CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209139Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 29, 2017
From	Sudharshan Hariharan
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 209139
Type	505(b)(2)
Applicant	Carmel Biosciences Inc.
Date of Submission	December 30, 2016
PDUFA Goal Date	October 30, 2017
Proprietary Name / Established (USAN) names	PREXXARTAN™ / Valsartan
Dosage forms / Strengths	Oral Solution / 4 mg/mL
Proposed Indication(s)	1. Treatment of adult and pediatric hypertension 2. Treatment of heart failure 3. Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction
Recommended:	*'Approval'*

Material Reviewed/Consulted	
Quality Assessment (10/13/17)	Mariappan Chelliah, Wendy Wilson-Lee, Akm Khairuzzaman, Hang Guo, Christina Capacci-Daniel, Derek Smith, Wenzheng Zhang, Yang Zhao, Neal Sweeney, Denise Miller, Grafton Adams, Dahlia Woody, Mohan Sapru (Application Technical Lead)
Pharmacology-Toxicology Review (04/05, 09/27/17)	Gowra Jagadeesh, Thomas Papoian
Clinical Pharmacology Review (10/24/17)	Snehal Samant, Sudharshan Hariharan
Clinical Review (07/31/17)	Kimberly Smith, Aliza Thompson
Division of Medication Error Prevention and Analysis Reviews (03/23, 06/12, 07/11, 09/19/17)	Ashleigh Lowery, Sarah Thomas, Chi-Ming (Alice) Tu
Maternal Health Review (06/06/2017)	Carrie Ceresa, Jane Liedtka, Lynne Yao
Division of New Drug Bioequivalence Evaluation Review (04/17/17)	Shila Nkah
Office of Prescription Drug Promotion Review (08/15/17)	Zarna Patel

1. Introduction

On December 30, 2016, Carmel Biosciences Inc. submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PREXXARTAN™, an oral solution of valsartan, for the following proposed indications:

- For treatment of hypertension in adults and in children six years and older, to reduce blood pressure
- For the treatment of heart failure (NYHA class II-IV)
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, Diovan® tablets (NDA 21283, approved 2001).

2. Background

Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor.

The reference listed drug, Diovan tablets, has the same indications proposed for Prexxartan (valsartan) oral solution. The Applicant proposes the same dose and dosing regimen for Prexxartan as approved for Diovan for the proposed indications. The Applicant has developed an oral solution containing valsartan at a concentration of 4 mg/mL to facilitate administration of valsartan in patients who cannot swallow tablets and/or require administration of the drug via nasogastric or other gastronomy tubes. The approved labeling for Diovan contains a procedure to prepare an extemporaneous oral suspension by compounding. The Applicant's rationale for developing an oral solution product is to eliminate the potential product quality risks associated with extemporaneous preparation.

3. CMC

Office of Product Quality (OPQ) recommends approval of the application from a quality perspective. The Applicant has satisfactorily addressed all the deficiencies that were communicated during the review. There are no unresolved issues at this time and no phase 4 commitments are needed.

Drug substance:
The Applicant has cross-referenced DMFs (b) (4) which has been reviewed and found to be adequate. The drug substance used in stability batches were manufactured using (b) (4) however, for the commercial batches the Applicant proposes to use (b) (4). The OPQ review states that the drug substance synthesized from these processes have similar impurity profiles. Based on stability data, the drug substance has a retest period of (b) (4)

months at (b) (4) Further, the OPQ review states that based on drug substance specification and batch analysis data, the control strategy is adequate to assure quality of the synthesized drug substance.

Drug product:
The proposed drug product is an oral solution. Each 1 mL of the oral solution contains 4 mg of valsartan. The product is supplied in 120 mL and 473 mL bottles with unit dose cups measuring 20 mL. The inactive ingredients used in the formulation include poloxamer (NF), grape flavor (b) (4) sodium citrate dehydrate (USP), sucralose (NF), propylene glycol (USP), purified water (USP) and (b) (4) potassium sorbate (NF), and methylparaben (NF). Grape flavor and sucralose (b) (4) the drug product. The batch data demonstrate that the drug product can be manufactured with consistent quality.

Expiration Date and Storage Conditions:
Based on the OPQ's assessment of stability data, the proposed product shelf-life of 24 months, when stored in commercial container closure system at 20°C - 25°C (68°F - 77°F), with excursions permitted at 15° - 30°C (59° - 86°F), is acceptable.

Facilities review/inspection:
All currently listed manufacturing facilities are deemed acceptable by Office of Process and Facilities.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted as part of the application. All nonclinical findings with Diovan can be borrowed based on an acceptable bridge to the listed drug.

