# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204308Orig1s000

# MEDICAL REVIEW(S)

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS

***Divisional Memo***

**NDA**: 204308 Epaned; enalapril for hypertension in children 12 years.

**Sponsor**: Silvergate Pharmaceuticals

**Review date**: 6 June 2013

**Reviewer**: N. Stockbridge, M.D., Ph.D., HFD-110

**Distribution**: NDA 204308

This memo conveys the Division's recommendation to issue a Complete Response letter for this application.

This application has been the subject of reviews of CMC (McLamore, 6 December 2012 and 10 May 2013), clinical pharmacology (Sahre, 14 December 2012), and medical (U, 5 December 2012). There is a comprehensive CDTL memo (Madabushi, 5 June 2013) with which I am in full agreement.

Enalapril is the pro-drug for enalaprilat, an inhibitor of angiotensin converting enzyme. Enalapril was originally approved in 1985 as Vasotec, then acquired labeling for use in children 1 month to 16 years, following a study conducted in response to a Pediatric Written Request.

Labeling for Vasotec refers to an extemporaneous formulation in which Vasotec tablets are dissolved in Bicitra plus Ora-Sweet SF, to form a 1 mg/mL solution[1]. The proposed product is enalapril powder packaged with Ora-Sweet. In either case, the solution has a storage lifetime that is much shorter than the shelf-life of the tablet or powder.

The current application, other than to establish the properties of the powder and solution, relies upon the Agency's findings of safety and efficacy with Vasotec per 505(b)(2). Fasted, the proposed formulation is formally bioequivalent to Vasotec tablets; with a high-fat meal, Cmax does not meet bioequivalence, but AUC does. I agree with the review team that effects of enalapril on blood pressure and cardiovascular outcomes are not likely to be adversely affected by this degree of bioinequivalence.

The sponsor sought a Priority Review based on GMP-compliance and ease of use, but the Division denied this, saying that any benefit was too small to merit priority review. However, the sponsor did get Orphan Designation on this basis.

The sponsor proposed labeling only for use in children, but the formulation seems suitable for use in adults, where doses range from 2.5 mg to 40 mg per day. The Division added back adult labeling for hypertension, on the basis that the restriction to children was artificial. The sponsor also did not incorporate other cardiovascular claims Vasotec has, and the Division went along with that[2].

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*[1] The label refers to this as a suspension, but what is suspended is the tablet's excipients; enalapril is quite soluble.*

*[2] The distinction is that there is no specific indication for pediatric hypertension. Hypertension in children is considered to be the same disease as in adults. To get the extension for pediatric use, a sponsor has to re-establish pharmacokinetics and pharmacodynamic responsiveness—in a single blood pressure study. If one thought these were distinct entities one would need two studies of the blood pressure effects, and, probably, cardiovascular outcomes, which have not been demonstrated in the pediatric population with any antihypertensive.*

(b) (4)

This is also consistent with my action in this case, for the Epaned dosage form and volume are entirely reasonable for many adults.

There are no CMC issues, but the CMC review concludes that the stability data support an 18-month expiry for the product as manufactured and an (b) (4) expiry for the solution, the former being somewhat less than the sponsor requested.

Agreement on labeling is the only open issue responsible for the Complete Response action.

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NORMAN L STOCKBRIDGE
06/06/2013

**Memo to file**

| | |
|---|---|
| **Date:** | 29-May-2013 |
| **Through:** | Norman Stockbridge, Division Director, DCRP |
| **From:** | Khin Maung U, Medical Officer, DCRP |
| **To:** | Gayatri R. Rao, Director, Office of Orphan Products Development (OOPD)<br>Henry Startzman, Director, Drug Designation Program, OOPD |
| **Cc:** | Michael Monteleone, RPHM, DCRP |
| **Subject:** | Opinion of "clinical superiority" of EPANED compared to RLD Vasotec® |
| **NDA:** | 204-308 **Orphan Drug Designation** #: 12-3767 |
| **Drug Name:** | EPANED (Enalapril maleate USP) Powder for Oral Solution |
| **Sponsor**: | Silvergate Pharmaceuticals, Inc. |
| **Indication**: | Treatment of hypertension in pediatric patients 1 month to 16 years |

## BACKGROUND

Office of Orphan Products Development (OODP) requests the Division's opinion regarding the clinical superiority of EPANED (Enalapril maleate USP) Powder for Oral Solution compared to the RLD VASOTEC® to treat hypertension in pediatric patients 1 month to 16 years age. Since enalapril (the active moiety) is already approved for pediatric hypertension, the sponsor needed to demonstrate that their enalapril solution is an improved formulation which is clinically superior to the approved tablets in order to be eligible for orphan drug designation (21 CFR 316.20(a)).

## SUBMISSION and REVIEWER's COMMENTS

The submission consists of a letter explaining the sponsor's rationale for claiming that EPANED is superior to a compounded product of enalapril tablets in a solution. The sponsor outlined issues of efficacy with respect to pill splitting and subsequent accuracy in dosing and compliance in the currently available therapy. The sponsor's arguments consist of the following:

(i) EPANED is in the form of a kit manufactured under GMP conditions. None of the components of the kit can be substituted or altered
(ii) The kit is simple to prepare and does not require tools or step.
(iii) After constitution, the solution is stable for 60 days.
(iv) The enalapril is in solution form (whereas, in the compounded VASOTEC® solution, the sponsor claims that the enalapril is in suspension form requiring shaking at each dosing).

*Reviewer's comment*: The Orphan approval letter requires the sponsor to *demonstrate* that their drug is clinically superior to the already approved VASOTEC® for the same indication.

(i) The sponsor has not submitted data to demonstrate that using their kit is superior to compounded enalapril.
(ii) While the sponsor claims that their preparation is in solution form compared to the compounded enalapril which is in suspension form, the labeling instructions for VASOTEC® involves dissolving VASOTEC® tablets in Bicitra® solvent and adding Ora-Sweet SF™. I think both pediatric products appear to be in solution form.
(iii) Prior to dispensing to the patient, both EPANED solution and the compounded VASOTEC® product will be prepared by the pharmacist to be ready for consumption by the patient. Thus, there is no advantage of EPANED over compounded VASOTEC® solution.

## CONCLUSION

There is no data to support a superiority claim of EPANED over VASOTEC® for the indication: "treatment of hypertension in pediatric patients 1 month to 16 years of age."

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KHIN M U
05/31/2013

NORMAN L STOCKBRIDGE
05/31/2013

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 204-308 |
| Priority or Standard | Standard |
| Submit Date(s) | 10-Aug-2012 |
| Received Date(s) | 10-Aug-2012 |
| PDUFA Goal Date | 10-Jun-2013 |
| Division / Office | DCaRP/ODE I/OND |
| Reviewer Name(s) | Khin Maung U, M.D. |
| Review Completion Date | 05-Dec-2012 |
| Established Name | Enalapril maleate, USP |
| (Proposed) Trade Name | (b) (4) |
| Therapeutic Class | Angiotensin Converting Enzyme Inhibitor |
| Applicant | Silvergate Pharmaceuticals, Inc. |
| Formulation(s) | Power for Oral Solution (150 mg of enalapril maleate in a powder blend) Reconstitution with 150 ml of Ora-Sweet® SF results in a 1 mg/ml oral solution of enalapril maleate. |
| Dosing Regimen | 0.08 mg/kg (up to 5 mg) once daily; dosage to be adjusted according to BP response |
| Indication(s) | Treatment of hypertension in pediatric patients 1 month to 16 years |
| Intended Population(s) | Pediatric patients 1 month to 16 years of age |

Template Version: March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

This New Drug Application (NDA) is submitted under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (b) (4)™ (enalapril maleate, USP) Powder for Oral Solution for the treatment of hypertension in pediatric patients (b) (4). Enalapril (as VASOTEC®, the referenced listed drug) is labeled for the treatment of hypertension in pediatric patients 1 month to 16 years.

The submission contains data from one pharmacokinetic (PK) and food effect study conducted on 53 healthy *adults* comparing enalapril solution to VASOTEC®. The PK study shows bioequivalence between the enalapril solution and VASOTEC® under fasted conditions; after a high-fat meal, there are reductions in $C_{max}$ and AUCs which do not fall within the accepted 80% to 125% range. However, the trough plasma concentrations of enalaprilat are similar (at 16 hours till 36 hours) between fasted and fed administrations, and they are also not distinguishable between (b) (4)™ and VASOTEC®. For enalapril plasma concentrations, the trough concentrations (from 6 hour through 12 hours) are zero for both formulations and the fed application of (b) (4)™.

The apparent similarity in bioavailability of (b) (4)™ and VASOTEC® establishes a bridge between (b) (4)™ and VASOTEC to the existing labeled indication of VASOTEC® for the treatment of hypertension in pediatric patients, and supports the consideration for the **approval** of (b) (4)™ for the treatment of hypertension in pediatric patients, pending labeling changes and safety updates to be addressed by the sponsor.

## 1.2 Risk Benefit Assessment

The application does not contain data to evaluate risk and benefit of (b) (4)™ for its antihypertensive effect in pediatric patients. This 505(b)(2) NDA relies on the previous findings of safety and effectiveness of enalapril tablets (VASOTEC®) in hypertensive pediatric patients 1 month to 16 years of age based on clinical trials (adequate and well-controlled) and published literature reports of enalapril in pediatric patients.

The submission contains no data from pediatric hypertensive patients treated with (b) (4)™ to make risk benefit evaluation in the intended pediatric population.

The NDA contains one analyzable PK and food effect study of the enalapril solution compared to the approved product VASOTEC® in 53 healthy *adults*, and exposure of the enalapril solution to a total of 93 healthy *adults* in PK studies to evaluate safety information:

- Regarding risk, the adverse event (AE) profiles following the enalapril solution ((b) (4)™) in fasted and fed conditions and VASOTEC® are consistent with the known effects of enalapril.
- For benefit assessment, the PK parameters show bioequivalence between enalapril maleate pediatric solution ((b) (4)™) and VASOTEC® in healthy *adults* under fasted conditions. However, after a high-fat meal, there are: (i) 36% reduction in $C_{max}$ and 20-23% reduction in AUCs for enalaprilat, and (ii) 46% reduction in $C_{max}$ and 14-15% reduction in AUCs for enalapril, both of which do not fall within the accepted 80% to 125% range.
- Despite the reductions in $C_{max}$ and AUCs, the trough plasma concentrations of enalapril (from 6 hour through 12 hours) and enalaprilat (from 16 hours till 36 hours) are similar between fasted and fed administrations, and also similar to those of VASOTEC® suggesting that the trough response on blood pressure will not be different for the two formulations and the fed administration.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

## 1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

# 2 Introduction and Regulatory Background

Silvergate Pharmaceuticals, Inc. (the sponsor), seeks marketing approval for (b) (4) ™ (enalapril maleate, USP) Powder for Oral Solution for the treatment of hypertension in pediatric patients (b) (4), under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and §21 CFR 314.54

This application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, VASOTEC® (enalapril maleate) tablets, distributed by Valeant Pharmaceuticals, North America LLC under NDA 018-998 (initially approved in tablet form on 24-Dec-1985 for the treatment of hypertension, and later for the treatment of heart failure, and treatment of asymptomatic left ventricular dysfunction).

