CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208686Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW - ADDENDUM

Brand Name	Epaned®
INN Name	Enalapril Maleate
NDA Number and Type	NDA 208,686
Applicant Name	Silvergate Pharmaceuticals Inc
Submission Date	11/24/2015
Indication	Treatment of hypertension, heart failure, asymptomatic left ventricular dysfunction
Dosage Form & Strengths	Oral solution 1 mg/mL
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
Reviewer	Lars Johannesen, PhD
Secondary reviewer	Martina Sahre, PhD
Team Leader	Sudharshan Hariharan, PhD

This is an addendum to the clinical pharmacology review (DARRTS: 8/17/2016, ID: 3973707) for enalapril oral solution (NDA 208,686), to provide further clarity concerning the three-way bridge used to support the 505(b)(2) application. Specifically, the application relied on bridging to the RLD (vasotec tablets) by showing that the oral solution was bioequivalent (BE) to the powder for oral solution, which was previously shown to be BE to the RLD (DARRTS: 12/14/2012, ID: 3231665). It should be noted that Silvergate Pharmaceuticals, Inc. is the applicant for both powder for oral solution and oral solution 505(b)(2) NDA applications.

The concept of the three-way bridge was discussed early in the review cycle and Ms. LoCicero from the 505(b)(2) committee wrote in an email (1/12/2016) that four criteria had to be met for the three-way bridge to be acceptable:

1. Bridge for the oral solution to powder is acceptable
2. Bridged to vasotec in the b2 application for the powder for oral solution
3. Cited reliance for efficacy and safety on vasotec in the b2 application for the oral solution
4. Cross-referenced their approved b2 application (powder for oral solution)

The second criterion is met in their previous NDA 204,308, and the remaining criteria are supported by the NDA for the oral solution (NDA 208,686) and the primary clinical pharmacology review for that application. The comparison of the $AUC_{0\text{-}inf}$ and C_{max} for both the RLD (vasotec tablets) to the powder and the powder to the solution is summarized in **Table 1**. This table shows that the BE criteria was met for powder vs tablet and solution vs powder for both the prodrug (enalapril) and the active metabolite (enalaprilat). While the upper-bound for the geometric ratio for C_{max} for the enalapril is near the upper BE boundary (125) it is important to keep in mind that: 1) enalapril is the prodrug and is rapidly converted to the active moiety (**Figure 1**), which was well within the boundaries for BE and 2) the geometric ratio for the powder compared to the tablet was ~8% lower than unity. Overall, the available information from the two studies in the

two applications support a three-way bridge from both a regulatory and scientific standpoint.

Table 1: Comparison of $AUC_{0\text{-}inf}$ and C_{max} between SG 01-03 (powder/tablet) and SG 04-01 (powder/solution). In each cell the top number represents enalapril and the bottom number enalaprilat with as geometric mean. *[Source: SG 01-03 (tables 8 and 9) and SG 04-01 (tables 11.4.3.5-6) study reports]*

