CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204308Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 204308; Resubmission Class I

Brand Name: Epaned; enalapril for hypertension in adults and children older than one month.

Sponsor: Silvergate Pharmaceuticals

Review date: 12 August 2013

Type: 505 (b) (2)

Reviewer: R. Madabushi, Ph.D., and N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 204308

This memo conveys the Division's recommendation to issue an Approval letter for this application.

This application has been the subject of reviews of CMC (McLamore, 6 December 2012, 10 May 2013, and 24 July 2013), clinical pharmacology (Sahre, 14 December 2012), medical error prevention and risk management (Defronzo, 10 July 2013 and 18 July 2013), medical (U, 5 December 2012), and CDTL memo (Madabushi, 05 June 2013).

A Complete Response Letter was issued on 07 June 2013. The reason for the action was applicant's proposal to limit the indication to a subpopulation that is <12 years old. No appropriate scientific justification was provided in support of the indication and an agreement on labeling could not be achieved within the duration of the review cycle.

In response to the Complete Response Letter, on 14 June 2013, applicant re-submitted to the NDA addressing the labeling and also provided additional product quality information. An Acknowledgement Letter stating a Class I complete response was communicated to the applicant on 27 June 2013.

Based on the revised labeling and the review of the product quality information, Division approves Epaned, Enalapril powder for Oral Solution, for treatment of hypertension in adults and children older than one month to lower blood pressure. Epaned is approved with an 18-month expiry and an 8 week in-use period for the reconstituted drug product.

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/s/

RAJANIKANTH MADABUSHI
08/13/2013

NORMAN L STOCKBRIDGE
08/13/2013

Cross-Discipline Team Leader Review

Date	May 30, 2013
From	Rajanikanth Madabushi, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204308
Applicant	Silvergate Pharmaceuticals Inc.,
Date of Submission	August 10, 2012
PDUFA Goal Date	June 10, 2013
Proprietary Name / Established Name	Epaned® (enalapril maleate, USP)
Dosage forms / Strength	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.
Proposed Indication(s)	Hypertension in pediatric patients (b) (4)
Recommended:	Approval

This secondary review is based, on the primary reviews of:

- Chemistry (McLamore, Sherita), 05/10/2013 & 12/06/2012
- Clinical Pharmacology (Sahre, Martina), 12/14/2012
- Clinical (U, Khin), 12/05/2012

Cross Discipline Team Leader Review

1. Introduction

In the current submission [redacted] (b) (4) Silvergate Pharmaceuticals Inc., is seeking authorization to market Epaned®, powder for oral solution, for the treatment of hypertension in pediatric patients [redacted] (b) (4). Enalapril maleate (Vasotec® Tablets) was approved in 1985 and is currently indicated for the treatment of hypertension in adults and pediatrics (1 month to 16 years of age) and for the treatment of symptomatic congestive heart failure and asymptomatic left ventricular dysfunction in adults.

2. Background

This New Drug Application (NDA) is submitted under the provisions of Section 505(b)(2) of the FD&C 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® Tablets (enalapril maleate) approved under the NDA 018998.

The approval of enalapril in hypertensive pediatric patients 1 month to 16 years of age is supported by adequate well controlled studies in pediatric and adult patients. A multiple dose pharmacokinetic study 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 showed that the pharmacokinetics across all the age groups was consistent and comparable to the pharmacokinetic historic data in adults. In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of enalapril daily.

Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. In these studies, for children and infants who could not swallow tablets or required a lower dose than is available, enalapril was administered as a suspension formulation (prepared extemporaneously, see US Package Insert for details[1]). Based on this, the usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response.[1]

The primary basis in support of this new drug application comes from a pivotal comparative bioavailability study aimed at establishing the pharmacokinetic bridge between the applicant's proposed powder for solution and Vasotec® Tablets in healthy volunteers.

The applicant requested Priority Review based on the contention that their product:

[1] US Package Insert for Vasotec Tablets.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018998s077lbl.pdf (accessed on 05/30/2012)

- ensures standardized amount of enalapril in a standardized volume and ease of constituting the oral solution, and
- provides ease of patient use because the Epaned® oral solution can be kept without refrigeration, and does not require shaking the bottle before consumption.