FDA had also approved enalapril in tablet form for use in hypertensive pediatric patients 1 month to 16 years of age (supported by adequate and well-controlled studies of enalapril in pediatric and adult patients, and by published literature in pediatric patients).

VASOTEC® is currently listed in the electronic version of the Agency's *Orange Book.* The sponsor contends that based upon information published in Orange Book, there is no unexpired exclusivity for VASOTEC® tablets and also no unexpired patents.

The chemistry, manufacturing, and controls sections of this application are supported by original data developed by the sponsor for (b) (4) ™ describing the drug substance and drug product.

The nonclinical sections of this application are supported by reference to the VASOTEC® tablet NDA 018998.

The clinical sections of this application are supported by data obtained from a pivotal comparative bioavailability study using (b) (4) ™ and VASOTEC tablets and by reference to the VASOTEC® tablet NDA 018-998.

## 2.1 Product Information

(b) (4) ™ Powder for Oral Solution contains 150 mg of enalapril maleate in a powder blend, which upon reconstitution with Ora-Sweet SF yields a 1 mg/mL oral solution of enalapril maleate. Each bottle of (b) (4) ™ Powder for Oral Solution is co-packaged with a 150 mL bottle of Ora-Sweet SF.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Drugs available in the US for treatment of chronic pediatric hypertension include calcium channel blockers (Type I such as verapamil, diltiazem, and Type II such as nifedipine, amlodipine, nicardipine and felodipine), angiotensin-converting enzyme inhibitors (such as enalapril, captopril, and lisinopril), diuretics (such as thiazides), and β-blockers (such as propranolol, atenolol, metoprolol and labetalol).[1]

## 2.3 Availability of Proposed Active Ingredient in the United States

Enalapril is a FDA-approved commercial antihypertensive drug and available in the US.

## 2.4 Important Safety Issues With Consideration to Related Drugs

In pediatric hypertensive patients, ACE inhibitors do not have a dose-response effect. The BP tends to fall gradually until the converting enzyme is inhibited by 90%; as inhibition increases, a precipitous drop in BP may occur.[2,3]

Neonates and infants respond to ACE inhibitors to a greater extent and for a longer duration than older children.[4] The reason for this increased sensitivity of neonates to ACE inhibitors is not known, but thought to be due to high renin levels in the first few months of life which may increase dependence on the renin-angiotensin system (RAS); modifications in the RAS by ACE inhibitors may change cardiovascular homeostasis dramatically. Underdeveloped renal and hepatic drug clearance, too, may play a role.

The most serious AE is significantly reduced renal function in the presence of bilateral renal artery stenosis; ACE inhibitors should be avoided in these patients.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

### 2.5.1 Regulatory activity related to the submission

During a pre-IND (PIND 109473) meeting between the Division of Cardiovascular Renal Products and the sponsor on October 1, 2010, it was agreed that a 505(b)(2) NDA submission referencing VASOTEC® (enalapril maleate) tablets (NDA 018998) as the reference listed drug would be acceptable for the (b) (4)™ (enalapril maleate, USP) Powder for Oral Solution application. In response to the sponsor's Question 5 (*Please confirm this type of study should provide suitable bioavailability information for review for approval and that no additional studies would be required if the bioavailability results are comparable*), the Division responded that "…*the study design in healthy adult male and female subjects appears to be adequate to assess bioavailability. Please note that demonstrating bioequivalence to Vasotec® would be ideal. If the pharmacokinetic time course of the pediatric formulation differs significantly from that of Vasotec® in the peak to trough (interdosing interval) ratio or if the $C_{min}$ of your product is less than that of Vasotec®, then you will have to establish effectiveness similar to Vasotec®.*"

The sponsor agreed to include 6 months accelerated and room-temperature stability data on three registration batches in the original application with submission of 12 months of room-temperature stability data on three registration batches at the midpoint of the review cycle.

The sponsor also submitted an Orphan Drug Designation request for (b) (4)™ for

the treatment of hypertension in pediatric patients (b) (4) to FDA on 07/19/2012 (b) (4) (b) (4) ™ (enalapril maleate, USP) Powder for Oral Solution (Section 527 of the Federal Food, Drug, and Cosmetic Act).

Note: This request was denied by the Office of Orphan Products Development.

### 2.5.2 Request for Priority Review

The sponsor requested Priority (P) review based on their contention that their product:

(i) ensures standardized amount of enalapril in a standardized volume and ease of constituting the oral solution, and

(ii) provides ease of patient use because the (b) (4) ™ oral solution can be kept without refrigeration, and does not require shaking the bottle before consumption.

However, the above properties of this drug product do not fulfill the FDA Criteria for Priority Review, which require that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following:

(1) safe and effective therapy where no satisfactory alternative therapy exists (unmet medical need); or

(2) a significant improvement compared to marketed products (approved, if approval is required), including nondrug products or therapies. Significant improvement is illustrated by the following examples:
   (a) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;
   (b) elimination or substantial reduction of a treatment-limiting drug reaction;
   (c) documented enhancement of patient compliance; or
   (d) evidence of safety and effectiveness in a new subpopulation.

*Reviewer's comments*: The data in submission do not support a Priority review designation for this NDA.

## 2.6 Other Relevant Background Information

Enalapril maleate (in tablet form) is approved by FDA for use in adults for the treatment of hypertension, heart failure, and asymptomatic left ventricular dysfunction, and for the treatment of hypertensive pediatric patients 1 month to 16 years of age.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The sponsor provided study drug administration times and blood sample collection times (including sample time deviations due to need to restick the subjects) which do not appear to be of concern with regard to data quality.

The study was conducted at the (b) (4) and outsourced to labs in (b) (4)

Site monitoring was performed by (b) (4) based in (b) (4), with medical monitoring by the sponsor's staff (b) (4). There was no sponsor audit.

PK statistical analyses, and data management and production of tables, figures and listings were performed by Worldwide Clinical Trials based in San Antonio, Texas, and the final integrated report was prepared by (b) (4).

## 3.2 Compliance with Good Clinical Practices

The sponsor certified that this study was carried out in accordance with the protocol, the International Conference on Harmonisation (ICH), the Guideline for Good Clinical Practice: Consolidated Guidance (E6), basic ethical principles in the Declaration of Helsinki, and applicable regulatory requirements including clinical research guidelines established by the basic principles defined in the US CFR Parts 50, 56, and 312.

The sponsor also certified that the study protocol dated March 27, 2012, and amendments dated April 5, 2012, April 10, 2012, and April 18, 2012, were submitted for ethical review by the principal investigator (Cynthia A. Zamora, MD, Worldwide Clinical Trials, San Antonio, Texas) and approval by the Institutional Review Board (IRB), namely, (b) (4).

Following team discussions at the Filing Meeting, no requests were made to OSI for GCP inspections.

## 3.3 Financial Disclosures

The sponsor submitted (i) that none of the clinical investigators who conducted Studies SG01-01, SG01-02, or SG01-03 were employees of Silvergate Pharmaceuticals, Inc., and (ii) the completed Form FDA 3454 providing certification as to the financial interests and arrangements of the clinical investigators who conducted Studies SG01-01, SG01-02, or SG01-03.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Not applicable. This is a 505(b)(2) NDA submission with VASOTEC® (enalapril maleate) tablets (NDA 018-998) as the reference listed drug. Reference is also made to the VASOTEC® product label for a summary of chemistry manufacturing and controls.

## 4.2 Clinical Microbiology

Not applicable. This is a 505(b)(2) NDA submission with VASOTEC® (enalapril maleate) tablets (NDA 018-998) as the reference listed drug.

## 4.3 Preclinical Pharmacology/Toxicology

Not applicable. This is a 505(b)(2) NDA submission with VASOTEC® (enalapril maleate) tablets (NDA 018-998) as the reference listed drug. Reference is also made to the VASOTEC® product label for a summary of preclinical pharmacology and toxicology.

## 4.4 Clinical Pharmacology

Enalapril maleate is a pro-drug. Following oral administration, it undergoes hydrolysis to enalaprilat, which is the active ACE inhibitor.

### 4.4.1 Mechanism of Action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and decreased aldosterone secretion.

### 4.4.2 Pharmacodynamics

Not applicable. Pharmacodynamics was not evaluated in this NDA. This is a 505(b)(2)

NDA submission with VASOTEC® (enalapril maleate) tablets (NDA 018-998) as the reference listed drug. Reference is also made to the VASOTEC® product label for a summary of the pharmacodynamics.

### 4.4.3 Pharmacokinetics

This is a 505(b)(2) NDA submission with VASOTEC® (enalapril maleate) tablets (NDA 018-998) as the reference listed drug. Reference is also made to the VASOTEC® product label for a summary of the pharmacokinetics and metabolism of enalapril maleate (*Vasotec prescribing information*).

With respect to key points related to pharmacokinetics of enalapril,

- Peak serum concentrations of enalapril when taken orally occur within an hour.
- When absorbed, enalapril is hydrolyzed to the active entity enalaprilat,
- Peak serum concentrations of enalaprilat occur 3 to 4 hours after oral dosing of enalapril maleate,
- VASOTEC® is primarily excreted via the kidneys.
- 94% of the dose is recovered in urine and feces as enalapril or enalaprilat; the principal components in urine are enalaprilat (accounting for about 40% of the dose) and intact enalapril, and
- The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

# 5 Sources of Clinical Data

Three bioavailability studies (SG01-01, SG01-02, and SG01-03) are included in this 505(b)(2) submission.

Pharmacokinetic (PK) data are summarized for two of the studies: the pivotal Study SG01-03 and the supportive Study SG01-02.

The sponsor could not determine the PK data from Study SG01-01 due to a modification of the mixing instructions for reconstitution of the enalapril maleate powder which resulted in improper wetting and mixing of the formulated powder.

## 5.1 Tables of Studies/Clinical Trials

### Table 1 Listing of all clinical studies

| Study Number/Start Date/Completion Date | Study Design | Objectives | Baseline Demographics | Diagnosis and Criteria for Inclusion | Test Products: Dosage Regimen/Route of Administration/Number of Subjects |
|---|---|---|---|---|---|
| Phase I Single-Dose Studies | | | | | |
| *SG01-03* | Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover | To assess bioavailability of enalapril maleate pediatric solution versus Vasotec; food effect of enalapril maleate pediatric solution | Total subjects: 53<br>M/F: 42/11<br>Mean age: 32.4 years (range 18 to 55) | Healthy males or non-pregnant, non-breastfeeding females between 18 and 55 years of age | A: Oral enalapril maleate pediatric solution 10 mg (fasted) (*n* = 48)<br>B: Oral Vasotec tablet 10 mg (fasted) (*n* = 48)<br>C: Oral enalapril maleate pediatric solution 10 mg (fed, high-fat meal) (*n* =51) |
| *SG01-01* | Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover | To assess bioavailability of enalapril maleate pediatric solution versus Vasotec; food effect of enalapril maleate pediatric solution | Total subjects: 30<br>M/F: 16/14<br>Age range: 19 to 53 years | Healthy males or non-pregnant, non-breastfeeding females between 18 and 55 years of age | A: Oral enalapril maleate pediatric solution 10 mg (fasted) (*n* = 29)<br>B: Oral Vasotec tablet 10 mg (fasted) (*n* = 29)<br>C: Oral enalapril maleate pediatric solution 10 mg (fed, high-fat meal) (*n* = 29) |
| *SG01-02* | Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover | To confirm the low bioavailability finding for enalapril maleate pediatric solution in Study SG01-01 was due to inadequate mixing of the solution | Total subjects: 10<br>M/F: 5/5<br>Age range: 23 to 52 years | Healthy males or non-pregnant, non-breastfeeding females between 18 and 55 years of age | A: Oral enalapril maleate pediatric solution 10 mg (fasted) (*n* = 10)<br>B: Oral Vasotec tablet 10 mg (fasted) (*n* = 10) |

F= female; M= male

## 5.2 Review Strategy

Only Study SG01-03 contains PK data in support of the NDA; the other two PK studies submitted do not contain data relevant to the data evaluation for the NDA.