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

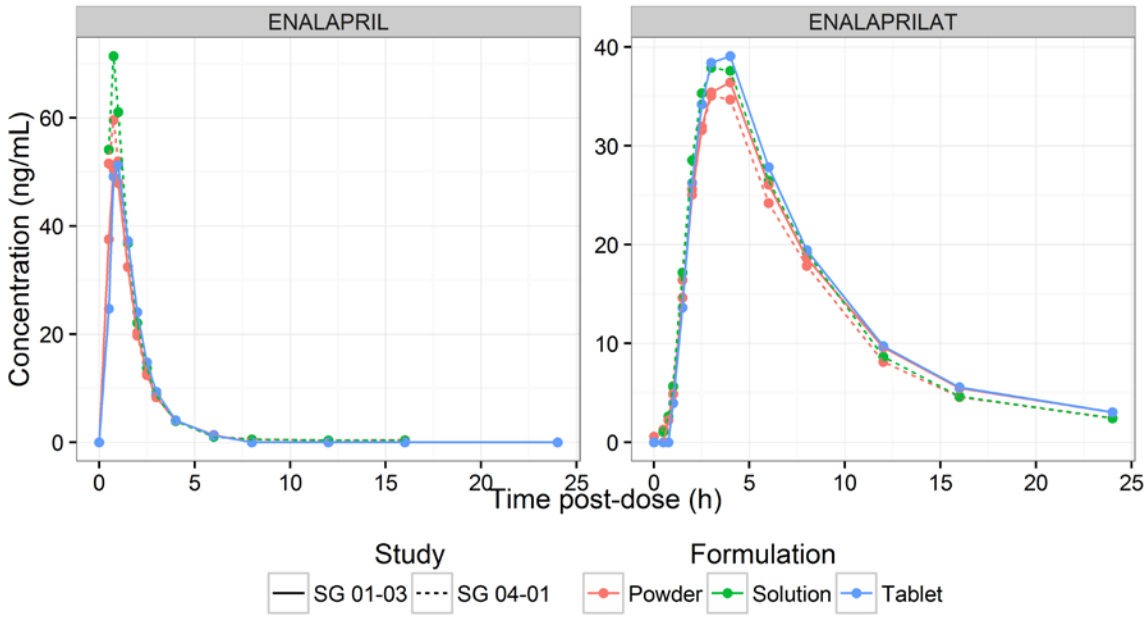

Figure 1: Comparison of the time-course of the geometric mean concentration of enalapril (left) and enalaprilat (right) for study SG 01-03 (solid), SG 04-01 (dashed). The different colors represents formulation: powder (red), solution (green) and tablet (blue). *[Source: Reviewer's analysis of SG 01-03 and SG 04-01]*

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/s/

LARS JOHANNESEN
09/01/2016

SUDHARSHAN HARIHARAN
09/01/2016

CLINICAL PHARMACOLOGY REVIEW

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1 Executive Summary

Enalapril maleate (Vasotec) was initially approved in 1985 and is currently indicated for the treatment of hypertension in pediatrics (1 month to 16 years of age) and adults. The treatment of symptomatic congestive heart failure and asymptomatic left ventricular dysfunction with enalapril is approved in adults only. Enalapril maleate powder for oral solution (Epaned® Kit) was approved for the treatment of hypertension in 2013. In 2014 indications for heart failure and treatment of asymptomatic left ventricular dysfunction were added to match Vasotec indications. The currently approved powder formulation requires a reconstitution step. (b) (4) the applicant has developed a ready-to-use oral solution, which forms the basis for this NDA.

To show that safety and efficacy of the listed drug, Vasotec, can be relied on, the applicant conducted a relative bioavailability study, comparing the proposed oral solution and the powder for oral solution. The oral solution and the powder for oral solution have similar bioavailability and meet bioequivalence criteria.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP1) reviewed the contents of the NDA. The recommended regulatory action is Approval, once labeling has been agreed upon with the applicant. OCP has proposed to add or modify language in sections 2, 8.4, 12.2 and 12.3 of the label to describe findings from a pharmacokinetic study of enalapril in pediatric patients and to update information about dosing in patients with renal impairment.

1.2 Identify recommended Phase 4 study commitments if the NDA is judged approvable

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical pharmacology findings of enalapril maleate were reviewed in NDA 18,998 (Vasotec).

The development program for enalapril oral solution was designed to bridge to the listed drug Vasotec 10 mg tablets (NDA 18,998) for efficacy and safety findings, by conducting a relative bioavailability study comparing enalapril oral solution to enalapril maleate powder for oral solution (Epaned® Kit, NDA 204,308). The study demonstrated bioequivalence between enalapril oral solution and Epaned® (Figure 2).

2 Question-Based Review

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

2.1 General attributes of the drug

Enalapril maleate oral solution will be distributed as a ready-to-use solution (1 mg/mL) packaged in a 150 mL bottle.

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

The oral solution includes the following inactive ingredients: citric acid, mixed berry flavor, purified water, sodium benzoate, sodium citrate, sucralose. It may also contain hydrochloric acid or sodium hydroxide for pH adjustment.

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

Enalapril is a prodrug, which is converted by hydrolysis to enalaprilat, the active metabolite. Enalaprilat acts on the renin-angiotensin-aldosterone system by inhibiting the conversion of angiotensin I to the vasoconstrictor substance angiotensin II by the angiotensin-converting enzyme (ACE).

Enalapril maleate is indicated for the treatment of hypertension, symptomatic heart failure, and asymptomatic left ventricular dysfunction.