As per the nonclinical review by Dr. Jagadeesh, drug product excipients other than sodium citrate, poloxamer, propylene glycol and methylparaben fall within the acceptable limits as specified in FDA Inactive Ingredient Guide (IIG). The Applicant submitted justification supporting the higher amount for the excipients mentioned above, and upon review they were found to be acceptable and considered safe for use in this oral liquid dosage form.

5. Clinical Pharmacology

Office of Clinical Pharmacology (OCP) recommends approval of Prexxartan for *twice-daily* administration, keeping the same total daily dose as with Diovan, for the treatment of hypertension in adults and in pediatrics six years and older. For the treatment of heart failure and post-MI indications, OCP is in alignment with the clinical review team to label Prexxartan only for use in patients who are unable to take the solid oral dosage form because of the potential risk associated with the higher peak concentration compared to Diovan.

The Applicant conducted two clinical studies in support of this development program – (i) a relative bioavailability (BA) study in healthy subjects comparing the pharmacokinetics of valsartan between Diovan tablets 320 mg and 80 mL of Prexxartan (4 mg/mL), and (ii) a food effect study to evaluate the impact of a high fat meal on the pharmacokinetics of valsartan following administration of 80 mL Prexxartan.

Bridge to the listed drug:
As noted in the clinical pharmacology review by Dr. Samant, the total systemic exposure to valsartan (AUC) is on an average 25% higher (90% CI: 1.15 – 1.38) and the peak concentration (C_{max}) 86% higher (90% CI: 1.69 – 2.05) for Prexxartan compared to Diovan. The time to achieve peak concentration is faster following Prexxartan (median T_{max}: 1.00 h) compared to Diovan (median T_{max}: 4.00 h). Although the AUC is not bioequivalent, it is at least similar or slightly higher compared to the listed drug. Given the shallow dose response relationship for valsartan, the 25% higher AUC is not clinically relevant. This allows borrowing the efficacy findings from the listed drug, Diovan, for all the proposed indications.

With regard to safety, the clinical pharmacology review notes a trend for dose dependent adverse events such as headache, dizziness and hypotension with Diovan. The review also notes a higher incidence of these adverse events from the healthy subject relative BA study in the Prexxartan treated group (headache 5.6%, vomiting 5.6%) compared to Diovan (0%). These events occurred around the time to peak concentration of Prexxartan suggesting the temporal association with the higher C_{max} of valsartan. Moreover, as noted in the clinical review, the higher C_{max} potentially increases the risk for hypotension, particularly in vulnerable patients such as heart failure and patients post-MI, so it may prevent reaching the same dose one would have achieved with Diovan.

Proposed dosing recommendations and/or management strategies to address higher C_{max}:
Any adjustment to the proposed dose or the regimen of Prexxartan should be considered to address this potential risk associated with a higher C_{max}. A simple dose reduction is not a viable option because the increase in C_{max} is much greater than observed for AUC. Therefore, OCP recommends a change in dosing regimen to twice-daily, and maintaining the same total daily dose, at least for use in hypertensive patients where Diovan is currently dosed once-daily. Since the peak concentration of valsartan is almost 86% higher, administering Prexxartan twice-daily following split dosing (e.g., 160 mg twice-daily) will result in similar C_{max} compared to a once-daily regimen of Diovan (e.g., 320 mg once-daily), maintaining the same AUC difference (25% higher) observed for the Prexxartan in the relative BA study.

Although altering the dosing frequency is a potential maneuver to address the higher C_{max} for use in hypertensive patients, such a strategy is not practical in patients with heart failure and in patients post-MI where Diovan is approved as a twice-daily regimen. In the absence of any adjustment to dose or dosing regimen, the review team considered not approving this product for use in heart failure or post-MI patients. However, considering the benefit that this drug offers, that of reducing the risk for cardiovascular morbidity and mortality, the review team thinks it would be prudent to make this product available to patients who are unable to swallow the solid oral dosage form. The review team also recommends including language describing the potential risk for hypotension under the Warning and Precaution section of the proposed product insert. I concur with their recommendations.

Food effect:
A high fat meal did not affect the AUC of valsartan significantly (8% decrease, fed/fasted ratio: 0.92, 90% CI: 0.85 – 1.00), but decreased the peak concentration by 44% (fed/fasted ratio: 0.56, 90% CI: 0.50 – 0.63) following administration of Prexxartan. T_{max} was delayed by an hour in the presence of food (median T_{max} of 1 h in fasted state vs 2 h in fed state). Because the total systemic exposure to valsartan is similar between the fed and the fasted states, the OCP review recommends to label the product to be taken without regard to food.