I will review the efficacy and safety data of Study SG01-03 from the clinical perspective, taking into consideration the Agency's response to the sponsor that the bioavailability "… *study design in healthy adult male and female subjects appears to be adequate to assess bioavailability,"* and *"… that demonstrating bioequivalence to Vasotec® would be ideal."* However, the agency also stated, *"If the pharmacokinetic time course of the pediatric formulation differs significantly from that of Vasotec® in the peak to trough (interdosing interval) ratio or if the $C_{min}$ of your product is less than that of Vasotec®, then you will have to establish effectiveness similar to Vasotec®."*

The clinical pharmacology perspective and analyses of PK parameters, which are the main analyses for this NDA, will be made by the clinical pharmacology reviewer.

## 5.3 Discussion of Individual Studies/Clinical Trials

The sponsor submitted 3 clinical studies:

(1) **Study SG01-01** was a randomized, open-label, single-dose, three-period, three-treatment, three-way crossover study in 30 healthy adult subjects. The objectives were to assess the bioavailability of (b) (4) ™ versus VASOTEC® tablets under fasted conditions and to assess the effect of food on (b) (4) ™. A low dose of 10 mg was used in both groups to avoid orthostatic hypotension in healthy volunteers.

The results from the SG01-01 study were considered ***not valid*** due to the method of reconstitution of the enalapril maleate powder to solution (which did not allow for shaking the bottle well for 30 seconds). Instead of the intended 10 mg dose, the subjects were found to have received a mean dose of 1.30 mg based on (1) the finding in plasma samples of enalapril and enalaprilat levels below the lower limit of quantification (LLOQ) in both fasted and fed test treatments, and (2) assay findings in contingency samples of the reconstituted enalapril maleate test formulations.

(2) **Study SG01-02** was a randomized, open-label, single-dose, two-period, two-treatment, two-way crossover study in 10 healthy adult subjects to confirm that the low bioavailability found after administration of enalapril maleate pediatric solution in Study SG01-01 was due to inadequate mixing of the solution during its preparation.

(3) **Study SG01-03**, which serves as the basis for this 505(b)(2) NDA submission, was a randomized, open-label, single-dose, three-period, three-treatment, three-way crossover study design essentially identical to SG01-01. Differences between SG01-01 and SG01-03 studies are (i) the number of healthy adult subjects (53 subjects enrolled for SG01-03 versus 30 subjects enrolled for SG01-01) and (ii) the method of reconstitution of the enalapril maleate pediatric solution.

# 6 Review of Efficacy

## ***Efficacy Summary***

In this 505(b)(2) New Drug Application (NDA) submission, Silvergate Pharmaceuticals, Inc. is relying on FDA's finding of efficacy for the previously approved enalapril maleate (VASOTEC®) (NDA 018-998) to support the approval of (b) (4) ™ (enalapril maleate, United States Pharmacopeia [USP]) Powder for Oral Solution ( (b) (4) ™ ) for the treatment of hypertension in pediatric patients 1 month to (b) (4) years of age.

Three bioavailability studies (SG01-01, SG01-02, and SG01-03) are included in this 505(b)(2) submission; pharmacokinetic (PK) data are summarized for two of the studies: the pivotal Study SG01-03 and the supportive Study SG01-02.

Study SG01-01, was a randomized, open-label, single-dose, three-period, three-treatment, three-way crossover study in 30 healthy adult subjects to assess the bioavailability of enalapril maleate pediatric solution versus VASOTEC® tablets under fasted conditions, and to assess the effect of food on the enalapril maleate pediatric solution. PK data from the SG01-01 study were considered ***not valid*** due to the method of reconstitution of the enalapril maleate powder to solution, which did not allow for shaking the bottle well for 30 seconds. This led to in improper mixing, so that instead of the intended 10 mg dose, the subjects received a mean dose of 1.30 mg. The low exposure resulted in enalapril and enalaprilat levels in plasma samples below the lower limit of quantification (LLOQ) in both fasted and fed test treatments.

Study SG01-02 was a pilot randomized, open-label, single-dose, two-period, two-treatment, two-way crossover study in 10 healthy adult subjects. The objective was to confirm that the low bioavailability of enalapril maleate pediatric solution observed in Study SG01-01 was due to inadequate mixing of the solution. In Study SG01-02, the 90% confidence intervals (C.I.) for the AUCs fell within the accepted range for both enalapril and enalaprilat, but the lower 90% C.I. for $C_{max}$ for enalapril and enalaprilat fell below the 80% accepted range, which was attributed to small sample size.

Study SG01-03, which is the pivotal study for this 505(b)(2) NDA submission, was a Phase I, randomized, open-label, single-dose, three-period, three-treatment, three-way crossover study conducted in 53 healthy adult subjects (median age 30 years) who were administered single 10 mg doses of enalapril maleate pediatric solution under fasted conditions, the same under fed conditions, and VASOTEC® (tablet) under fasted conditions (essentially identical in design to SG01-01). Differences between SG01-01 and SG01-03 studies are (i) the number of healthy adult subjects (53 subjects enrolled for SG01-03 versus 30 subjects enrolled for SG01-01) and (ii) the method of reconstitution of the enalapril maleate pediatric solution.

The PK findings with regard to the geometric mean ratios (solution/tablet) of enalapril AUCs and $C_{max}$ and the 90% C.I. about the geometric mean ratios were consistent with those for enalaprilat. The 90% C.I. for the AUCs and $C_{max}$ for both enalapril and enalaprilat fell within the accepted range. The mean PK parameters of $C_{max}$, $T_{max}$,

$AUC_{last}$, and $AUC_{inf}$ for the enalapril maleate pediatric solution were similar to those for VASOTEC®.

In the comparison across Studies SG01-02 and SG01-03, there were differences in the PK parameters: $T_{max}$ was slightly shorter for enalapril in Study SG01-02 than in Study SG01-03, and $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ were greater for both enalapril and enalaprilat in Study SG01-02 than in Study SG01-03.

Regarding food effect in Study SG01-03:

*For enalapril*, a high-fat meal decreased:

(i) the bioavailability of enalapril from the test formulation by approximately 14% to 15% based on the geometric mean ratios of enalapril AUCs (fed/ fasted for $AUC_{last}$ and $AUC_{inf}$); and,

(ii) $C_{max}$ by approximately 46%.

The 90% C.I. for the geometric mean AUC ratios (fed/fasted) were within the accepted 80% to 125% range, but the decrease in $C_{max}$ ***was*** not within the accepted 80% to 125% range.

*For enalaprilat*, a high-fat meal decreased $C_{max}$ by approximately 36% and AUCs by approximately 20% to 23%. The 90% C.I. for the geometric mean ratios (fed/fasted) of $C_{max}$ ***and*** AUCs for enalaprilat were ***not*** within the accepted 80% to 125% range.

Despite the reductions in $C_{max}$ ***and*** AUCs, the trough plasma concentrations of enalapril (from 6 hour through 12 hours) and enalaprilat (from 16 hours till 36 hours) were found by the clinical pharmacology reviewer to be similar between fasted and fed administrations, and also similar to those of VASOTEC® suggesting that the trough response on blood pressure will not be different for the two formulations and the fed administration.

## 6.1 Indication

The proposed indication for (b) (4) ™ Powder for Oral Solution is the treatment of hypertension in pediatric patients (b) (4).

### 6.1.1 Methods

Study SG01-03 was a single-dose, open-label, randomized, three-period, three-treatment, three-way crossover study in which 53 healthy adult subjects received each of the following three treatments in a randomized fashion during three study periods:

- Treatment A, Test Formulation: Enalapril maleate pediatric solution, 10 mg/10 mL, administered under fasted conditions
- Treatment B, Reference Product: VASOTEC®, one 10 mg tablet, administered under fasted conditions

- Treatment C, Test Formulation: Enalapril maleate pediatric solution, 10 mg/10 mL, administered under fed conditions

Screening assessments were performed by the investigator or designee within 28 days prior to study start. Subjects fulfilled the inclusion criteria of a male or non-pregnant, non-breastfeeding female, 18 to 55 years of age, with body mass index (BMI) between 18 and 30 kg/$m^2$ and weigh a minimum of 50 kg (110 pounds).

Subjects did not have a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results; and did not to have a history of chronic cough, hyperkalemia, renal insufficiency, renal artery stenosis, or angioedema related to previous treatment with an angiotensin-converting enzyme inhibitor.

Treatments A and B were administered after an overnight fast of at least 10 hours; Treatment C was administered following an overnight fast of at least 10 hours and an FDA standard high-calorie (approx 1000 Cal), high-fat (50% of total calorie content of the meal) breakfast meal beginning 30 minutes prior to administration of the study drug. Each dose was orally administered under supervision by the clinical study personnel with 240 mL (8 fl. oz.) of room temperature tap water; no food was allowed until 4 hours post-dose. Each drug administration was separated by a washout period of ≥ 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose.

During each treatment period, blood samples were obtained pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after dosing.

Plasma pharmacokinetic (PK) samples were analyzed for enalapril and enalaprilat using a validated analytical method; PK parameters {maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($T_{max}$), elimination rate constant ($\lambda_z$), last quantifiable drug concentration determined directly from individual concentration-time data ($C_{last}$), elimination half-life ($t_{1/2}$), area under the curve to the last quantifiable sample ($AUC_{last}$), and area under the curve extrapolated to infinity ($AUC_{inf}$)} were calculated for each formulation using non-compartmental methods.

Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Each subject received a total of three single doses, one dose at each of three study periods; the maximum duration of the study for each subject from screening to study exit was approximately 45 days.

### 6.1.2 Demographics

The median age of subjects was 30 years (range: 18 to 55 years); most subjects had

never used tobacco (83.0%), the majority were white (66.0%); and approximately half were Hispanic or Latino. Forty-two of the subjects were male and 11 were female. The median BMI value was 25.4 kg/$m^2$.

### 6.1.3 Subject Disposition

Fifty-three subjects were enrolled and treated; 45 subjects completed the study, defined as having completed dosing for all three periods. Eight subjects (15.1%) were withdrawn prior to receiving all three doses (4 before dosing in Period 2, and 4 before dosing in Period 3). The most common reason for withdrawal was protocol non-compliance (four subjects, 7.5%).

