the investigational pharmacy was instructed to shake the product and then let it stand at room temperature until dispensation. Thereafter, the product was to be poured gently along the side of a beaker and visually inspected for homogeneity before it was to be drawn into the syringe for administration.

Therefore, it may be prudent to instruct caregivers and patients not to shake the product before using it (which would be unnecessary because it is a solution) to avoid the inclusion of air. Entrapped air that may be included in the product by shaking can displace actual drug solution in the oral syringe and could thus cause an incorrect dose to be given. It is the understanding of the reviewer, that the product will be dispensed by the pharmacy as the final reconstituted solution.

### 2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Enalapril is a non-mercapto angiotensin converting enzyme inhibitor (ACEI) indicated for the treatment of hypertension. ACEIs exert their activity by fitting into the binding pocket of ACE, which is then no longer available to cleave angiotensin I to angiotensin II. This in turn prevents the increase in blood pressure through the renin-angiotensin-aldosterone system. Enalapril maleate pediatric oral solution will be indicated for the treatment of hypertension in children (b) (4).

### 2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage is 0.08 to 0.54 mg/kg of enalapril maleate pediatric oral solution 1 mg/mL given by mouth. This is also the recommended dose range in the current Vasotec® label.

## 2.2 General clinical pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology studies submitted to this NDA are summarized in Table 1. Three relative bioavailability studies in healthy volunteers were undertaken, of which two delivered interpretable results. The individual study reviews of these two studies are shown in Appendix 4.1.

**Table 1: Listing of clinical pharmacology studies**

| Study Number | Design | Treatments |
|---|---|---|
| SG01-01 | Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover | A: Enalapril maleate pediatric solution 10 mg, fasted<br>B: Vasotec® tablet 10 mg, fasted<br>C: Enalapril maleate pediatric solution 10 mg, with high-fat meal |
| SG01-02 | Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover | A: Enalapril maleate pediatric solution 10 mg, fasted<br>B: Vasotec® tablet 10 mg, fasted |
| SG01-03 | Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover | A: Enalapril maleate pediatric solution 10 mg, fasted<br>B: Vasotec® tablet 10 mg, fasted<br>C: Enalapril maleate pediatric solution 10 mg, with high-fat meal |

### 2.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, enalapril maleate is metabolized to enalaprilat, which is the active moiety. The analytical method for the studies in this review was validated for enalapril and enalaprilat. Please refer to section 2.4 for details of the bioanalytical method.

### 2.2.3 What are the PK characteristics of the drug and its major metabolite?

#### 2.2.3.1 What are the single dose and multiple dose PK parameters?

The pharmacokinetic properties of enalapril and enalaprilat have been reviewed under NDA 18-988 (Biopharmaceutics review from May 22, 1985).

After administration of a single dose of enalapril maleate 10 mg, peak plasma concentrations of enalapril and enalaprilat were observed at 45 to 55 minutes and 3.5 hours, respectively. The mean terminal elimination half-life of enalapril and enalaprilat is about 1.5 hours and 30 hours, respectively, however, steady-state concentrations are reached after three to four doses. After multiple doses, the accumulation ratio for enalapril is approximately 1.3 and is similar between children aged 2 months to 16 years and adults.

## 2.3 General Biopharmaceutics

### 2.3.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the reference drug?

Enalapril maleate pediatric solution 1 mg/mL is bioequivalent to the reference drug,

Vasotec® tablets (Figure 1). The point estimate and 90% CIs for AUCinf and Cmax are contained within the pre-determined BE criteria.

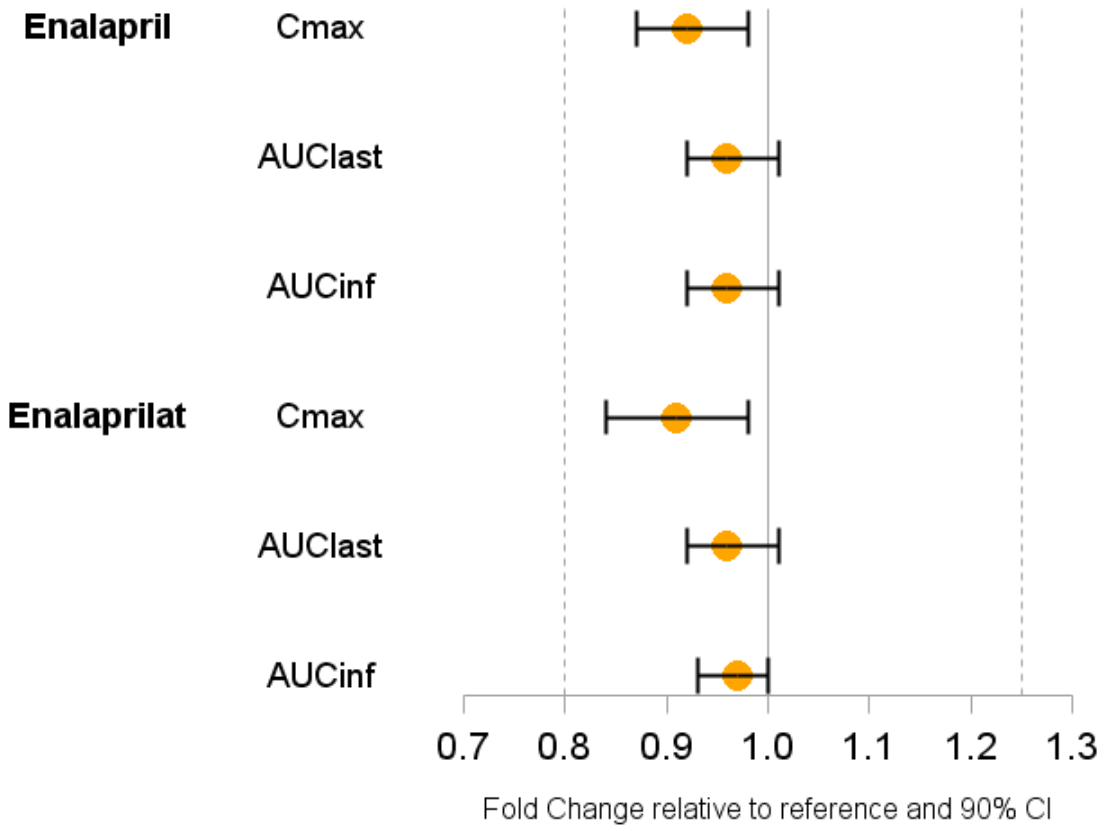



**Figure 1. Enalapril and enalaprilat exposure relative to Vasotec® tablets (reference)**
**Closed circles represent point estimate and the line represents the 90% CI. The x-axis shows the geometric mean ratio, and the pre-determined BE limits are represented by the dashed vertical lines.**

### 2.3.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Taking enalapril maleate solution after an FDA recommended standard high fat meal[2] decreased enalapril and enalaprilat $C_{max}$ by 46% and 36%, respectively. The $AUC_{inf}$ decreased by approximately 15% for enalapril, and 20% for enalaprilat, respectively (Figure 2).