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

The proposed dose is consistent with that of the current Epaned powder for oral solution (Table 1).

Table 1: Proposed dosing for Epaned oral solution

Indication	*Adults*	*Pediatrics >1 month*
Hypertension	Initial dose 5 mg or 2.5 mg QD for moderate/severe renal impairment or dialysis patients Titrate to 40 mg QD	Initial dose 0.08 mg/kg QD (up to 5 mg) Titrate to 0.58 mg/kg QD (up to 40 mg)
Heart failure	Initial dose 2.5 mg BID (up to 20 mg) or 2.5 mg QD in patients with hyponatremia	Not approved
Asymptomatic Left Ventricular Dysfunction	Initial dose 2.5 mg BID Titrate to 10 mg BID as tolerated	Not approved

2.2 General clinical pharmacology

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

This NDA contains one clinical pharmacology study (SG04-01), which is a single-dose, open-label, two-period crossover study to evaluate the relative bioavailability of enalapril oral solution and Epaned powder for oral solution reconstituted in Ora-Sweet®.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. The plasma concentrations of both enalapril maleate and enalaprilat are measured by a validated bioanalytical method, which was previously reviewed as a part of Epaned powder for oral solution (NDA 204,308).

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

The pharmacokinetic properties of enalapril maleate and the active metabolite enalaprilat have been reviewed under NDA 18,998 (Vasotec). Information supporting proposed labeling updates for pediatric pharmacokinetics and renal impairment and dialysis are described below.

2.2.3.1 Pediatric pharmacokinetics

OCP recommends revising the product insert with the description of results from a published study of the pharmacokinetics of enalapril in 2 months to <16 year olds by Wells et al. (Figure 1). In this study, it was observed that a higher weight-based dose was required in patients 2 months to <6 years of age to match the steady-state AUC of the 6 to <16 year olds, suggesting that the weight-normalized clearance of enalaprilat is higher in the younger age group.

	Group I	Group II	Group III	Group IV
Number	9	9	10	12
Male/female	6/3	5/4	6/4	7/5
Caucasian	5	3	5	4
African American	2	1	5	8
Hispanic	2	5	0	0
Actual age range	2-24 months	3-5 years	6-10 years	12-15 years
Weight range (kg)	3.5-13.8	11.4-25.9	23.1-59.5	38.7-160.6
Geometric mean dose (mg/kg)	0.14	0.13	0.11	0.07
Geometric mean dose (mg/m^2)	2.9	3.2	3.4	2.8

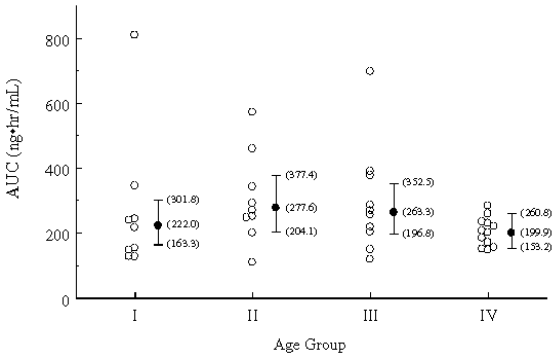

Figure 1: Results from a pharmacokinetic study of enalapril in children aged 2 months to <16 years. The table on the left shows the demographics by age group and the graphic on the right shows the steady state AUC of enalaprilat by age group. *[Source: Wells et al., J Clin Pharmacol 2001;41:1064-74]*

2.2.3.2 Renal impairment and dialysis

The label of the listed drug Vasotec includes dosing instructions based on creatinine clearance, without specifying how body weight should be included (i.e. as absolute, ideal, or adjusted body weight). The original study was published in a paper by Lowenthal et al. (Clin Pharmacol Ther 1985;38(6):661-6), which used creatinine clearance. A paper by Kelley et al. (Br J Clin Pharmacol 1986;21(1):63-9) used ^{51}Cr-EDTA to measure glomerular filtration rate and showed similar results. Further, differences between creatinine clearances calculated using ideal and actual body weight may not be as critical in this case, because enalapril is titrated to blood pressure effect. Given the fact that creatinine clearance calculated based on ideal body weight is less likely to result in a recommendation of the higher starting dose (5 mg), and the fact that the recommendation affects the starting dose only, it is recommended to use ideal body weight when calculating creatinine clearance rather than actual body weight.