Twenty subjects (37.7%) had one or more protocol deviations documented during the study. The deviations for 10 subjects occurred during the treatment period in which enalapril fed was administered, for eight subjects during the treatment period in which VASOTEC® fasted was administered, and for six subjects during the treatment period in which enalapril fasted was administered. The protocol deviation that occurred most often (five subjects) was "the 72-hour vital signs were not performed due to subject no show for outpatient visit."

### 6.1.4 Analysis of Primary Endpoint(s)

**Objectives:** The objectives of this single-dose, open-label, randomized, three-period, three-treatment, three-way crossover study SG01-03 were:

- To assess the bioavailability of a test formulation of 10 mg enalapril maleate pediatric solution from Silvergate Pharmaceuticals, Inc. versus VASOTEC® 10 mg tablets manufactured for Valeant Pharmaceuticals North America LLC under fasted conditions in healthy adults
- To assess the food effect on a test formulation of 10 mg enalapril maleate pediatric solution in healthy Adults

Pharmacokinetics (PK): Blood samples for PK measurements were collected and analyzed to obtain maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($T_{max}$), elimination rate constant ($\lambda_z$), last quantifiable drug concentration determined directly from individual concentration-time data ($C_{last}$), elimination half-life ($t_{1/2}$), area under the curve to the last quantifiable sample ($AUC_{last}$), and area under the curve extrapolated to infinity ($AUC_{inf}$).

Safety: Safety was assessed by frequencies of adverse events; and changes in laboratory values, vital signs, physical examination findings, and ECG measurements.

**Statistical Methods:** The sponsor analyzed natural logarithmic-transformed PK parameters – $ln(C_{max})$, $ln(AUC_{last})$, and $ln(AUC_{inf})$ – for differences between treatments using an ANOVA with factors for sequence, subject within sequence, period, and treatment. Bioequivalence or lack of significant food effect would be established if the

90% C.I. for $ln(C_{max})$, $ln(AUC_{last})$, and $ln(AUC_{inf})$ were within the 80% to 125% interval.

PK Results: Data from 48 subjects in the PK population were included in the PK and statistical analyses. Descriptive statistics of concentration-time data for enalapril and enalaprilat showed that the first quantifiable concentrations for both enalapril and enalaprilat were observed at the 0.50 hour sample time for each treatment.

**Table 2 Pharmacokinetic Parameters of 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 |

$AUC_{Extrap}$ = Percentage of $AUC_{inf}$ based on extrapolation
$AUC_{inf}$ = Area under the concentration-time curve from time-zero extrapolated to infinity
$AUC_{last}$ = Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration
$C_{last}$ = Last quantifiable drug concentration determined directly from individual concentration-time data
$C_{max}$ = Maximum drug concentration in plasma determined directly from individual concentration-time data
CV%=Coefficient of variance; h= hour; $\lambda_z$= Observed elimination rate constant; $t_{1/2}$= Observed terminal elimination half-life
$T_{last}$ = Time of the last quantifiable concentration; $T_{max}$ = Time to maximum concentration; SD = Standard deviation;
Note: Full precision data used in pharmacokinetic analysis. Source: *Pharmacokinetic Report for SG01-03*

**Test Product versus Reference Product (Fasted):** Based on the geometric mean ratios of enalapril and enalaprilat AUCs (Test/Reference for $AUC_{last}$ and $AUC_{inf}$), the bioavailability of the test formulation relative to the reference product was approximately 96% to 97%. The geometric mean ratios of enalapril and enalaprilat $C_{max}$ were 92.45% and 90.94%, respectively. The 90% C.I. about the geometric mean ratios (Test/ Reference) of enalapril and enalaprilat $C_{max}$ and AUCs were within the accepted 80% to 125% range, indicating no significant difference.

The p-values from the Wilcoxon signed rank test for enalapril and enalaprilat were 0.1136 and 0.5742, respectively, indicating that the difference in $T_{max}$ values between products was not significant ($p > 0.05$).

**Test Product (Fed) versus Test Product (Fasted):** Based on the geometric mean ratios of enalapril AUCs (Fed/Fasted for $AUC_{last}$ and $AUC_{inf}$), a high-fat meal decreases the bioavailability of enalapril from the test formulation by approximately 14% to 15% (Table 2); $C_{max}$ is decreased by approximately 46%. The 90% C.I. for the geometric mean ratios (Fed/Fasted) of enalapril were within the accepted 80% to 125% range, and

the decrease in oral bioavailability (based on AUCs) was not significant; the decrease in $C_{max}$ was significant.

**Table 3 Pharmacokinetic Parameters of 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 |

$AUC_{Extrap}$ = Percentage of $AUC_{inf}$ based on extrapolation
$AUC_{inf}$ = Area under the concentration-time curve from time-zero extrapolated to infinity
$AUC_{last}$ = Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration
$C_{last}$ = Last quantifiable drug concentration determined directly from individual concentration-time data
$C_{max}$ = Maximum drug concentration in plasma determined directly from individual concentration-time data
CV%=Coefficient of variance; h= hour; $\lambda_z$= Observed elimination rate constant; $t_{1/2}$= Observed terminal elimination half-life
$T_{last}$ = Time of the last quantifiable concentration; $T_{max}$ = Time to maximum concentration; SD = Standard deviation;
Note: Plasma samples analyzed using a bioanalytical method with a validated range 0.500 to 200 ng/mL; concentrations reported in ng/mL to three significant figures; concentrations below limit of quantification set to zero (0.00 ng/mL) in the data summarization.
Source: *Pharmacokinetic Report for SG01-03*

For enalaprilat, food decreases $C_{max}$ by approximately 36% and AUCs by approximately 20% to 23% (Table 3).

The 90% C.I. for the geometric mean ratios (Fed/Fasted) of $C_{max}$ and AUCs for enalaprilat were not within the accepted 80% to 125% range.

**Treatment A (Test - Fasted) Versus Treatment B (Reference - Fasted)**

Based on the geometric mean ratios of enalapril and enalaprilat AUCs (Test/Reference for $AUC_{last}$ and $AUC_{inf}$), the bioavailability of the test formulation relative to the reference product was approximately 96% to 97%. The geometric mean ratios of enalapril and enalaprilat $C_{max}$ were 92.45% and 90.94%, respectively (Table 4 and Table 5). The 90% C.I. about the geometric mean ratios (Test/Reference) of enalapril and enalaprilat $C_{max}$ and AUCs were within the accepted 80% to 125% range, indicating no significant difference.

Based on the geometric mean ratios of enalapril AUCs (Fed/Fasted for $AUC_{last}$ and $AUC_{inf}$), a high-fat meal decreases the bioavailability of enalapril from the test formulation by approximately 14% to 15%; $C_{max}$ is decreased by approximately 46%.

The 90% C.I. for the geometric mean ratios (Fed/Fasted) AUCs of enalapril were within the accepted 80% to 125% range; the decrease in bioavailability after a high-fat meal (based on AUCs) was not significant; the decrease in $C_{max}$ was significant.

**Table 4 Statistical Analysis of the Log-transformed Systemic Exposure Parameters of Enalapril Comparing Test Formulation-fasted (Treatment A) to the Reference Product (Treatment B)**

| Dependent Variable | Geometric Mean [a] | | Ratio (%)[b] | 90% CI[c] | | Power | ANOVA |
|---|---|---|---|---|---|---|---|
| | Test | Ref | (Test/Ref) | Lower | Upper | | CV% |
| $ln(C_{max})$ | 55.1568 | 59.6610 | 92.45 | 87.50 | 97.68 | 1.0000 | 15.60 |
| $ln(AUC_{last})$ | 99.6030 | 103.3847 | 96.34 | 92.03 | 100.86 | 1.0000 | 12.96 |
| $ln(AUC_{inf})$ | 100.6779 | 104.3616 | 96.47 | 92.19 | 100.95 | 1.0000 | 12.85 |

[a]= Geometric mean for test formulation-fasted (test) and reference product (ref) based on least squares mean of log transformed parameter values; [b] = Ratio(%) = geometric mean (test)/geometric mean (ref); [c] = 90% confidence interval.
Source: *Pharmacokinetic Report for SG01-03*

**Table 5 Statistical Analysis of the Log-transformed Systemic Exposure Parameters of Enalaprilat Comparing Test Formulation-fasted (Treatment A) to the Reference Product (Treatment B)**

| Dependent Variable | Geometric Mean[a] | | Ratio (%)[b] | 90% CI[c] | | Power | ANOVA |
|---|---|---|---|---|---|---|---|
| | Test | Ref | (Test/Ref) | Lower | Upper | | CV% |
| $ln(C_{max})$ | 37.5196 | 41.2572 | 90.94 | 84.11 | 98.32 | 0.9984 | 22.28 |
| $ln(AUC_{last})$ | 389.7524 | 405.3687 | 96.15 | 91.88 | 100.61 | 1.0000 | 12.84 |
| $ln(AUC_{inf})$ | 428.3031 | 443.6027 | 96.55 | 92.82 | 100.43 | 1.0000 | 11.13 |

**Table 6 Statistical Analysis of the Log-transformed Systemic Exposure Parameters of Enalapril Comparing Test Formulation-fed (Treatment C) to Test Formulation-fasted (Treatment A)**

| Dependent Variable | Geometric Mean[a] | | Ratio (%)[b] | 90% CI[c] | | Power | ANOVA |
|---|---|---|---|---|---|---|---|
| | Test | Ref | (Test/Ref) | Lower | Upper | | CV% |
| $ln(C_{max})$ | 29.7155 | 55.2999 | 53.74 | 49.25 | 58.62 | 0.9941 | 25.71 |
| $ln(AUC_{last})$ | 85.3850 | 99.0860 | 86.17 | 81.35 | 91.29 | 1.0000 | 16.87 |
| $ln(AUC_{inf})$ | 85.8637 | 100.7148 | 85.25 | 80.70 | 90.07 | 1.0000 | 15.86 |

[a]= Geometric mean for test formulation-fed (test) and test formulation-fasted (ref) based on least squares mean of log transformed parameter values; [b]= Ratio(%) = geometric mean (test)/geometric mean (ref); [c]= 90% confidence interval.
Note: $T_{½}$ and parameters based on extrapolation could not be calculated for all subjects; statistical analysis is based on n = 48 for $C_{max}$, $AUC_{last}$ and n = 47 for $AUC_{inf}$. Source: *Pharmacokinetic Report for SG01-03*

**Treatment C (Test - Fed) Versus Treatment A (Test - Fasted):** Based on (Table 6) the geometric mean ratios of enalapril AUCs (Fed/Fasted for $AUC_{last}$ and $AUC_{inf}$), a high-fat meal decreases the bioavailability of enalapril from the test formulation by approximately 14% to 15%; $C_{max}$ is decreased by approximately 46%. The 90% C.I. for the geometric mean ratios (Fed/Fasted) AUCs of enalapril were within the accepted

80% to 125% range, and the decrease in oral bioavailability after a high-fat meal (based on AUCs) was not significant; the decrease in $C_{max}$ was significant.