[2] High-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast

However, the observed decrease in $C_{max}$ and $AUC_{inf}$ are not expected to be clinically significant given the shallow dose-response relationship at steady state where a doubling of dose resulted in ~ 2 mmHg increase in effect[3]. Further, enalaprilat concentrations at trough (pre-dose) are similar between fasted and fed application (see Figure 3) indicating similar blood pressure reduction effect during the interdosing interval. The solution can be taken without regards to food.

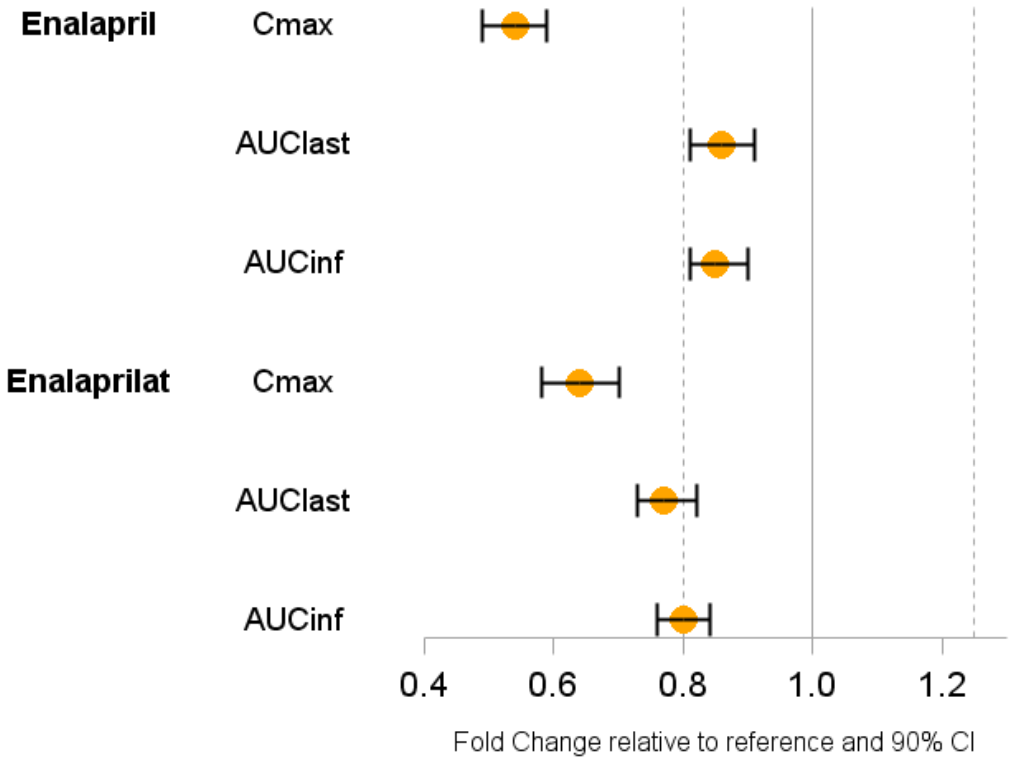



**Figure 2. Enalapril and enalaprilat exposure relative to enalapril maleate pediatric solution, fasted (reference).**
**Closed circles represent point estimate and the line represents the 90% CI. The x-axis shows the geometric mean ratio, and the pre-determined BE limits are represented by the dashed vertical lines.**

[3] Medical officer review for Vasotec (December 19, 1985; page 47, http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/018998_Vasotec.cfm)

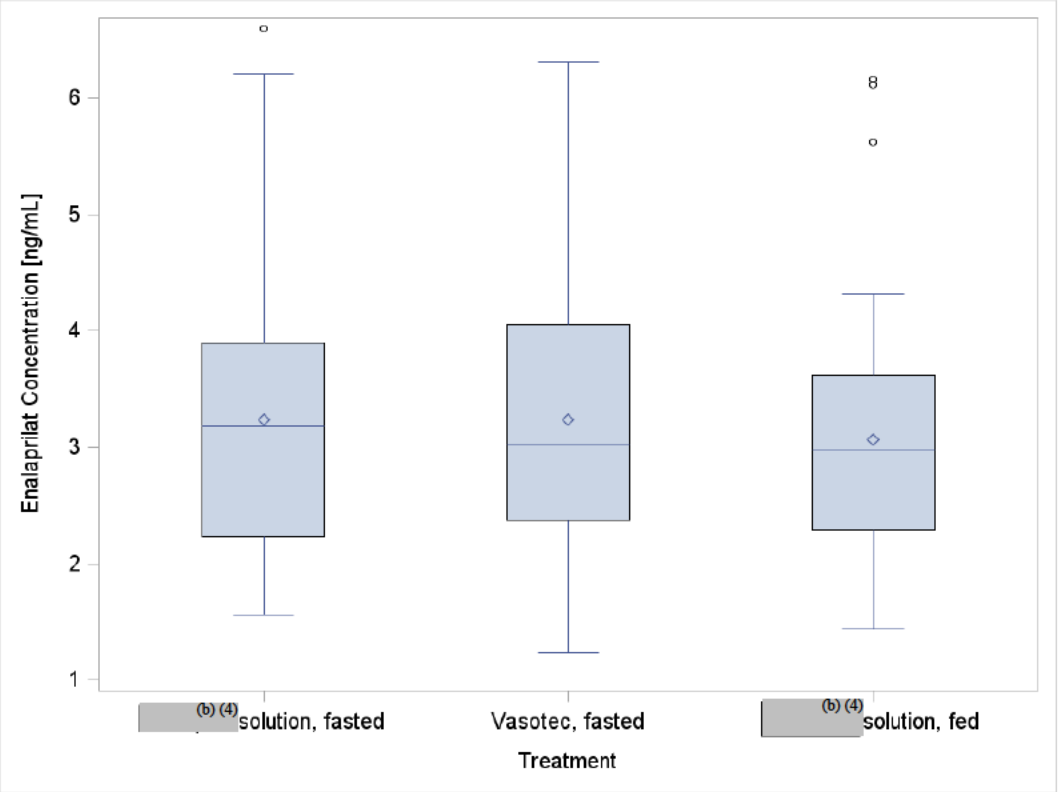



**Figure 3. Enalaprilat concentrations at 24 hours post dose (trough concentrations) are similar between treatments.**

## 2.4 Analytical section

### 2.4.1 What are the characteristics of the bioanalytical method used to assess concentrations?

Samples from all three trials were analyzed using an LC/MS/MS method. The validation is documented in report DCN 1004304. Total plasma concentrations of both enalapril and the active moiety enalaprilat were quantified. The properties of the validated method are shown in Table 2.