The requested Priority Review was not granted as the drug product does not fulfill the FDA Criteria for Priority Review, which requires that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following:

- safe and effective therapy where no satisfactory alternative therapy exists (unmet medical need); or
- a significant improvement compared to marketed products (approved, if approval is required), including nondrug products or therapies.

The product was granted orphan designation on 01/30/2013 by the Office of Orphan Products Development.

3. CMC

The CMC reviewer determined the drug substance to be safe, effective, and manufactured with inherent quality in DMF (b) (4). The drug product is presented as Powder for Oral Solution containing 150 mg of enalapril maleate per bottle.

Each bottle of the Powder for Oral Solution will be co-packaged with a bottle of Ora-Sweet® SF. Ora-Sweet SF is commercially available, manufactured by (b) (4) and is pre-packaged in 150 (b) (4) HDPE bottles. Reconstitution of the Powder for Oral Solution with 150 mL of Ora-Sweet® SF should be executed by the pharmacist prior to dispensing to patients and will result in a 1 mg/mL solution of enalapril maleate.

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

Based on the chemistry, manufacturing, controls and biopharmaceutics information provided in this submission, the CMC reviewer recommends approval.

Facilities review/inspection

Inspection by Office of Compliance was requested for one site for the manufacture of the drug substance (b) (4) where the commercial drug substance will be manufactured, packaged and released tested and one site where the drug product will be manufactured, packaged, release and stability tested (b) (4). The Office of Compliance inspected the sites and has provided an acceptable recommendation.

4. Nonclinical Pharmacology/Toxicology

The nonclinical sections of this application are supported by reference to the Vasotec® Tablets. No new non-clinical studies have been submitted in the current submission, hence, there is no specific review for this submission.

5. Clinical Pharmacology

The clinical pharmacology review concludes that there are no outstanding clinical pharmacology issues that preclude approval. No agreement has been reached with applicant about final labeling.

The submission consisted of three relative bioavailability studies, the results of which are used to bridge to the finding of efficacy and safety of the reference listed drug Vasotec® Tablets. One of the bioavailability study (Study SG01-01) was not reviewed as the results of the study were considered not valid by the applicant 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 resulted in improper wetting and instead of the intended 10 mg dose, the subjects were found to have received a mean dose of ~1.30 mg based on the finding in the plasma samples. The key findings of the two studies reviewed are:

- When administered in a fasted state, enalapril maleate pediatric oral solution 10 mL (1 mg/mL) was bioequivalent to Vasotec® 10 mg tablets.
- When enalapril maleate pediatric oral solution was administered in a fed state (after a high fat meal), the Cmax decreased by 46 and 36% for enalapril and enalaprilat, respectively. There was a lesser decrease in the area under the plasma concentration time curve (AUC_{inf}) of 15% and 20% for enalapril and enalaprilat, respectively. The observed decrease in Cmax and AUC is not expected to be clinically significant as the trough plasma concentrations of enalaprilat are similar between fasted and fed administration. Hence the blood pressure lowering effect at the end of inter-dosing interval is unlikely to be affected.

6. Clinical Microbiology

There are no specific clinical microbiology issues in the current submission.

7. Clinical/Statistical- Efficacy

The submission contains no data from pediatric hypertensive patients treated with the proposed Powder for Oral Solution product. The clinical reviewer concludes that the apparent similarity in bioavailability of Epaned®and Vasotec® Tablets establishes a bridge between Epaned® and Vasotec® Tablets to the existing labeled indication of VASOTEC® for the treatment of hypertension in pediatric patients, and supports the consideration for the approval of Epaned® for the treatment of hypertension in pediatric patients, pending labeling changes and safety updates to be addressed by the applicant.

Given the nature of the submission, it was decided at the Filing Meeting that a Statistical Review was not required.

8. Safety

A total of 93 healthy adults were exposed to Epaned® in these studies. No deaths were reported in the three studies. Overall, the AE profiles following Epaned® in fasted and fed conditions and Vasotec® Tablets were consistent with the known adverse effects of enalapril.

9. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

10. Pediatrics

Enalapril maleate (Vasotec® Tablets) is currently indicated for the treatment of hypertension in adults and pediatrics (1 month to 16 years of age). In the current submission, the Applicant is seeking approval of Epaned® for the treatment of hypertension in pediatric patients (b) (4) of age. There are no outstanding issues specific to pediatric population at this point of time.