**Table 7 Statistical Analysis of the Log-transformed Systemic Exposure Parameters of Enalaprilat Comparing Test Formulation-fed (Treatment C) to Test Formulation-fasted (Treatment A)**

| Dependent Variable | Geometric Mean[a] | | Ratio (%)[b] | 90% CI[c] | | Power | ANOVA |
|---|---|---|---|---|---|---|---|
| | Test | Ref | (Test/Ref) | Lower | Upper | | CV% |
| $ln(C_{max})$ | 24.1722 | 38.0223 | 63.57 | 57.75 | 69.98 | 0.9844 | 28.45 |
| $ln(AUC_{last})$ | 301.5468 | 391.6562 | 76.99 | 72.66 | 81.58 | 1.0000 | 16.93 |
| $ln(AUC_{inf})$ | 344.8236 | 429.8233 | 80.22 | 76.19 | 84.48 | 1.0000 | 15.09 |

[a]= Geometric mean for test formulation-fed (test) and test formulation-fasted (ref) based on least squares mean of log transformed parameter values; [b]= Ratio(%) = geometric mean (test)/geometric mean (ref); [c]= 90% confidence interval.
Source: *Pharmacokinetic Report for SG01-03*

For enalaprilat, food decreases $C_{max}$ by approximately 36% and AUCs by approximately 20% to 23% (Table 7). The 90% C.I. for the geometric mean ratios (Fed/Fasted) of $C_{max}$ and AUCs for enalaprilat were not within the accepted 80% to 125% range.

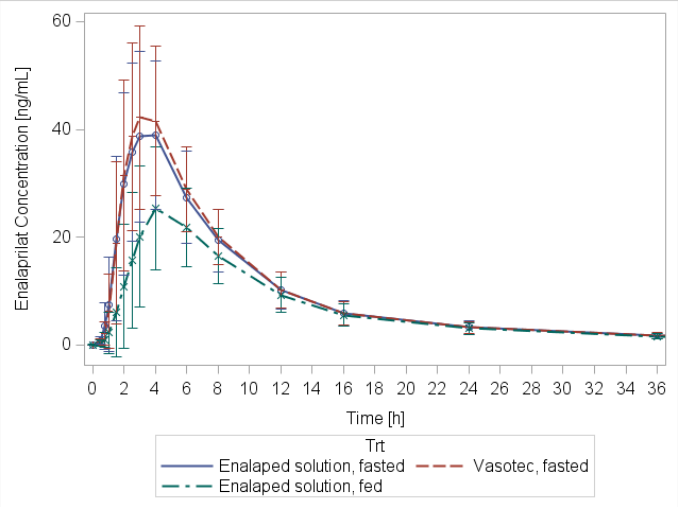
**Table 8 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Enalapril and Enalaprilat – Studies SG01-03 and SG01-02**

| | 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.
Source: Sponsor's *Table 2.7.1-7*, *Table 2.7.1-8*

*Reviewer's comments*: Despite the reductions in AUCs and $C_{max}$ in the fed state, the clinical pharmacology review showed that the trough concentrations of enalaprilat are similar (at 16 hours till 36 hours) between fasted and fed administrations, and also that they are not distinguishable for (b) (4) ™ vs. VASOTEC® (Figure 1).

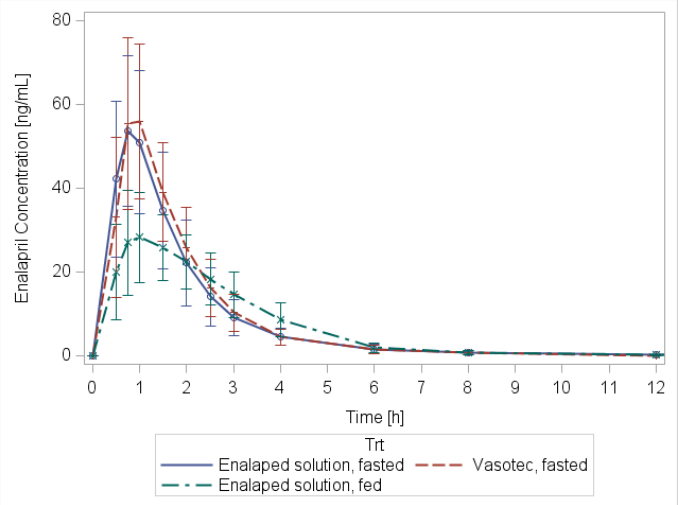
**Figure 1 Mean enalaprilat concentrations over time**




Clinical Pharmacology and Biopharmaceutics Review by Martina Sahre, PhD

For enalapril plasma concentrations the trough concentrations (from 6 hour through 12 hours) are zero for both formulations and the fed application of (b) (4) ™ (Figure 2).

**Figure 2 Mean enalapril concentrations over time**




Clinical Pharmacology and Biopharmaceutics Review by Martina Sahre, PhD

The above findings suggest that the trough response on blood pressure will not be different for the two formulations and the fed application.

The PK conclusions of studySG01-03 are:

- The 90% C.I. for enalapril and the active metabolite enalaprilat for $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ of the test formulation of 10 mg enalapril maleate pediatric solution relative to the reference product VASOTEC® 10 mg tablets are within the accepted 80% to 125% range, demonstrating bioequivalence of the enalapril maleate pediatric solution to VASOTEC® 10 mg tablets.
- When administered with a high-fat meal, the $C_{max}$ of enalapril is decreased (46%) but the 90% C.I. for the geometric mean ratios of enalapril AUCs are within the accepted 80% to 125% range when compared to the fasted test formulation of 10 mg enalapril maleate pediatric solution. A high-fat meal decreases exposure to enalaprilat by approximately 20% to 23% (based on AUCs) and decreases maximum exposure to enalaprilat by 36% (based on $C_{max}$); the 90% C.I. for the geometric mean ratios (Fed/Fasted) of AUCs and $C_{max}$ are not within the acceptable 80% to 125% range.
- Despite the reductions in AUCs and $C_{max}$ in the fed state, the trough concentrations of enalaprilat and enalapril between fasted and fed administrations are similar and are indistinguishable from VASOTEC®, suggesting that the trough response on blood pressure will not be different for the two formulations and the fed application.

### 6.1.5 Analysis of Secondary Endpoints(s)

There are no protocol specified secondary endpoints.

### 6.1.6 Other Endpoints

There are no protocol specified other endpoints.

### 6.1.7 Subpopulations

Not applicable. No subpopulation study was made.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable. No dose-ranging study was made.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

## 6.1.10 Additional Efficacy Issues/Analyses

PK parameters in Study SG01-02 are shown in Table 9, Table 10, Table 11, and Table 12. In the comparison across Studies SG01-02 and SG01-03, there were differences in the PK parameters:

- $T_{max}$ was slightly shorter for enalapril in Study SG01-02 than in Study SG01-03, and
- $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ and their corresponding log-transformed systemic exposure parameters were greater for both enalapril and enalaprilat in Study SG01-02 than in Study SG01-03.

**Table 9 PK parameters of enalapril in Study SG01-02**

| 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: Sponsor's Table 3 in Study SG01-02 Study Report

**Table 10 PK parameters of enalaprilat in Study SG01-02**

| 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: Sponsor's Table 4 in Study SG01-02 Study Report

**Table 11 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Enalapril in Study SG01-02**

| Dependent Variable | Geometric Mean[a] | | Ratio (%)[b] | 90% CI[c] | | Power | ANOVA |
|---|---|---|---|---|---|---|---|
| | Test | Ref | (Test/Ref) | Lower | Upper | | CV% |
| $\ln(C_{max})$ | 68.0893 | 73.6998 | 92.39 | 79.54 | 107.31 | 0.8064 | 18.16 |
| $\ln(AUC_{last})$ | 112.7762 | 118.3692 | 95.27 | 88.76 | 102.27 | 0.9980 | 8.53 |
| $\ln(AUC_{inf})$ | 115.3986 | 118.3452 | 97.51 | 91.55 | 103.86 | 0.9991 | 7.03 |

[a]Geometric Mean for Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values; [b]Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref); [c]90% Confidence Interval
Note: $T_{½}$ and parameters based on extrapolation could not be calculated for all subjects; statistical analysis is based on n = 10 for $C_{max}$, $AUC_{last}$, and n = 9 for $AUC_{inf}$; Source: Sponsor's Table 5 in Study SG01-02 Study Report

**Table 12 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Enalaprilat in Study SG01-02**

| Dependent Variable | Geometric Mean[a] | | Ratio (%)[b] | 90% CI[c] | | Power | ANOVA |
|---|---|---|---|---|---|---|---|
| | Test | Ref | (Test/Ref) | Lower | Upper | | CV% |
| $\ln(C_{max})$ | 42.7442 | 49.4415 | 86.45 | 71.55 | 104.46 | 0.6284 | 23.04 |
| $\ln(AUC_{last})$ | 432.3016 | 474.1818 | 91.17 | 82.84 | 100.34 | 0.9808 | 11.56 |
| $\ln(AUC_{inf})$ | 480.4456 | 533.6789 | 90.03 | 81.83 | 99.04 | 0.9807 | 10.65 |

[a]Geometric Mean for Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values; [b]Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref); [c]90% Confidence Interval
Note: $T_{1/2}$ and parameters based on extrapolation could not be calculated for all subjects; statistical analysis is based on n = 10 for $C_{max}$, $AUC_{last}$, and n = 9 for $AUC_{inf}$; Source: Sponsor's Table 6 in Study SG01-02 Study Report

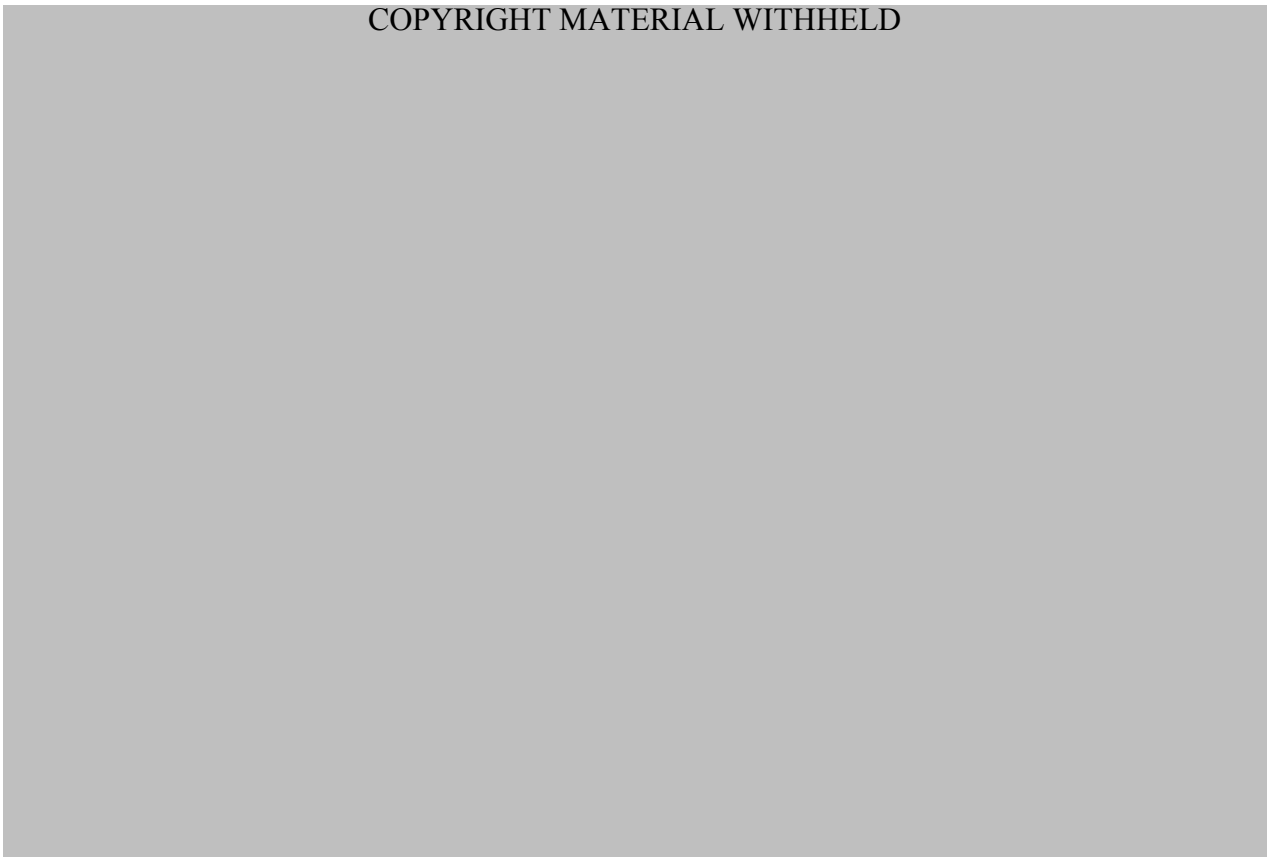
*Reviewer's comments*: *Comparison of PK parameters in Study SG01-03 with PK parameters of enalapril in children and infants with hypertension in the literature*