**Table 2: Characteristics of the bioanalytical method and its performance during assay validation**

| | Parameter | Enalapril | Enalaprilat |
|---|---|---|---|
| Assay | LLOQ and ULOQ | 0.520 and 100 ng/mL | 0.500 and 200 ng/mL |
| | Reference standard | Enalapril maleate, USP<br>Lot J1C267 | Enalaprilat, USP<br>Lot J1G349 |
| | Internal standard | Enalapril-D5 Maleate<br>(b) (4) | Enalaprilat-D5<br>(b) (4) |
| | Specificity | Lot L48P42<br>No interference | Lot G514P26<br>No interference |
| Calibration samples | Calibration range | 0.250 to 100 ng/mL<br>weighting: $1/x^2$ | 0.500 to 200 ng/mL<br>weighting: $1/x^2$ |
| | Accuracy (%Bias) | -4.0 to 3.0% | -3.8 to 4.0% |
| | Precision (%CV) | 0.6 to 3.4 | 0.6 to 3.4% |
| Quality control samples | Concentration | 0.750, 8.00, 80.0 ng/mL | 1.50, 16.0, 160 ng/mL |
| | Intra run | | |
| | Accuracy (%Bias) | 2.9 to 8.0% | -2.5 to 2.5% |
| | Precision (%CV) | 0.9 to 5.0% | 1.5 to 6.9% |
| | Inter run | | |
| | Accuracy (%Bias) | 4.1 to 6.3% | 0.0 to 0.7% |
| | Precision (%CV) | 2.5 to 4.1% | 3.1 to 5.3% |
| Stability | Freeze-thaw cycles | 5 | |
| | Room temperature | 27 h | |
| | Refrigeration at 4 °C | 117 h | |

## 3 Labeling Recommendations (Draft)

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for NDA 204-308 and finds it acceptable pending the following changes. The final labeling should reflect the results from the bioavailability and food effects study and recommendations for changes in this part of Section 12.3 of the labeling are made below. Further labeling discussions are currently ongoing and therefore the final label may not contain the below recommendations verbatim.

(*Strikethrough text is recommended to be deleted and underlined text is recommended to be added.)*

**Section 12.3 Pharmacokinetics**

The pharmacokinetics of (b) (4) Oral Solution were shown to be similar to Vasotec® tablets (b) (4) under fasted conditions. A high-fat meal reduced the Cmax of enalapril and enalaprilat by 46% and 36%, respectively. The exposure, as measured by AUC, of enalaprilat was reduced by 23% The time to peak concentrations (Cmax) was delayed by 20 minutes for enalapril and 62 minutes for enalaprilat.

# 4 Appendices

## 4.1 Clinical pharmacology and biopharmaceutics individual study review

### 4.1.1 Study SG01-02

| Report #: SG01-02 | Study Period: March 09, 2012 to March 19, 2012 |
|---|---|
| EDR Link: \\Cdsesub1\evsprod\NDA204308\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-sg01-02\report-body.pdf | |
| **Title** | A Pilot Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioavailability Study of 10 mg Enalapril Maleate Pediatric Solution vs Vasotec® 10 mg Tablets under Fasted Conditions in Healthy Adults |
| **Rationale** | This study was done as a result of very low observed bioavailability from the Enalapril pediatric oral solution in study SG01-01, which was supposed to be the pivotal BA study. The sponsor, when analyzing samples from the administered gel from study SG01-01, found that it contained very little measurable enalapril maleate. This was attributed to problems in the reconstitution of enalapril maleate powder in Ora-Sweet SF. The study that is reviewed in this document, study SG01-02, was done (1) to confirm that the low BA found in study SG01-01 was indeed due to incomplete reconstitution and (2) to assess the bioavailability of the pediatric oral solution 10 mg/10 mL to that of Vasotec® 10 mg tablets. |
| **Study Design** | |
| ☐ Bioequivalence | ☑ Bioavailability, Relative |
| Single-Dose - Randomized - Open-Label - Cross-Over - Single-Center - 2-Period - Healthy Volunteers | |
| **Screening:** ≤ 28 days | **Washout:** ≥ 7 days, outpatient |
| **Period 1/2** | 9 days, Inpatient stay ☐Y ☒ N: Subjects were admitted to the research unit in a time frame permitting at least a 10-hour fast prior to dosing. Subjects were followed at the research unit until the 24-hour study observations and returned for the 36, 24, and 72 hour observations. |

**Treatments:** (Active Ingredient: Enalapril maleate)
Treatment A: Enalapril maleate pediatric solution 1 mg/mL x 10 mL (labeled: Test Formulation)
Treatment B: Vasotec® 10 mg tablets (labeled: Reference Product)

| | (b) (4) **pediatric oral solution** | **Vasotec®** |
|---|---|---|
| Dosage Form | Powder for oral solution | Tablet |
| Dosage Strength | 1 mg/1 mL | 10 mg |
| Batch #. | Lot 111003 | Lot 11D015P |
| Administration | Per os | Per os |

**Sampling Times (PK, plasma)**
Samples for PK analysis were collected at pre-dose (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 h post-dose.

**Analytical Method:** The performance of the analytical method is acceptable. Yes ☑ No ☐
*Reviewer's note: In the fourth and last bioanalytical run, the sponsor added one level of QC for enalapril at 32.0 ng/mL, to cover a greater part of the upper range of the assay. However, this particular analytical run was used to analyze repeat samples of enalapril.*

| Analyte | Enalapril | | | Enalaprilat | | |
|---|---|---|---|---|---|---|
| Method | LC/MS/MS | | | LC/MS/MS | | |
| Internal Standard | Enalapril-$D_5$-maleate (phenyl-$D_5$) | | | Enalaprilat-$D_5$ (phenyl-$D_5$) | | |
| Matrix | human $K_2$-EDTA plasma | | | | | |
| Calibration Range | 0.250, 0.500, 1.00, 5.00, 10.0, 50.0, 90.0, 100 ng/mL | | | 0.500, 1.00, 2.00, 10.0, 20.0, 100, 180, 200 ng/mL | | |
| QC Range | 0.750, 8.00, (32.0*),80.0, (500*) ng/mL | | | 1.50, 16.0, 160 ng/mL | | |
| IS Concentration | 0.750 µg/mL | | | 1.00 µg/mL | | |
| LLOQ | 0.250 ng/mL | | | 0.500 ng/mL | | |
| Inter-run QC results For patient sample runs | QC Level [ng/mL] | Accuracy/ Bias [%] | CV [%] | QC Level [ng/mL] | Accuracy/ Bias [%] | CV [%] |
| | 0.750 | 0.9 | 4.7 | 1.50 | 1.3 | 5.8 |
| | 8.00 | 3.3 | 1.7 | 16.0 | -1.3 | 2.7 |
| | 32.0* | 4.7 | ** | 160 | 2.5 | 2.4 |
| | 80.0 | 3.3 | 1.7 | | | |

* Bioanalytical run4, which was only done to analyze repeat samples for enalapril.
** No CV available, because only 2 QCs were available and only in one run (run 4)

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, subject within sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 10/10/0 |
| Age [Median (range)] | 36 (23-52) |
| Male/Female | 5/5 |
| Race (American Indian or Alaska Native/Black or African American/White) | 1/3/6 |
| Ethnicity (Hispanic or Latino/Not Hispanic or Latino) | 8/2 |

**Results**

Two subjects had quantifiable enalaprilat concentrations prior to treatment A (test treatment) in period 2. Both had measured concentrations less than 5% of their respective Cmax values.