11. Other Relevant Regulatory Issues

- Financial disclosures: There are no significant issues related to financial disclosure.
- Orphan Drug Designation: In accordance with 21 CFR Section 316.20(b), the applicant submitted an Orphan Drug Designation for their product for the treatment of hypertension in pediatric patients (b) (4) on 07/19/2012 (Designation request # 12-3767). This request was initially denied by the Office of Orphan Products Development. An amendment to the orphan designation request was submitted by the applicant on December 20, 2012. In response, the Office of Orphan Products Development granted the orphan designation on 01/30/2012. The designation was based on a plausible hypothesis that the applicant's drug may be clinically superior to the same drug that is already approved for the same orphan indication. Further the Orphan Drug Designation Approval Letter states that "*In order to obtain orphan-drug exclusivity upon approval, you will need to demonstrate that your drug is clinically superior to already approved drug.*"

Reviewer Comment: In the current submission, the applicant has not performed any efficacy/safety trials in adult or pediatric hypertensive population to demonstrate clinical superiority. The applicant contends that Epaned® has inherently superior

safety due to the characteristics of its product i.e., a kit of components manufactured in accordance with cGMPs that result in a solution is inherently safer than an extraneously compounded suspension from tablets. (Letter by the applicant to the Agency dated 05/31/2013). While there are merits of a kit whose components are manufactured and packaged under cGMP, the compounding step is not eliminated with the applicant's product. Further, it should be noted that enalapril maleate has an aqueous solubility of 25 mg/mL. Therefore, in an aqueous formulation with a concentration of 1 mg/mL, the drug substance is in solution whether it is an extemporaneously prepared suspension from Vasotec® Tablets or applicant's Epaned® Powder for Oral Solution. Further, the formulation extemporaneously compounded with Vasotec Tablets® is a suspension of the inactive excipients. Thus in the view of this reviewer, there is no data that clearly establishes superiority of applicant's product over the extemporaneously compounded suspension from Vasotec® Tablets. Also see the Clinical Reviewer's Memo on this subject dated 05/31/2013.

12. Labeling

- **Proprietary Name:** The proposed proprietary name (b) (4) have been reviewed by the Division of Medication Error Prevention and Analysis and were found to be unacceptable from both a promotional and safety perspective. Based on an email communication (dated: 04/18/2013 by Liu, Liu), the Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed proprietary name, Epaned® (Enalapril Maleate) for NDA 204308 is acceptable.
- **Labeling without age restriction:** At the time of the review, a draft proposal for labeling changes that include recommendations from the Division have been communicated to the Applicant. The Division proposed the indication be broadened to include pediatric hypertensive patients of all ages and adult hypertensive patients. Epaned® does not have unique characteristics that limit the administration only to pediatric patients under the age of 12 years. In the interests of the public health, the product can be considered for treatment of hypertension in patients who have difficulty in swallowing tablets irrespective of the age or cannot swallow (e.g., hypertensive patients with NG tube, etc). (b) (4) It should be noted that the adult dose of Vasotec® Tablets for the treatment of hypertension ranges from 5 mg once a day to 40 mg per day. In certain situations (e.g., a diuretic cannot be discontinued or for patients with creatinine clearance ≤ 30 mL/min) the initial doses of 2.5 mg once daily are recommended. For these doses, Epaned® can be a very useful formulation especially for patients who have difficulty swallowing a tablet. Further, even for the highest dose, when treatment is required for short durations when the patient cannot swallow, Epaned® can be a very useful formulation. Hence, the review team recommends that age restriction be removed in the label. If the submission were to

be approved at this time, agreement with the applicant needs to be reached on the Division's recommendation.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action:
  All the three primary reviews are unanimous in their recommendation for approval. I concur with the primary reviewers. The recommended regulatory action is approval of Epaned® for the treatment of hypertension in adults and pediatrics (1 month to 16 years of age).

- Risk Benefit Assessment
  The application does not contain data to evaluate risk and benefit of Epaned® for its antihypertensive effect in pediatric patients. The risk-benefit of this product is not expected to be any different compared to Vasotec® Tablets.

- Recommendation for other Postmarketing Requirements and Commitments
  There are no specific recommendations for post-market risk evaluation and mitigation strategies.

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/s/

RAJANIKANTH MADABUSHI
06/05/2013