A comparison of PK parameters of enalaprilat in Study SG01-03 (Table 3) with single dose PK values in children with hypertension 2 months to 15 years administered 0.07 to 0.14 mg/kg of enalapril[5] shows that the unadjusted $AUC_{0-24h}$ in children (Figure 3) were about half of that observed in adults in Study SG01-03 (Table 3).

The children's AUC adjusted to 0.15 mg/kg showed that the mean $AUC_{0-24h}$ in Group IV (children age 12 to <16 years, Figure 3) was 409.1 (95% CI 295.9, 565.5) which is approximately similar to the mean (±SD) AUCs (405.3±112.3 and 443.3±115.0 for $AUC_{last}$ and $AUC_{inf}$, respectively) observed for fasted adults in Study AG01-03 (Table 3).

This similarity, however, does not hold true for other age groups (Group I: 1-24 months; Group II: 25 months to <6 years; and Group III: 6 to <12 years). Group I was dosed on a mg/kg basis, and Group IV was not, and the difference is thought to be due to the way patients were dosed; Groups II and III were significantly different from the other two groups. When the data were adjusted based on a standard body surface area (per $1mg/m^2$), differences between groups were no longer seen.

**Figure 3 Individual values, geometric means and 95% C.I. of serum enalaprilat for observed single-dose and steady-state $AUC_{0-12h}$ (unadjusted and per 0.15 mg/kg) in hypertensive infants and children**



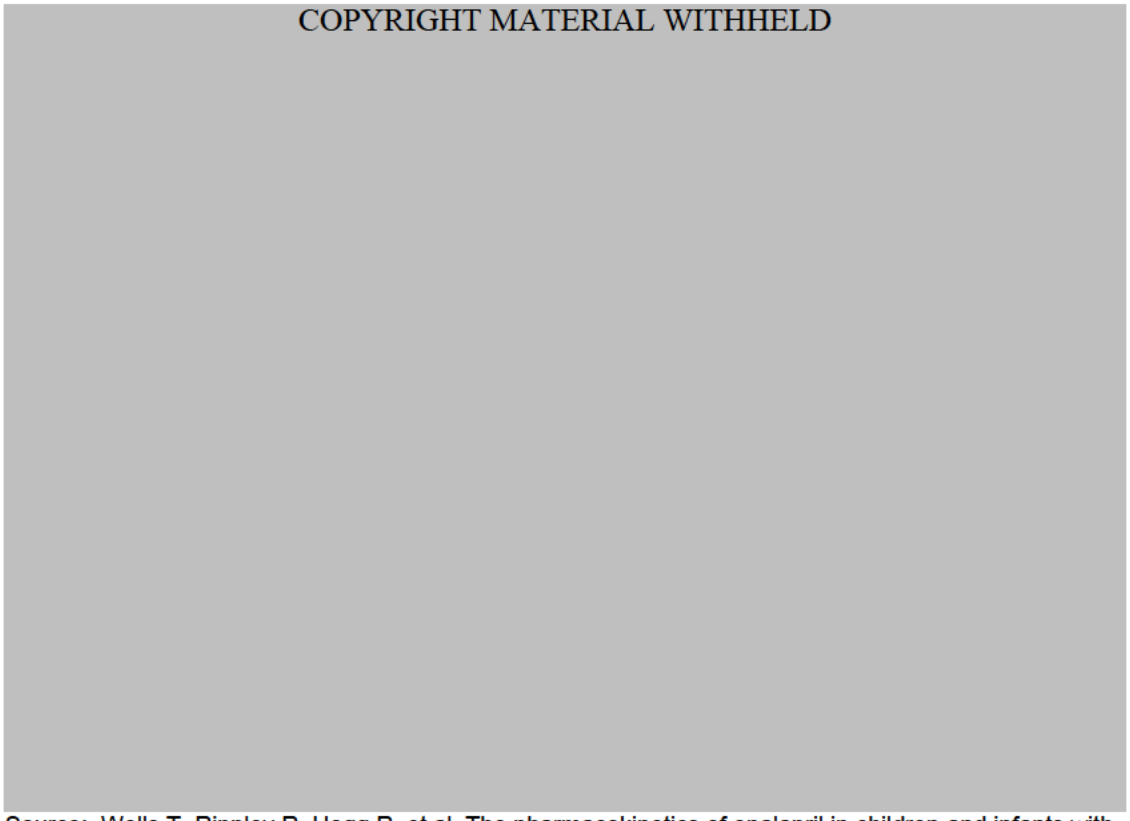

Source: Wells T, Rippley R, Hogg R, et al. The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; 41: 1064-74.

A similar trend is also observed for a comparison of $C_{max}$ of enalaprilat in Study SG01-03 (Table 3) with single dose PK values in children with hypertension 2 months to 15 years administered 0.07 to 0.14 mg/kg of enalapril. The unadjusted $C_{max}$ in children (Figure 4) were a third to half of that observed in adults in Study SG01-03 (Table 3).

The children's $C_{max}$ adjusted to 0.15 mg/kg shows that the mean $C_{max}$ in Group IV (children age 12 to <16 years, Figure 4) was 40.9 (95% CI 28.3, 59.1) which appears approximately similar to the mean±SD $C_{max}$ (41.0±16.1) observed for fasted adults in Study AG01-03 (Table 3). Again, this similarity does not hold true for other age groups. When the data were adjusted based on a standard body surface area (per 1mg/$m^2$), differences between groups were no longer seen.

The median $T_{max}$ for enalaprilat in the four groups of hypertensive children (Table 13) are also longer than the mean±SD $T_{max}$ (3.45±0.77 h) observed in adults in Study SG01-03 (Table 3).

**Figure 4 Individual values, geometric means and 95% C.I. of serum enalaprilat for observed single-dose and steady-state $C_{max}$ (unadjusted and per 0.15 mg/kg) in hypertensive infants and children**




Source: Wells T, Rippley R, Hogg R, et al. The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; 41: 1064-74.

**Table 13 Median $t_{max}$(h) for serum enalaprilat in hypertensive children ages 2 months to 15 years**

| | Single Dose | | |
|---|---|---|---|
| Age Group | Number | Median[b] | 95% CI[c] |
| COPYRIGHT MATERIAL WITHHELD | | | |

[b]= Hodges-Lehmann estimate; = Distribution-free confidence interval based on Hodges-Lehmann estimation.
Source: Wells T, Rippley R, Hogg R, et al. The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; 41: 1064-74.

*Reviewer's comments*: It appears that adjustment of AUC for body surface area reduces the variability observed among age groups for the AUCs suggesting that the *bioavailability of the suspension used in the literature study for younger children did not differ from that seen with standard tablets administered in older children and adults.*

# 7 Review of Safety

## *Safety Summary*

This NDA is submitted under the provisions of Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The submission contains three Phase I studies: SG01-03, which is the pivotal study, and two supportive studies, SG01-01 and SG01-02. A total of 93 *healthy adults* were exposed to (b) (4)™ in these studies. No pediatric patients with hypertension were enrolled.

In the pivotal Study SG01-03, 53 adult subjects were enrolled and received at least one of 3 single-dose treatments ((b) (4)™ under fasted conditions, VASOTEC®, or (b) (4)™ under fed conditions). Forty-five subjects received all 3 treatments.

Nine subjects experienced one or more treatment-emergent adverse events (TEAEs): 4 subjects (8.3%) experienced at least one TEAE after receiving VASOTEC®, 3 subjects (6.3%) after receiving (b) (4)™ (fasted), and 2 subjects (3.9%) after receiving (b) (4)™ (fed). One subject discontinued for hypotension and dysphagia during treatment with (b) (4)™ (fed). No severe TEAEs or TEAEs meeting serious criteria were reported. All AEs were reported as mild or moderate.

Clinical chemistry and hematology results showed no adverse trends. Systolic and diastolic BP and pulse measured pre-dose and at 2 hours, 4 hours, 24 hours, and 72 hours after each dose showed that the lowest measurement occurred at 4 hours after all three of the treatments. No adverse trends were noted for ECGs at the end-of-study.

Study SG01-01 enrolled 30 healthy adult subjects who were exposed to a mean dose of 1.3 mg (instead of the intended 10 mg dose). In this under-exposed study, 11 subjects experienced one or more TEAEs: 8 subjects (27.6%) experienced one or more AEs after receiving VASOTEC®, 4 subjects (13.8%) after receiving (b) (4)™ (fasted), and 2 subjects (6.9%) after receiving (b) (4)™ (fed). Headache was reported in two subjects after receiving VASOTEC®; other AEs (anorexia, nausea, dizziness, diarrhea, arthralgias bilateral hips, dyspepsia, post nasal drip) were reported in one subject each. All TEAEs were reported as “mild” or “moderate,” and all resolved.

Study SG01-02 enrolled 10 healthy adults. Five subjects experienced one or more TEAEs: 3 subjects (30%) experienced one or more TEAEs after (b) (4)™ (fasted), and 4 subjects (40%) after VASOTEC®. All TEAEs were reported as “mild” or “moderate,” and all resolved with the exception of an AE of upper respiratory tract infection, which was ongoing as of the end of the study. One subject, #106, reported 3 TEAEs: nausea in Period 1 after receiving VASOTEC®, and nausea and somnolence in Period 2 after receiving (b) (4)™ (fasted). Another subject, #107, reported 4 TEAEs: numbness left knee and headache after receiving (b) (4)™ (fasted), and upper respiratory tract infection and dizziness after receiving VASOTEC®.

Overall, the AE profiles following (b) (4)™ in fasted and fed conditions and VASOTEC® were consistent with the known adverse effects of enalapril.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data are from three Phase I studies (SG01-03, which is the pivotal study) and two supportive studies, SG01-01 and SG01-02) which were conducted in a total of 93 healthy adults. The study designs for all three studies were the same with the exception that SG01-02 was a pilot two-way crossover study design.