**Table 1: Mean (arithmetic) PK parameters for enalapril**

| Parameter | Treatment A: Test Formulation | | | | Treatment B: Reference Product (Vasotec) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | CV% | n | Mean | SD | CV% |
| $T_{max}$ (hr) | 10 | 0.75 | 0.49 | 64.79 | 10 | 0.75 | 0.26 | 35.14 |
| $C_{max}$ (ng/mL) | 10 | 69.9 | 15.9 | 22.69 | 10 | 77.0 | 27.3 | 35.39 |
| $AUC_{last}$ (hr*ng/mL) | 10 | 120.2 | 51.72 | 43.03 | 10 | 126.7 | 61.08 | 48.21 |
| $AUC_{inf}$ (hr*ng/mL) | 10 | 121.4 | 51.51 | 42.45 | 9 | 128.7 | 64.87 | 50.42 |
| $AUC_{Extrap}$ (%) | 10 | 1.11 | 0.99 | 89.43 | 9 | 0.92 | 0.53 | 57.61 |
| $\lambda_z$ ($hr^{-1}$) | 10 | 0.5584 | 0.2007 | 35.95 | 9 | 0.5951 | 0.2276 | 38.24 |
| $T_{1/2}$ (hr) | 10 | 1.43 | 0.62 | 43.17 | 9 | 1.39 | 0.71 | 50.79 |
| $T_{last}$ (hr) | 10 | 8.40 | 2.07 | 24.66 | 10 | 10.00 | 5.33 | 53.32 |
| $C_{last}$ (ng/mL) | 10 | 0.543 | 0.279 | 51.40 | 10 | 0.545 | 0.289 | 53.08 |

Source: CSR page 30/228

**Table 2: Mean (arithmetic) PK parameters for enalaprilat**

| Parameter | Treatment A: Test Formulation | | | | Treatment B: Reference Product (Vasotec) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | CV% | n | Mean | SD | CV% |
| $T_{max}$ (hr) | 10 | 3.45 | 0.60 | 17.35 | 10 | 3.35 | 0.75 | 22.23 |
| $C_{max}$ (ng/mL) | 10 | 44.5 | 12.8 | 28.74 | 10 | 52.8 | 19.5 | 36.86 |
| $AUC_{last}$ (hr*ng/mL) | 10 | 438.0 | 77.42 | 17.68 | 10 | 485.4 | 114.7 | 23.63 |
| $AUC_{inf}$ (hr*ng/mL) | 10 | 479.4 | 71.84 | 14.99 | 9 | 539.4 | 98.77 | 18.31 |
| $AUC_{Extrap}$ (%) | 10 | 8.82 | 5.20 | 58.95 | 9 | 9.09 | 5.63 | 61.95 |
| $\lambda_z$ ($hr^{-1}$) | 10 | 0.0281 | 0.0160 | 57.09 | 9 | 0.0285 | 0.0244 | 85.78 |
| $T_{1/2}$ (hr) | 10 | 30.90 | 12.34 | 39.94 | 9 | 36.73 | 18.08 | 49.23 |
| $T_{last}$ (hr) | 10 | 69.60 | 7.59 | 10.90 | 10 | 69.64 | 7.60 | 10.92 |
| $C_{last}$ (ng/mL) | 10 | 0.893 | 0.259 | 29.01 | 10 | 0.955 | 0.379 | 39.70 |

Source: CSR page 30/228

**Table 3: Comparison of Enalapril oral solution (10 mg) and Vasotec® tablets (10 mg)**

| Analyte | Parameter | N | Test | Reference | Mean Ratio | 90% CI | %CV |
|---|---|---|---|---|---|---|---|
| Enalapril | $C_{max}$ [ng/mL] | 10 | 68.09 | 73.70 | 92.39 | 79.54-107.31 | 18.16 |
| | $AUC_{last}$ [ng h/mL] | 10 | 112.78 | 118.37 | 95.27 | 88.76-102.27 | 8.53 |
| | $AUC_{inf}$ [ng h/mL] | 9 | 115.40 | 118.35 | 97.51 | 91.55-103.86 | 7.03 |
| Enalaprilat | $C_{max}$ [ng/mL] | 10 | 42.74 | 49.44 | 86.45 | 71.55-104.46 | 23.04 |
| | $AUC_{last}$ [ng h/mL mg] | 10 | 432.30 | 474.18 | 91.17 | 82.84-100.34 | 11.56 |
| | $AUC_{inf}$ [ng h/mL mg] | 9 | 480.45 | 533.68 | 90.03 | 81.83-99.04 | 10.65 |

**Site Inspected**

**Requested:** Yes ☐ No ☒ **Performed:** Yes ☐ No ☒

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

There were no serious adverse events reported.

**Conclusion**

The pharmacokinetics of test and reference products were similar. The present study showed that low BA in study SG01-01 seems to have indeed been due to improper reconstitution.

**Comments**

none

### 4.1.2 Study SG01-03 (Pivotal relative BA study)

| Report #: SG01-03 | Study Period: April 6, 2012 to May 23, 2012 |
|---|---|
| EDR Link: \\Cdsesub1\evsprod\NDA204308\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-sg01-03\report-body.pdf | |
| **Title** | A Single dose, three-period, three-treatment, three-way crossover bioavailability study of 10 mg enalapril maleate pediatric solution vs Vasotec® 10 mg tablets under fasted conditions and 10 mg enalapril maleate pediatric solution under fed conditions in healthy adults |
| **Rationale** | Assess relative bioavailability of enalapril maleate pediatric solution 10 mg to Vasotec® 10 mg tablets and evaluate the effect of a high –fat meal on the bioavailability of enalapril maleate pediatric solution. |

**Study Design**

| ☐ Bioequivalence | ☑ Bioavailability, Relative |
|---|---|
| Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Volunteers | |
| **Screening:** ≤ 28 days | **Washout:** ≥ 7 days, outpatient |
| **Period 1/2/3** | 9 days, Inpatient stay ☑Y ☐ N: |

**Treatments:** (Active Ingredient: Enalapril maleate)

The dose selected for testing (10 mg) is not the highest marketed dose for Vasotec®, which is 20 mg. However, there was concern that a dose of 20 mg could lead to cases of orthostatic hypotension in healthy volunteers and the sponsor proposed the use of a 10 mg dose. To this end, the sponsor provided the agency with evidence that the PK of enalapril maleate is linear at least up until the 20 mg dose. Therefore, it was agreed with the sponsor that using a 10 mg dose was reasonable.

| | [redacted] (b) (4) **pediatric oral solution** | **Vasotec®** |
|---|---|---|
| Dosage Form | Powder for oral solution | Tablet |
| Dosage Strength | 1 mg/1 mL | 10 mg |
| Batch #. | Lot 111003 | Lot 11D004P |
| Administration | Per os | Per os |

**Sampling Times (PK, plasma)**

Samples for PK analysis were collected at pre-dose (0 h) and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 h post-dose.