In addition, a reduction of ~50% in enalaprilat AUC_{0-6} was previously reported when enalapril was administered 1 h after dialysis, compared to non-dialysis days (Lowenthal et al. 1985). The dosing instruction for dialysis patients should be updated to recommend that on dialysis days, enalapril should be administered after dialysis.

2.3 General Biopharmaceutics

2.3.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Enalapril solution is bioequivalent to Epaned powder for oral solution for both enalapril maleate and the active metabolite enalaprilat (Figure 2).

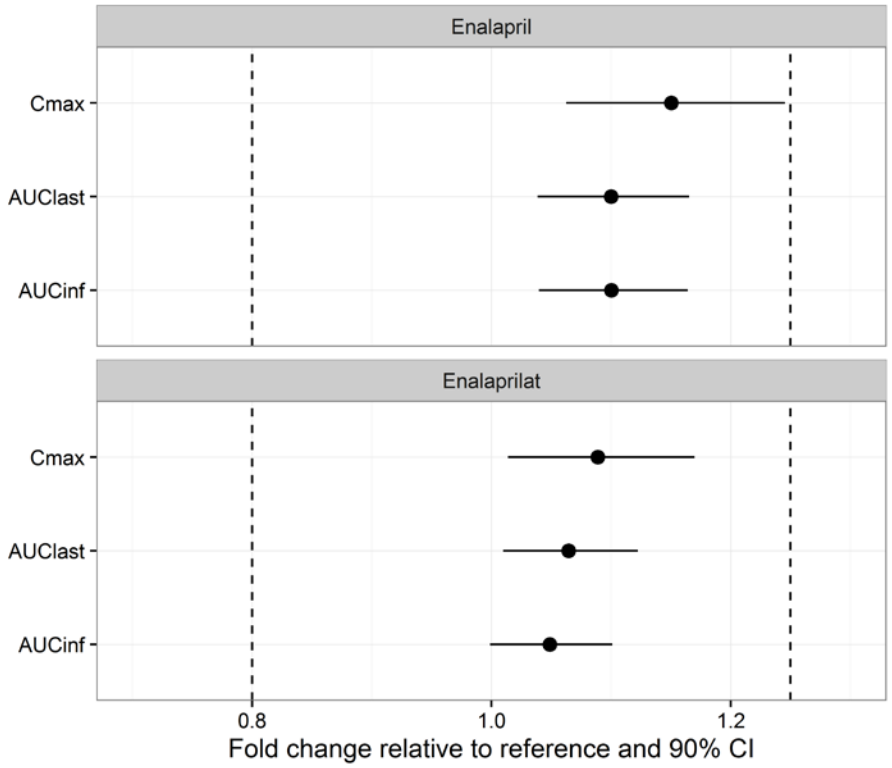

Figure 2: Primary analysis of bioequivalence between reference product (Epaned powder for oral solution) and enalapril solution *[Source: Reviewer's analysis of data from SG04-01]*.

2.4 Analytical section

Samples from study SG04-01 were analyzed using a validated LC-MS/MS method described in report DCN 1004304, reviewed in the clinical pharmacology review for Epaned powder for oral solution (NDA 204,308). The method performed within acceptable limits during sample analysis.

3 Appendix - Detailed Study Review

Report #: SG04-01	Study period: 20 July 2015 to 30 July 2015
EDR link: \\cdsesub1\evsprod\nda208686\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\sg04-01\report-body.pdf	
Title: A Randomized, Single-Dose, Two-Way Crossover Study to Determine the Relative Bioavailability of 10 mg Epaned Oral Solution, 1 mg/mL, vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted), 1 mg/mL, under Fasted Conditions in Healthy Adults	
Rationale: The objective of this study was to assess the relative bioavailability of a test formulation of 10 mg Epaned Oral Solution, 1 mg/ml (Silvergate Pharmaceuticals, Inc.) versus Epaned (enalapril maleate) Powder for Oral Solution, 1 mg/mL, reconstituted, (Silvergate Pharmaceuticals, Inc.), under fasted conditions in healthy adults.	
Study design	
☐ Bioequivalence	☒ Bioavailability, Relative
Single-dose, Randomized, Open-label,	
Screening: ≤28 days	**Washout:** >7 days, outpatient
Period 1/2	In patient stay ☐ Yes ☒ No: Subjects were to return to the research unit the evening before to ensure a 10 h fast. The subjects will remain confined in the research unit until completion of the 24-hour procedures, and will return for the 36, 48 and hour visits.