### 7.1.2 Categorization of Adverse Events

The safety data for the three studies were based on the collection of pre- and post-treatment AEs, clinical laboratory testing, vital signs, and ECGs. Both vital signs and ECGs were collected after a period of rest: vital signs after subjects had been sitting for a minimum of 3 min, and ECGs after being supine for a minimum of 5 min.

For Study SG01-03, treatment-emergent adverse events (TEAEs), defined as events starting on or after the first dose of study drug up to 14 days after the final dose of study drug, were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0. For Studies SG01-01 and SG01-02, AEs were not coded using MedDRA.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The NDA contains only 3 Phase I bioavailability studies conducted in 93 healthy adult subjects. In Study SG01-01, due to an error in the method of reconstitution of (b) (4)™, 30 healthy subjects were exposed to a mean dose of 1.3 mg (instead of the intended 10 mg dose), which led to enalapril and enalaprilat being below the lower limit of quantification in many plasma samples. Study SG01-02 was conducted to confirm the low bioavailability in Study SG01-01. Due to the differences in the objectives and exposure to study drug of the three Phase I bioavailability studies, the data were not pooled across studies.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Ninety-three healthy subjects from the three Phase 1 studies in this submission (SG01-03, SG01-02, and SG01-01) were exposed to single 10 mg doses of at least one of the following treatments: (b) (4)™ under fasted conditions, VASOTEC® tablets, or (b) (4)™ under fed conditions (Table 14).

**Table 14 Overall exposure to study drug**

| | Enalapril Maleate Pediatric Solution 10 mg (Fasted) | Vasotec® Tablet 10 mg (Fasted) | Enalapril Maleate Pediatric Solution 10 mg (Fed) | Total |
|---|---|---|---|---|
| Study SG01-03 | 48 | 48 | 51 | **53** |
| Study SG01-01 | 29[a] | 29 | 29[a] | **30** |
| Study SG01-02 | 10 | 10 | – | **10** |
| **Total** | **87** | **87** | **80** | **93** |

[a] = In Study SG01-01, it was determined post-study that the mean dose of enalapril maleate pediatric solution delivered was 1.3 ± 1.55 mg rather than 10 mg.

Baseline demographics for subjects in the 3 PK studies are shown in Table 15. Across the three studies (93 subjects), age ranged from 18 to 55 years, BMI ranged from 19.3 to 30.0 kg/m$^2$, and the percentage of white subjects was ≥60%. In Study SG01-03, 79% of the subjects were male; whereas in Studies SG01-01 and SG01-02, the percentage of males and females were generally evenly divided. The percentage of Hispanic or Latino subjects also varied across the three studies, being about half (49.1%) in Study SG01-03, and 63.3% and 80.0%, respectively in Studies SG01-01 and SG01-02.

**Table 15 Demographics and baseline characteristics**

| Parameter | | | Study SG01-03 (N = 53) | Study SG01-01 (N = 30) | Study SG01-02 (N = 10) |
|---|---|---|---|---|---|
| Age (Years) Mean (SD) | | | 32.4 (10.29) | NA | NA |
| Median | | | 30.0 | NA | NA |
| Minimum, Maximum | | | 18, 55 | 19, 53 | 23,52 |
| Gender | Male | n (%) | 42 (79.2) | 16 (53.3) | 5 (50.0) |
| | Female | n (%) | 11 (20.8) | 14 (46.7) | 5 (50.0) |
| Race | White | n (%) | 35 (66.0) | 22 (73.3) | 6 (60.0) |
| | Black or African American | n (%) | 14 (26.4) | 7 (23.3) | 3 (30.0) |
| | American Indian or Alaskan Native | n (%) | 4 (7.5) | 1 (3.3) | 1 (10.0) |
| Ethnicity | Not Hispanic or Latino | n (%) | 27 (50.9) | 11 (36.7) | 2 (20.0) |
| | Hispanic or Latino | n (%) | 26 (49.1) | 19 (63.3) | 8 (80.0) |
| BMI (kg/m$^2$) Mean (SD) | | | 25.1 (3.09) | NA | NA |
| Median | | | 25.4 | NA | NA |
| Minimum, Maximum | | | 19.3, 30.0 | 21.0, 29.9 | 20.6, 27.5 |

NA = Not available; SD = Standard deviation; Source: *Study SG01-03, Table 5; Study SG01-02 & Study SG01-01, Clinical Listings*

## 7.2.2 Explorations for Dose Response

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.2.4 Routine Clinical Testing

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths in the 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.3.2 Nonfatal Serious Adverse Events

There were no SAEs in the 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.3.3 Dropouts and/or Discontinuations

In Study SG01-03, 8 subjects discontinued *prior to* receiving all 3 treatments. One subject (#340) discontinued as a result of an AE (hypotension and dysphagia) after receiving (b) (4) ™ under fed conditions.

In Study SG01-01, 2 subjects discontinued *prior to* receiving all 3 treatments.

In Study SG01-02, all 10 subjects received both of the treatments.

In Studies SG01-01 and SG01-02, no subjects discontinued as a result of an AE.

### 7.3.4 Significant Adverse Events

One subject (subject #340, a 40-year-old white Hispanic/Latino female) in Study SG01-03 discontinued due to an AE (hypotension (BP 85/50 and 78/51 mmHg 2 h postdose, and 95/51 mmHg 4 h post dose) during Period 1, and dysphagia. The subject also experienced 3 additional AEs on the same day: abdominal pain, nausea and dizziness.

### 7.3.5 Submission Specific Primary Safety Concerns

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

TEAEs in Study SG01-03 are summarized in Table 16. There were no severe events reported, most being reported as “mild” or “moderate.”

**Table 16 Treatment emergent AEs by treatment group in Study SG01-03**

| Preferred Term | Enalapril Pediatric Solution – Fasted (N = 48) | VASOTEC® Fasted (N = 48) | Enalapril Pediatric Solution – Fed (N = 51) |
|---|---|---|---|
| Subjects with at Least One TEAE | 3 (6.3) | 4 (8.3) | 2 (3.9) |
| Palpitations | 1 (2.1) | 0 | 0 |
| Dyspepsia | 1 (2.1) | 0 | 0 |
| Proteinuria | 1 (2.1) | 0 | 0 |
| Abdominal Pain | 0 | 0 | 1 (2.0) |
| Dysphagia | 0 | 0 | 1 (2.0) |
| Nausea | 0 | 0 | 1 (2.0) |
| Chest Discomfort | 0 | 1 (2.1) | 0 |
| Chills | 0 | 0 | 1 (2.0) |
| Infusion Site Paresthesia | 0 | 1 (2.1) | 0 |
| Urine Analysis Abnormal | 0 | 1 (2.1) | 0 |
| Dizziness | 0 | 0 | 1 (2.0) |
| Headache | 0 | 0 | 1 (2.0) |
| Oropharyngeal Pain | 0 | 1 (2.1) | 0 |
| Hypotension | 0 | 0 | 1 (2.0) |

Note: TEAEs are classified according to the last treatment received prior to the onset date of the TEAE, regardless of when the TEAE terminated. Adverse events were coded using MedDRA Version 15.0.
Note: Subjects with multiple episodes of the same event within a treatment period were counted once; if the multiple events occurred during different periods, they were included.
Source: *Study SG01-03, Table 14*

In study SG01-01, 11 subjects experienced one or more TEAEs. By treatment period

(Table 17), 8 subjects (27.6%) experienced one or more AEs after receiving VASOTEC®, 4 subjects (13.8%) after receiving (b) (4) ™ (fasted), and 2 subjects (6.9%) after receiving (b) (4) ™ (fed). Headache was reported in two subjects after receiving VASOTEC®; all other events were reported in one subject per treatment. All of the TEAEs were either "mild" or "moderate" and all resolved.

**Table 17 Treatment-emergent adverse events by treatment group (Study SG01-01)**

| Preferred Term | n (%) | | |
|---|---|---|---|
| | Enalapril Pediatric Solution – Fasted[a] (N = 29) | Vasotec – Fasted (N = 29) | Enalapril Pediatric Solution – Fed[a] (N = 29) |
| Subjects with at least one TEAE | 4 (13.8) | 8 (27.6) | 2 (6.9) |
| Headache | 0 | 2 (6.9) | 1 (3.4) |
| Upper Respiratory Infection | 1 (3.4) | 1 (3.4) | 0 |
| Nausea | 1 (3.4) | 1 (3.4) | 0 |
| Toothache | 1 (3.4) | 0 | 1 (3.4) |
| Dizziness | 1 (3.4) | 0 | 0 |
| Rash | 1 (3.4) | 0 | 0 |
| Anorexia | 0 | 1 (3.4) | 0 |
| Diarrhea, multiple episodes | 0 | 1 (3.4) | 0 |
| Arthralgias, bilateral hips | 0 | 1 (3.4) | 0 |
| Dyspepsia | 0 | 1 (3.4) | 0 |
| Post nasal drip | 0 | 1 (3.4) | 0 |
| Right ankle sprain | 0 | 1 (3.4) | 0 |
| Rhinorrhea | 0 | 0 | 1 (3.4) |

[a] = In this study, it was determined post-study that the mean dose of enalapril maleate pediatric solution delivered was 1.3 ±1.55 mg rather than 10 mg. TEAE = Treatment-emergent adverse event. Adverse events were not coded.
Source: *Study SG01-01, Clinical L*

**Table 18 Treatment-emergent adverse events by treatment group (Study SG01-02)**

| Preferred Term | n (%) | |
|---|---|---|
| | Enalapril Pediatric Solution – Fasted[a] (N = 10) | Vasotec – Fasted (N = 10) |
| Subjects with at least one TEAE | 3 (30.0) | 4 (40.0) |
| Upper Respiratory Infection | 0 | 1 (10.0) |
| Elevated transaminase | 0 | 1 (10.0) |
| Headache, Intermittent | 1 (10.0) | 0 |
| Nasal congestion | 1 (10.0) | 0 |
| Dizziness | 0 | 1 (10.0) |
| Nausea | 1 (10.0) | 1 (10.0) |
| Rash | 1 (3.4) | 0 |
| Somnolence | 1 (10.0) | 0 |
| Numbness, left knee | 1 (10.0) | 0 |
| Abrasion, right ankle | 0 | 1 (10.0) |

In Study SG01-02 (Table 18), 5 subjects experienced one or more TEAEs: 3 subjects

(30.0%) experienced one or more TEAEs after receiving (b) (4) ™ (fasted), and 4 subjects (40.0%) after receiving VASOTEC® (fasted). All of the TEAEs were "mild" or "moderate," and all resolved with the exception of an AE of upper respiratory tract infection, which was ongoing as of the end of the study. One subject, 106, reported 3 TEAEs: nausea in Period 1 after receiving VASOTEC® (fasted), and nausea and somnolence in Period 2 after receiving (b) (4) ™ (fasted). One other subject, 107, reported 4 TEAEs: numbness left knee and headache in Period 1 after receiving (b) (4) ™ (fasted), and upper respiratory tract infection and dizziness in Period 2 after receiving VASOTEC® (fasted).