*Reviewer's note: Based on previous information on the pharmacokinetics of enalapril and enalaprilat, the expected Tmax is about 1 and 3 to 4 hours for enalapril and enalaprilat, respectively. The elimination half-life of enalapril is about 2 hours, whereas that of enalaprilat is about 30 hours[4]. Therefore, the sampling time points cover more than 5 half-lives for enalapril and about 2.5 half-lives for enalaprilat. Therefore, the sampling scheme is reasonable.*

*Based on the Draft Guidance on Enalapril Maleate (2008), bioequivalence is based on the enalapril AUC*

[4] *Vasotec label, MacFadyen et al., Clinical Pharmacokinetics. 1993;25(4):274-82*

*and Cmax geometric mean ratios and 90% CIs.*

**Analytical Method:** The performance of the analytical method is acceptable. Yes ☑ No ☐

*Reviewer's note: In the last bioanalytical run, the sponsor added one level of QC for enalapril and enalaprilat at 32.0 and 64.0 ng/mL, respectively, to cover a greater part of the upper range of the assay than what was evaluated for the validation of the assay. However, these concentrations were injected in addition to quality control standards previously used in the validated assay. Being that the new QC levels are within accepted levels of accuracy and precision and not at the tail ends of quality control standard concentrations, this is acceptable. During the assay of patient samples, the performance of the method was acceptable based on the QC and standard samples being within ±15% of their nominal value and the CV% of the measured concentrations being within ±15% as well.*

| Analyte | Enalapril | | | Enalaprilat | | |
|---|---|---|---|---|---|---|
| Method | LC/MS/MS | | | LC/MS/MS | | |
| Internal Standard | Enalapril-$D_5$-maleate (phenyl-$D_5$) | | | Enalaprilat-$D_5$ (phenyl-$D_5$) | | |
| Matrix | human $K_2$-EDTA plasma | | | | | |
| Calibration Range | 0.250, 0.500, 1.00, 5.00, 10.0, 50.0, 90.0, 100 ng/mL | | | 0.500, 1.00, 2.00, 10.0, 20.0, 100, 180, 200 ng/mL | | |
| QC Range | 0.750, 8.00, (32.0*),80.0 ng/mL | | | 1.50, 16.0, (64.0*), 160 ng/mL | | |
| IS Concentration | 0.750 µg/mL | | | 1.00 µg/mL | | |
| LLOQ | 0.250 ng/mL | | | 0.500 ng/mL | | |
| Inter-run QC results For patient sample runs | QC Level [ng/mL] | Accuracy [%] | CV [%] | QC Level [ng/mL] | Accuracy [%] | CV [%] |
| | 0.750 | 5.2 | 4.3 | 1.50 | 3.3 | 6.1 |
| | 8.00 | 2.4 | 4.0 | 16.0 | 2.5 | 5.1 |
| | 32.0 | -5.6 | 4.1 | 64.0 | -3.4 | 5.0 |
| | 80.0 | -4.9 | 3.5 | 160 | -1.9 | 5.6 |

* Bioanalytical samples only

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, subject within sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 53/45/1 |
| Age [Median (range)] | 53 (18-55) |
| Male/Female | 42/11 |
| Race (American Indian or Alaska Native/Black or African American/White) | 4/14/35 |

Subjects 304, 307, 342 and 349 were withdrawn for non-protocol compliance (positive drug screen at check-in to one of the study periods). Subject 340 was withdrawn for treatment-related AEs and subjects 306, 350 and 353 withdrew their consent. Of the eight subjects not completing the study, four had only one period completed (#307, 340, 342, 353), and they were excluded from the PK analysis. Another four subjects were studied in two periods (#304, 306, 349, 350); however, subject 349 had only comparison of Vasotec® reference to enalapril pediatric solution administered fed and was also not included in the PK analysis. Thus

of the 53 subjects enrolled, 48 subjects had evaluable PK data and are included in the bioequivalence determination. This should not affect the outcome of the study, as it was still sufficiently powered.

**Results**

One subject had a pre-dose quantifiable enalaprilat concentration in period 3, however, the concentrations was lower than 5% of the Cmax. The subject's sequential order was reference product (B), test product fasted, and then test product fed.

**Mean (arithmetic) PK parameters for enalapril**

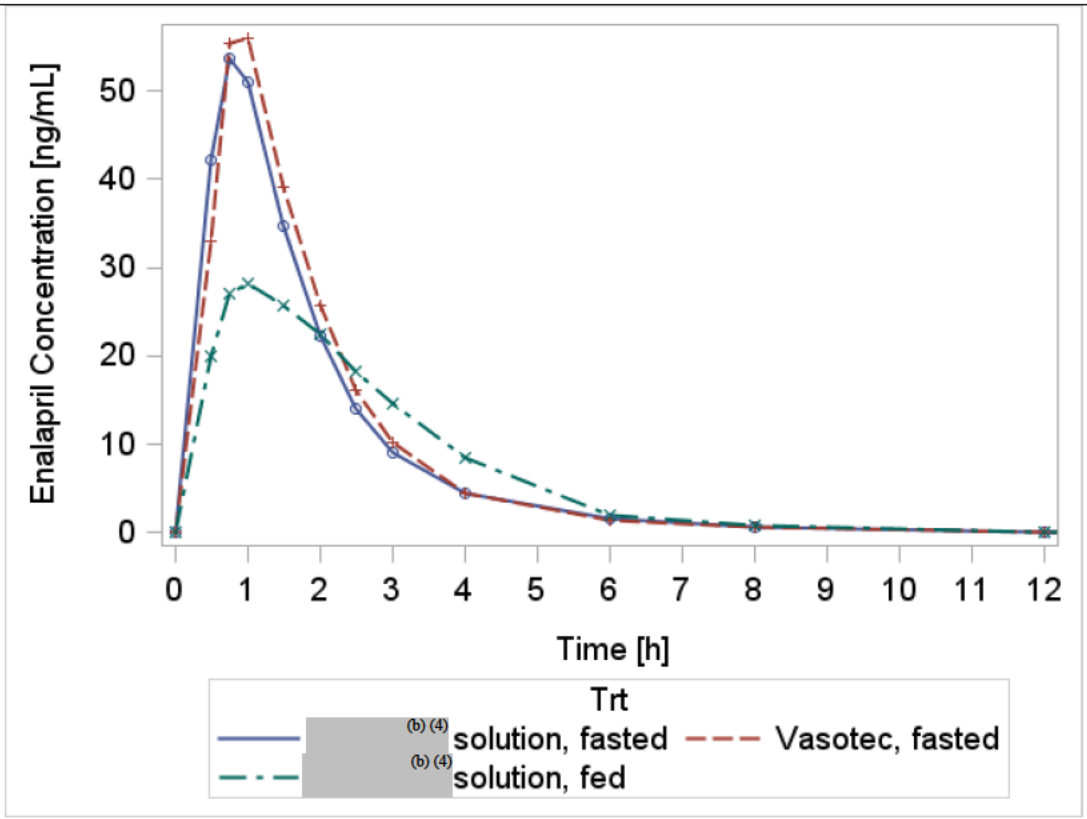
| | Treatment A: Test Formulation-Fasted | | | | Treatment B: Reference Product (Vasotec) Fasted | | | | Treatment C: Test Formulation-Fed | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **n** | **Mean** | **SD** | **CV%** | **n** | **Mean** | **SD** | **CV%** | **n** | **Mean** | **SD** | **CV%** |
| $T_{max}$ (h) | 48 | 0.87 | 0.33 | 37.68 | 45 | 0.92 | 0.27 | 29.15 | 48 | 1.21 | 0.55 | 45.37 |
| $C_{max}$ (ng/mL) | 48 | 58.0 | 17.0 | 29.41 | 45 | 61.8 | 16.1 | 26.11 | 48 | 31.3 | 10.7 | 34.07 |
| $AUC_{last}$ (h*ng/mL) | 48 | 102.6 | 26.91 | 26.23 | 45 | 106.5 | 27.59 | 25.91 | 48 | 88.47 | 22.35 | 25.26 |
| $AUC_{inf}$ (h*ng/mL) | 48 | 103.7 | 26.93 | 25.97 | 45 | 107.5 | 27.64 | 25.73 | 47 | 88.70 | 21.95 | 24.74 |
| $AUC_{Extrap}$ (%) | 48 | 1.10 | 0.70 | 64.04 | 45 | 0.95 | 0.63 | 66.54 | 47 | 1.16 | 0.81 | 70.08 |
| $\lambda_z$ ($h^{-1}$) | 48 | 0.5130 | 0.2095 | 40.83 | 45 | 0.5496 | 0.1843 | 33.54 | 47 | 0.5935 | 0.1848 | 31.13 |
| $T_{1/2}$ (h) | 48 | 1.70 | 1.03 | 60.45 | 45 | 1.45 | 0.61 | 41.86 | 47 | 1.34 | 0.59 | 44.17 |
| $T_{last}$ (h) | 48 | 9.55 | 2.84 | 29.74 | 45 | 9.20 | 2.39 | 25.97 | 48 | 10.58 | 9.31 | 87.93 |
| $C_{last}$ (ng/mL) | 48 | 0.460 | 0.175 | 38.04 | 45 | 0.467 | 0.230 | 49.35 | 48 | 0.507 | 0.273 | 53.80 |