Treatments: (Active ingredient: Enalapril maleate)

Treatment A: Enalapril Oral Solution

Treatment B: Epaned® (enalapril maleate powder for oral solution) (labeled: reference product)

	Epaned oral solution	**Epaned powder for oral solution**
Dosage form	Solution	Powder, reconstituted with Ora-Sweet SF as diluent
Dosage strength	1 mg/mL	1 mg/mL
Batch #	Lot: HCP-C	Lot: 150605 / Ora-Sweet: 3334058
Administration	Per os	Per os

Sampling times (PK , plasma):

0 (pre-dose), 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0 , 36.0, 48.0 and 72.0 hours post-dose

Analytical method: The performance of the analytical method is acceptable. Yes ☒ No ☐

Analyte	*Enalapril*			*Enalaprilat*		
Method	LC/MS/MS			LC/MS/MS		
Reference	Enalapril maleate			Enalaprilat		
Lot	K0L429			R024A0		
Expiration date	Current lot not verified			Current lot not verified		
Internal standard	Enalapril-d_5 Maleate			Enalaprilat-d_5		
Lot	L484P42			AC109AP4		
Expiration date	06 July 2018			06 July 2016		
Matrix	Human K_2-EDTA Plasma			Human K_2-EDTA Plasma		
Calibration range	0.25 to 100 ng/mL			0.5 to 200 ng/mL		
QC range	0.750, 8.0, 80.0 ng/mL			1.5, 16, 160 ng/mL		
IS Concentration	0.750 µg/mL			1.0 µg/mL		
LLOQ	0.25 ng/mL			0.50 ng/mL		
Inter-run QC results For patient sample runs	QC Level [ng/mL]	Bias [%]	CV [%]	QC Level [ng/mL]	Bias [%]	CV [%]
	0.750	1.1	4.8	1.5	-10.0	6.2
	8.0	0.9	3.7	16	-9.4	5.0
	80.0	-3.4	2.7	160	-11.3	3.5

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

Study population:

Randomized/Completed/Discontinued Due to AE	32 / 29 / 0
Age [Median (range)]	34.0 [19 to 54]
Male / Female	14 / 18
Race (Asian / Black or African American / White)	2 / 5 / 25
Ethnicity (Hispanic or Latino / Not Hispanic or Latino)	20 / 12

Results

Quantifiable enalaprilat pre-dose concentrations were observed for three subjects in Period 2 at less than 5% of the subject's C_{max}. The observed values were included in the analysis without adjustment. In addition, one 48 hour sample for Epaned solution revealed an unexpected concentration and was reanalyzed, the reanalysis did not confirm the high concentration and the re-measured value was included in the analysis dataset.

Enalapril:

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	72.4495	62.9828	115.03	106.26	124.52	0.9977	17.86
$\ln(AUC_{last})$	114.8872	104.4341	110.01	103.86	116.52	1.0000	12.91
$\ln(AUC_{inf})$	115.9764	105.4182	110.02	103.97	116.41	1.0000	12.67

Source: CSR SG04-01, *page 48*

Enalaprilat:

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	40.0115	36.7409	108.90	101.38	116.98	0.9994	16.09
$ln(AUC_{last})$	379.9720	356.9115	106.46	100.97	112.25	1.0000	11.86
$ln(AUC_{inf})$	412.2499	393.0436	104.89	99.90	110.12	1.0000	10.92

Source: CSR SG04-01, *page 49*

Site inspected

Requested: ☒ Yes ☐ No	Performed: ☐ Yes ☒ No OSIS recommended to accept data without an on-site inspection on March 7th 2015, due to results of a recent site inspection, which was classified as No Action Indicated.

Safety

Were there any deaths or serious adverse events? ☐Yes ☒No ☐NA

Conclusion

The bioequivalence criteria were met for both enalapril and enalaprilat, and both oral solution and Epaned powder for oral solution were well-tolerated.

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/s/

LARS JOHANNESEN
08/17/2016

MARTINA D SAHRE
08/17/2016