### 7.4.2 Laboratory Findings

Study SG01-03: There were no clinically relevant changes from screening in the following laboratory tests performed:

- Clinical chemistry: sodium, calcium, potassium, chloride, creatinine, BUN, albumin, total bilirubin, AST, ALT, alkaline phosphatase, glucose, LDH, and uric acid. No abnormal chemistry value was reported as a TEAE. Two subjects had elevated BUN values (highest = 24.0 mg/dl in Subject 312), and two subjects had elevated uric acid values (highest = 8.6 mg/dL).
- Clinical hematology: hematocrit, hemoglobin, RBCs, WBCs, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils. No abnormal hematology value was reported as a TEAE. Post-treatment abnormalities included low neutrophil count (1.5 x $10^3$/µL, Subject 344), low WBC counts (lowest=3.3 x $10^3$/µL, Subject 313), and anemia (lowest hemoglobin= 10.2 g/dL, Subject 351).

Clinical urinalysis values were normal except for proteinuria in one subject (329).

Individual laboratory data were reported for Studies SG01-01 and SG01-02, which did not reveal clinically important abnormal laboratory values.

### 7.4.3 Vital Signs

In Study SG01-03, the median values for systolic and diastolic BP were similar across the 3 treatment groups at all of the time points. For all 3 treatment groups, the lowest measurement occurred at 4 hours (systolic ranged from 103.0 to 107.0 mmHg; diastolic ranged from 59.0 to 62.0 mmHg), after which time the values increased. By 72 hours after dosing, values were similar to baseline. The changes from baseline at 4 hours ranged from -14.0 to - 15.5 mmHg for systolic and -12.5 to -14.0 mmHg for diastolic.

The summary of pulse rate followed the same trend, with the greatest median change-from baseline at 4 hours (-4.0 to -9.0 beats per minute).

One subject (340) experienced a TEAE of hypotension during Period 1 that led to discontinuation from the study (see section 7.3.4).

In Studies SG01-01 and SG01-02, too, most subjects experienced a drop in BP to the

lowest point post-dose between 2 and 4 hours after dose administration.

### 7.4.4 Electrocardiograms (ECGs)

For Study SG01-03, 12-lead ECGs at screening and end-of-study for most subjects were interpreted as normal. ECG reports included 10 subjects (18.9%) at screening with ECGs abnormal / not clinically significant, and 10 subjects (19.2%) at end-of-study with ECGs abnormal / not clinically significant. No subject exhibited an ECG determined to be abnormal *and* clinically significant.

ECGs for Studies SG01-01 and SG01-02 were not summarized. They were archived in subjects' CRFs. A review of a sample of CRFs showed no abnormal ECGs.

### 7.4.5 Special Safety Studies/Clinical Trials

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.4.6 Immunogenicity

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.5.2 Time Dependency for Adverse Events

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.5.3 Drug-Demographic Interactions

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.5.4 Drug-Disease Interactions

The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult

subjects. The sponsor references the VASOTEC® label for the drug-disease interactions.

### 7.5.5 Drug-Drug Interactions

Possible drug-drug interactions with (b) (4) Powder for Oral Solution were not investigated. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects. The potential for drug interactions were referenced to the VASOTEC® label.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.6.2 Human Reproduction and Pregnancy Data

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

## 7.7 Additional Submissions / Safety Issues

Not applicable. The NDA contains only 3 Phase I bioavailability studies conducted in healthy adult subjects.

# 8 Postmarket Experience

The NDA contains only 3 Phase I bioavailability studies conducted in 93 healthy adult subjects.

The sponsor conducted a search of FDA's Adverse Event Reporting System (AERS) for AEs involving the use of various enalapril formulations (enalapril, enalaprilat, Lexxel, Teczem, Vasaretic and VASOTEC®) in patients <13 years of age for the period January 2000 through March 2012. During this 12 year period, 78 cases, which may include more than one individual safety report per case, were found with VASOTEC®, enalapril, enalapril maleate, enalapril maleate and hydrochlorothiazide, or enalapril dura (long acting enalapril) listed as the primary suspect for causing the AE.

Of the 78 AERS case reports identified, the majority involved cardiovascular and/or renal AEs. The outcomes were: hospitalization in 29 cases, life-threatening in 13 cases, disability in 5 cases, and death in 3 cases.

The outcomes of 16 of the other cardiovascular and renal AEs reported were reported as "other" with no additional information provided.

Six cases were reported in which maternal use of enalapril resulted in transplacental exposure of the drug to the fetus leading to congenital anomalies and/or death of the child.

It appears that the AEs found in this review of the AERS database identified no new or unexpected findings that have not been identified in clinical trials with enalapril, in enalapril product labels, or in the literature reports.

*Reviewer's comments*: If the indication in the (b) (4) ™ label is amended to include **pediatric patients 1 month to 16 years** (see section 9.2), the sponsor will need to perform a search of FDA's Adverse Event Reporting System (AERS) for AEs involving the use of various enalapril formulations in patients up to 16 years of age, and submit the postmarket experience information in pediatric patients up to 16years to the NDA.

# 9 Appendices

## 9.1 Literature Review/References

A multi-center open-label study[5] of 40 children with hypertension between 2 months and 15 years of age suggests that the PK parameters of enalapril and enalaprilat in children 2 months to 15 years appear to be similar to that reported previously in healthy adults and in young children with heart failure.[6,7]

## 9.2 Labeling Recommendations

(b) (4)

The following sections in the VASOTEC® PI are also considered for labeling corrections:

(b) (4)

**12.3 Pharmacokinetics** *Pediatric Patients*

A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged **2 months to ≤16 years** following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate..... The overall results of this study indicate that the pharmacokinetics of enalapril in hypertensive children aged 2 months to ≤16 years are consistent across the studied age groups and consistent with pharmacokinetic historic data in healthy adults.

(b) (4)


## 9.3 Advisory Committee Meeting

Not applicable.

## REFERENCES

[1] Temple ME, Nahata MC. Treatment of pediatric hypertension. *Pharmacotherapy* 2000; 20(2): 140-150

[2] Sinaiko A, Kashtan CE, Mirkin BL. Antihypertensive drug therapy with captopril in children and adolescents. Clin *Exp Theory Pract* 1986;8:829–39.

[3] Schneeweiss A. Cardiovascular drugs in children. Angiotensin converting enzyme inhibitors in pediatric patients. *Pediatr Cardiol* 1990;11:199–207.

[4] Tack ED, Perlman JM. Renal failure in sick hypertensive premature infants receiving captopril therapy. *J Pediatr* 1988;112:805–10.

[5] Wells T, Rippley R, Hogg R, Sakaran A, Blowey D, Walson P, Vogt B, Delucchi A, Lo MW, Hand E, Panebianco D, Shaw W and Shahinfar S. The pharmacokinetics of enalapril in children and infants with hypertension. *J Clin Pharmacol* 2001; 41: 1064-74.

[6] Nakamura H, Ishii M, Sugimura T, Chiba K, Kato H, Ishizaki T. The kinetic profiles of enalapril and enalaprilat and their possible developmental changes in pediatric patients with congestive heart failure. *Clin Pharmacol Ther* 1994; 56:160-8.

[7] Lloyd TR, Mahoney LT, Knoedel D, Marvin WJ, Robillard JE, Lauer RM. Orally administered enalapril for infants with congestive heart failure: a dose-finding study. *J Pediatr* 1989; 114:650-4.

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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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KHIN M U

12/05/2012

Similar bioavailability between [redacted] (b) (4) and VASOTEC, existing labelled indication of VASOTEC for treatment of hypertension in pediatric patients, and similar trough plasma concentrations of enalapril in fasted and fed administrations support the consideration for approval of [redacted] (b) (4) for the treatment of hypertension in pediatric patients.

# CLINICAL FILING CHECKLIST FOR NDA 204308 (b) (4)™

**NDA/BLA Number: 204-308** **Applicant: Silvergate Pharmaceuticals, Inc.** **Stamp Date: 10-Aug-2012**

**Drug Name:** (b) (4) (enalapril maleate, USP, powder for oral solution) **NDA/BLA Type: NDA** **New NDA: Powder for oral solution to treat pediatric hypertensive patients <12 years**

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **FORMAT/ORGANIZATION/LEGIBILITY** | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | √ | | | |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | √ | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | √ | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | √ | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | √ | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | √ | | | |
| **LABELING** | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | √ | | | |
| **SUMMARIES** | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | √ | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | √ | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | √ | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | √ | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | √ | | | **505(b)(2).** The reference drug is: VASOTEC® (enalapril maleate) tablets |
| **DOSE** | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?<br>Study Number:<br>Study Title:<br>Sample Size: Arms:<br>Location in submission: | | | √ | Three bioavailability studies are submitted. The sponsor relies on the dosage & schedule of the reference listed drug (VASOTEC® tablets) |
| **EFFICACY** | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application?<br><br>Pivotal Study #1 | | | √ | Three bioavailability studies are submitted. The sponsor relies on the safety and efficacy |

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | Indication:<br>Pivotal Study #2<br>Indication: | | | | data of the reference listed drug (VASOTEC® tablets) |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | | | √ | Bioequivalence endpoints only |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | | | √ | Bioequivalence endpoints only |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | √ | No foreign data. |
| **SAFETY** | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | √ | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | | | √ | **505(b)(2).** The sponsor relies on QT studies of the reference listed drug (VASOTEC® tablets) |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | √ | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? | √ | | | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | √ | **505(b)(2).** The sponsor relies on the safety data of the reference listed drug (VASOTEC® tablets) |
| 23. | Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms? | | | √ | **505(b)(2).** The sponsor relies on the safety data of the reference listed drug (VASOTEC® tablets) |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | | | √ | **505(b)(2).** The sponsor relies on the safety data of the reference listed drug (VASOTEC® tablets) |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | | | √ | **505(b)(2).** Three bioavailability studies are submitted. There were no deaths. The |

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.
[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | | | | | sponsor relies on the safety data of the reference listed drug (VASOTEC® tablets) |
| **OTHER STUDIES** | | | | | |
| 26. | Has the applicant submitted all special studies/data request -ed by the Division during pre-submission discussions? | | | √ | **505(b)(2).** |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | √ | **505(b)(2).** |
| **PEDIATRIC USE** | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | | | √ | This drug product is for use in children |
| **ABUSE LIABILITY** | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | √ | **505(b)(2).** The sponsor relies on the abuse liability information of the reference listed drug (VASOTEC® tablets) |
| **FOREIGN STUDIES** | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | √ | There are no foreign data. |
| **DATASETS** | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | √ | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | √ | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | √ | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | √ | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | √ | | | |
| **CASE REPORT FORMS** | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | √ | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | √ | |
| **FINANCIAL DISCLOSURE** | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | √ | | | |
| **GOOD CLINICAL PRACTICE** | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | √ | | | |

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

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA 204308 [redacted]™ Powder for Oral Solution

# CLINICAL FILING CHECKLIST FOR NDA 204308 (b) (4)™

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

None.

Filed in DARRTS 07-Sep-2012

Reviewing Medical Officer (Khin Maung U, MD) Date 09/07/2012

Clinical Team Leader (Tom Marciniak, MD) Date 09/07/2012

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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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KHIN M U
09/07/2012

THOMAS A MARCINIAK
09/07/2012