Source: Study report, Section 16.2.6, page 22/3093

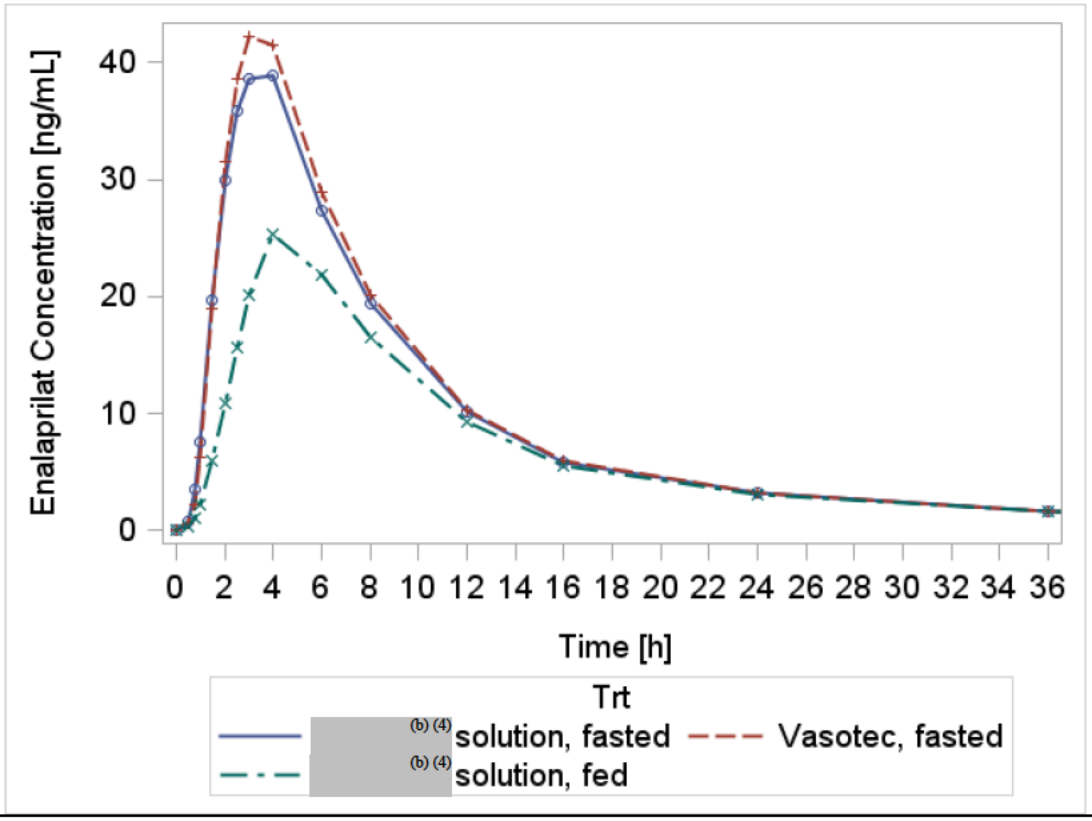
**Mean (arithmetic) PK parameters for enalaprilat**

| | Treatment A: Test Formulation-Fasted | | | | Treatment B: Reference Product (Vasotec) Fasted | | | | Treatment C: Test Formulation-Fed | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **n** | **Mean** | **SD** | **CV%** | **n** | **Mean** | **SD** | **CV%** | **n** | **Mean** | **SD** | **CV%** |
| $T_{max}$ (h) | 48 | 3.45 | 0.77 | 22.28 | 45 | 3.51 | 0.82 | 23.35 | 48 | 4.49 | 1.16 | 25.94 |
| $C_{max}$ (ng/mL) | 48 | 41.0 | 16.1 | 39.33 | 45 | 44.5 | 16.6 | 37.29 | 48 | 26.4 | 11.6 | 43.82 |
| $AUC_{last}$ (h*ng/mL) | 48 | 405.3 | 112.3 | 27.72 | 45 | 417.1 | 96.78 | 23.20 | 48 | 315.7 | 96.92 | 30.70 |
| $AUC_{inf}$ (h*ng/mL) | 48 | 443.3 | 115.0 | 25.94 | 45 | 455.9 | 102.5 | 22.49 | 48 | 360.1 | 104.9 | 29.14 |
| $AUC_{Extrap}$ (%) | 48 | 8.81 | 4.57 | 51.89 | 45 | 8.56 | 4.87 | 56.90 | 48 | 12.39 | 5.49 | 44.30 |
| $\lambda_z$ ($h^{-1}$) | 48 | 0.0273 | 0.0133 | 48.73 | 45 | 0.0292 | 0.0174 | 59.72 | 48 | 0.0241 | 0.0115 | 47.92 |
| $T_{1/2}$ (h) | 48 | 30.49 | 11.59 | 38.02 | 45 | 30.78 | 14.02 | 45.53 | 48 | 33.94 | 12.15 | 35.80 |
| $T_{last}$ (h) | 48 | 68.51 | 8.56 | 12.50 | 45 | 67.21 | 10.67 | 15.88 | 48 | 69.14 | 8.12 | 11.74 |
| $C_{last}$ (ng/mL) | 48 | 0.841 | 0.227 | 26.96 | 45 | 0.860 | 0.299 | 34.81 | 48 | 0.889 | 0.276 | 31.07 |