Moreover, as noted in the clinical pharmacology review, if the impact of a low fat/regular diet on valsartan pharmacokinetics following administration of Prexxartan were to be available and if the results were to be similar as that observed with a high fat meal, a potential consideration would be to label this product to be taken with food to address the potential concerns associated with a higher C_{max} of Prexxartan.

Site Inspection:
OCP requested inspection of the clinical and bioanalytical site, (b) (4) , for the relative BA study CR-055-BE-2013. OSIS recommends accepting data from these studies without an on-site inspection because the site was found to be compliant during the recently conducted inspection.

6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative BA study CR-055-BE-2013 provides the bridge to the efficacy findings of the listed drug, Diovan.

7. Safety

This application primarily relies on the Agency's previous determination of safety for the listed drug, Diovan. The clinical review focused on the safety findings in the clinical studies conducted by the Applicant, safety findings reported in the published literature, and results of a search of the FDA's Adverse Event Reporting System (FAERS).

As per Dr. Smith's review, these data do not raise any new safety concerns.

As discussed earlier, because of the higher peak concentration for Prexxartan compared to Diovan, the clinical review notes that there might be a potential for increased risk of hypotension particularly in heart failure and post-MI patients who are more vulnerable than hypertensive patients. To address this potential risk, the review team proposes to label this product as a second line treatment in patients who cannot swallow the solid oral dosage form. As mentioned earlier, I concur with this recommendation. It is logical that patients who are otherwise able to swallow a solid dosage form should not be exposed to an unwarranted risk.

8. Advisory Committee Meeting

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

9. Pediatrics

This application triggers Pediatric Research Equity Act (PREA) because it is a new dosage form. The Applicant is seeking the following waivers of pediatric studies:

- *Hypertension (0 to <2 years)*: On the basis that the use of RAAS inhibitors before renal maturation is complete may have long and deleterious effects on the kidneys.
- *Heart failure (all pediatric age groups)*: On the basis that studies are impossible or highly impractical because the causes and mechanisms of heart failure are different in children compared to adults.
- *Post-MI (all pediatric age groups)*: On the basis that atherosclerotic cardiovascular disease rarely or never occurs in pediatrics.

Given that Diovan is approved for the treatment of hypertension in pediatric patients 6 to <17 years of age, studies are not needed to establish safety and effectiveness in this population.

The Applicant has requested a deferral of pediatric studies in patients 2 to 5 years of age with hypertension, which will require the development of a revised formulation containing a lower quantity of propylene glycol (b) (4) The Applicant has proposed to conduct two studies:

(b) (4)

The Division and the PeRC agreed to the proposed waivers. The Division and the PeRC also agreed to the PMR and the deferral for studying Prexxartan in pediatric hypertension patients aged 2 to 5 years. The PeRC recommended that the proposed language in 8.4 *Pediatric Use* be revised to include a statement that the drug is not recommended for use in patients less than 2 years of age due to the renal maturation issues.

10. Other Relevant Regulatory Issues

There are no issues related to financial disclosure. One investigator participated in the clinical studies conducted by Carmel Biosciences Inc. and the investigator did not have disclosable financial arrangements for the study sponsored by the Applicant as per Form 3454 provided with the submission (see section 13).

11. Labeling

There are no unresolved labeling issues at this time. An agreement with the Applicant has been reached on the proposed alterations to the dosing recommendation in hypertensive patients and the management strategy with regards to the use of this product in heart failure and post-MI patients.

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

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval

Risk Benefit Assessment
For hypertension indication, the risk-benefit of Prexxartan when used as directed (twice-daily) in the proposed label is not expected to be different compared to Diovan.

For heart failure and post-MI patients who cannot swallow a solid oral dosage form, there is a potential risk for hypotension due to higher C_{max} with Prexxartan. However, this potential risk is outweighed by the benefit of reducing the risk for cardiovascular morbidity and mortality events in these patients.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for other Postmarketing Requirements (PMR) and Commitments

- A deferred pediatric study under PREA in patients 2 to 5 years of age with hypertension using a revised formulation of Prexxartan containing lower propylene glycol content.
- A relative BA study in adults to compare the exposure to valsartan between the revised formulation of Prexxartan containing (b) (4) propylene glycol and the currently to-be-marketed formulation containing (b) (4) propylene glycol (to be conducted prior to the pediatric study).

Recommended Comments to Applicant
None

13. Appendix

Clinical Investigator Financial Disclosure Review

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

SUDHARSHAN HARIHARAN
10/29/2017

NORMAN L STOCKBRIDGE
10/30/2017
I concur.