Source: Study report, Section 16.2.6, page 23/3093




**Mean enalapril concentrations over time**



**Mean enalaprilat concentrations over time**

**Comparison of Enalapril oral solution (10 mg) and Vasotec® tablets (10 mg) - fasted**

| Analyte | Parameter | N | Test | Reference | Mean Ratio | 95% CI | %CV |
|---|---|---|---|---|---|---|---|
| Enalapril | $C_{max}$ [ng/mL] | 48 | 55.1568 | 59.6610 | 92.45 | 87.50-97.68 | 15.60 |
| | $AUC_{last}$ [ng h/mL] | 48 | 99.6030 | 103.3847 | 96.34 | 92.03-100.86 | 12.96 |
| | $AUC_{inf}$ [ng h/mL] | 47 | 100.6779 | 104.3616 | 96.47 | 92.19-100.95 | 12.85 |
| Enalaprilat | $C_{max}$ [ng/mL] | 48 | 37.5196 | 41.2572 | 90.94 | 84.11-98.32 | 22.28 |
| | $AUC_{last}$ [ng h/mL] | 48 | 389.7524 | 405.3687 | 96.15 | 91.88-100.61 | 12.84 |
| | $AUC_{inf}$ [ng h/mL] | 47 | 428.3031 | 443.6027 | 96.55 | 92.82-100.43 | 11.13 |

**Comparison of Enalapril oral solution (10 mg) after high fat meal and enalapril oral solution (10 mg) fasted**

| Analyte | Parameter | N | Test | Reference | Mean Ratio | 95% CI | %CV |
|---|---|---|---|---|---|---|---|
| Enalapril | $C_{max}$ [ng/mL] | 48 | 29.7155 | 55.2999 | 53.74 | 49.25-58.62 | 25.71 |
| | $AUC_{last}$ [ng h/mL mg] | 48 | 85.3850 | 99.0860 | 86.17 | 81.35-91.29 | 16.87 |
| | $AUC_{inf}$ [ng h/mL mg] | 48 | 85.8637 | 100.7148 | 85.25 | 80.70-90.07 | 15.86 |
| Enalaprilat | $C_{max}$ [ng/mL] | 48 | 24.1722 | 38.0223 | 63.57 | 57.75-69.98 | 28.45 |
| | $AUC_{last}$ [ng h/mL] | 48 | 301.5468 | 391.6562 | 76.99 | 72.66-81.58 | 16.93 |
| | $AUC_{inf}$ [ng h/mL] | 48 | 344.8236 | 429.8233 | 80.22 | 76.19-84.48 | 15.09 |

*Reviewer's note: After administration of a standard FDA high-fat breakfast, enalapril AUC decreases by 15% and Cmax decreases by 46%. The AUC and Cmax of enalaprilat are reduced by 23 and 36%, respectively.*
*Trough concentrations of enalapril maleate are similar between fasted and fed application. Moreover, while there is an increased response with increased doses, the increase is small[5] (~2 mmHg with doubling of dose). Therefore, it is not expected that trough response will differ, while any effect on peak response might be marginal and may not be significant.*

**Site Inspection**

**Requested:** Yes ☐ No ☒ | **Performed:** Yes ☐ No ☒ N/A ☐

**Safety**

[5] Medical officer review for Vasotec (December 19, 1985; page 47, http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/018998_Vasotec.cfm)

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

The safety database was comprised of all subjects who had received at least one of the three treatments. One subject (#340) was withdrawn from the study after period 1. This volunteer received enalapril maleate pediatric solution after a high-fat meal in period 1 and experienced hypotension 2 hours after administration of drug and also mild abdominal pain and dysphagia and moderate dizziness and nausea. All adverse events resolved and were considered related to study drug by the investigator.

There were no serious AEs reported.

**Conclusion**

- Enalapril oral solution given at a dose of 10 mL of a 1 mg/mL solution ( (b) (4) ) is bioequivalent to Vasotec® 10 mg tablets under fasted conditions.
- The reduction in Cmax and AUC does not require dose adjustment. While there is an increased response with increased doses, the increase is small (~2 mmHg) and trough concentrations of enalapril maleate are similar between fasted and fed application. Therefore, it is not expected that trough response will differ, while any effect on peak response might be marginal.

**Comments**

Section 12.3 in the proposed labeling does not contain recommendations with regard to lowering of AUC of 23% when enalapril maleate pediatric solution is administered with a high-fat meal. The following sentence should be added: "No dose adjustment is required."

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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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MARTINA D SAHRE
12/14/2012

DIVYA MENON ANDERSEN
12/14/2012

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Office of Clinical Pharmacology

*New Drug Application Filing and Review Form*

***General Information About the Submission***

The sponsor, Silvergate Pharmaceuticals, Inc. is seeking approval for enalapril maleate pediatric solution (b) (4)) under section 505(b)(2) of the FD&C Act. The reference listed drug for this application is Vasotec® (NDA 018998). The indication for this new formulation of enalapril is the treatment of hypertension in pediatric patients (b) (4). To bridge to the efficacy and safety data of the reference listed drug, the sponsor conducted a relative bioavailability study to compare the pharmacokinetics of (b) (4) 10 mg/10 mL to Vasotec® 10 mg tablets and to compare the bioavailability of (b) (4) under fed and fasted conditions. The pediatric formulation will consist of 150 mg enalapril maleate in a powder blend and is co-packaged with Ora-Sweet® SF for reconstitution of the powder. Upon reconstitution the oral solution will have a concentration of 1 mg/mL.

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | **204308** | **Brand Name** | **(b) (4)** |
| **OCP Division (I, II, III, IV, V)** | **I** | **Generic Name** | **Enalapril maleate** |
| **Medical Division** | **DCRP** | **Drug Class** | **ACE-Inhibitor** |
| **OCP Reviewer**<br>**OCP Secondary Reviewer** | **Martina Sahre, PhD**<br>**Divya Menon-Andersen, PhD** | **Indication(s)** | **Treatment of hypertensio (b) (4)** |
| **OCP Team Leader** | **Rajanikanth Madabushi, PhD** | **Dosage Form** | **Powder for oral solution** |
| **Pharmacometrics Reviewer** | | **Dosing Regimen** | **5 to <40 mg once daily** |
| **Date of Submission** | **August 8, 2012 (received)** | **Route of Administration** | **Per os** |
| **Estimated Due Date of OCP Review** | **May 2, 2013** | **Sponsor** | **Silvergate Pharmaceuticals, Inc.** |
| **Medical Division Due Date** | | **Priority Classification** | **No** |
| PDUFA Due Date | **June 10, 2013** | | |

### *Clin. Pharm. and Biopharm. Information*

| STUDY TYPE | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| STUDY TYPE | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **Tabular Listing of All Human Studies** | **X** | **3** | **2** | **The sponsor conducted three studies. Study SG01-01 had the same design as study SG01-03, however the reconstitution of the powder was different for both studies and resulted in improper wetting and therefore lower availability of enalapril maleate from the solution. Study SG01-02 was conducted to confirm that improper reconstitution was the cause for low bioavailability of enalapril maleate from the formulation in study SG01-01. The sponsor then conducted study SG01-03 (same design as SG01-01) with a new reconstitution protocol.** |
| **HPK Summary** | **X** | | | **Vasotec label includes PK information**<br>**Wells et al study of PK in children 2 months to 15 years** |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | **2** | **2** | **Bioanalytical and method validation available for study SG01-03.** |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD -** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| STUDY TYPE | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | **X** | **3** | **2** | **Study SG01-01 failed because of issues with the formulation and Study SG01-02 was a pilot study to confirm that the issues were due to the formulation. Study SG01-03 is the pivotal relative BA study.** |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | **X** | **1** | | **Study SG01-03 included a high-fat meal group.** |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | **X** | | | |
| **Total Number of Studies** | | **3** | **3** | |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | X | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | X | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | X | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | | | X | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate | X | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| | hyperlinks and do the hyperlinks work? | | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | X | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | X | | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**Yes.**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Martina Sahre 09/10/2012
Reviewing Clinical Pharmacologist Date

Divya Menon-Andersen 09/10/2012
Secondary Reviewer Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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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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MARTINA D SAHRE
09/10/2012

DIVYA MENON ANDERSEN
09/11/2012

| BIOPHARMACEUTICS FILING REVIEW<br>Office of New Drugs Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 204-308 | **Reviewer**:<br>Akm Khairuzzaman, Ph.D. | |
| **Submission Date:** | 08/10/2012 | | |
| **Division:** | Division of Cardiovascular and Renal Products | **Team Lead:**<br>Angelica Dorantes, PhD | |
| **Sponsor:** | Silvergate Pharmaceuticals | | |
| **Trade Name:** | (b) (4) | **Date Assigned:** | 08/10/2012 |
| **Established Name:** | Enalapril maleate, USP | **Date of Review:** | 08/29/2012 |
| **Indication:** | Treatment of hypertension in pediatric patients (b) (4) | **Type of Submission:**<br>Original NDA 505(b)2 | |
| **Formulation/strengths** | Powder for oral solution, 1mg/mL after reconstitution | | |
| **Route of Administration** | Oral | | |

**SUBMISSION:** 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. This formulation is claimed to be a superior formulation which is easier to use and allows for more accurate dosing for the pediatric population compared to that of the tablet dosage form.

**BIOPHARMACEUTIC INFORMATION:**

(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. Since the physical state of the formulation after reconstitution is solution, therefore there is no dissolution test in the drug product specification. This appears to be reasonable for a solution product.

In order to bridge this new formulation with that of the reference product, applicant conducted the following three comparative bioavailability and bioequivalence studies:

(i) Study # SG01-03: A Single-dose, Three-period, Three-treatment, Three-way Crossover Bioavailability Study of 10 mg Enalapril Maleate Pediatric Solution vs. Vasotec® 10 mg Tablets Under **Fasted** Conditions and 10 mg Enalapril Maleate Pediatric Solution Under Fed Conditions in Healthy Adults.

(ii) Study # SG01-01: A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioavailability Study of 10 mg Enalapril Maleate Pediatric Solution vs Vasotec® 10 mg Tablets under **Fasted** Conditions and 10 mg Enalapril Maleate Pediatric Solution under **Fed** Conditions in Healthy Adults.

(iii) Study # SG01-02: A Pilot Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioavailability Study of 10 mg Enalapril Maleate Pediatric Solution vs Vasotec® 10 mg Tablets under Fasted Conditions in Healthy Adults

The pharmacokinetic (PK) data from the two of these studies (study SG01-03 and the supportive Study SG01-02) are summarized below. The PK data from Study SG01-01 were unable to be determined due to a modification of the mixing instructions with respect to reconstitution of the enalapril maleate powder that resulted in improper wetting and mixing of the formulated powder.

**Table 1.** Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Enalapril and Enalaprilat – Studies SG01-03 and SG01-02

| | Study SG01-03 | | | Study SG01-02 | | |
|---|---|---|---|---|---|---|
| | ln ($C_{max}$) | ln ($AUC_{last}$) | ln ($AUC_{inf}$) | ln ($C_{max}$) | ln ($AUC_{last}$) | ln ($AUC_{inf}$) |
| **Enalapril: Treatment A (Test - Fasted) Versus Treatment B (Reference - Fasted)** | | | | | | |
| Geometric Mean Ratio[a] (%) | 92.45 | 96.34 | 96.47 | 92.39 | 95.27 | 97.51 |
| 90% Lower CI | 87.50 | 92.03 | 92.19 | 79.54 | 88.76 | 91.55 |
| 90% Upper CI | 97.68 | 100.86 | 100.95 | 107.31 | 102.27 | 103.86 |
| **Enalapril: Treatment C (Test - Fed) Versus Treatment A (Test - Fasted)** | | | | | | |
| Geometric Mean Ratio[a] (%) | 53.74 | 86.17 | 85.25 | – | – | – |
| 90% Lower CI | 49.25 | 81.35 | 80.70 | – | – | – |
| 90% Upper CI | 58.62 | 91.29 | 90.07 | – | – | – |
| **Enalaprilat: Treatment A (Test - Fasted) Versus Treatment B (Reference - Fasted)** | | | | | | |
| Geometric Mean Ratio[a] (%) | 90.94 | 96.15 | 96.55 | 86.45 | 91.17 | 90.03 |
| 90% Lower CI | 84.11 | 91.88 | 92.82 | 71.55 | 82.84 | 81.83 |
| 90% Upper CI | 98.32 | 100.61 | 100.43 | 104.46 | 100.34 | 99.04 |
| **Enalaprilat: Treatment C (Test - Fed) Versus Treatment A (Test - Fasted)** | | | | | | |
| Geometric Mean Ratio[a] (%) | 63.57 | 76.99 | 80.22 | – | – | – |
| 90% Lower CI | 57.75 | 72.66 | 76.19 | – | – | – |
| 90% Upper CI | 69.98 | 81.58 | 84.48 | – | – | – |

[a] = Geometric mean for treatments as noted in table (test formulation-fasted [test] and reference product [ref] OR test formulation-fed [test] and test formulation [fasted]) based on least squares mean of log transformed parameter values.
CI = Confidence interval.

The evaluation and acceptability of these PK data supporting the approval of 505(b)(2) NDA 204-308 for (b) (4) Powder for Oral Solution are under the jurisdiction of the Office of Clinical Pharmacology.

**RECOMMENDATION:**
NDA 204-308 for (b) (4) (enalapril maleate) Powder for Oral Solution is **fileable** from Biopharmaceutics point of view.

Since this NDA does not include any Biopharmaceutics elements to be reviewed (i.e., biowaiver request, and/or dissolution information), a further review under the jurisdiction of ONDQA-Biopharmaceutics responsibility is NOT needed for NDA 204-308.

**Akm Khairuzzaman, Ph.D.**
Biopharmaceutics Reviewer, ONDQA

**Angelica Dorantes, Ph.D.**
Biopharmaceutics Team Lead, ONDQA

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/s/

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AKM KHAIRUZZAMAN
08/31/2012
Fileable from Biopharmaceutics point of view

ANGELICA DORANTES
08/31/2012