CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209139Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	209139
SDN	001
Submission Date	12/30/2016
Submission Type	505(b)(2)
Generic name	Valsartan
Brand name	PREXXARTAN™
Applicant	Carmel Biosciences Inc.
Dosage form	Oral solution
Strength	4 mg/mL
Drug Class	Angiotensin II receptor blocker (ARB)
Indications	Treatment of hypertension, to lower blood pressure. 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.
Associated IND	119968
OCP Division	Division of Clinical Pharmacology-1 (DCP-1)
OND Division	Division of Cardiovascular and Renal Products (DCRP)
Reviewer	Snehal Samant, PhD
Team Leader	Sudharshan Hariharan, PhD

Table of Contents

1. EXECUTIVE SUMMARY

Carmel Biosciences Inc. has submitted a New Drug Application for valsartan oral solution 4 mg/mL (PREXXARTAN™) under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act. The application relies on Agency's safety and efficacy findings for the listed drug Diovan® tablets approved as NDA 021283 in 2001. The applicant is seeking approval for the following indications at the same dose as approved for Diovan:

- Treatment of hypertension, to lower blood pressure.
- 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 applicant has submitted two clinical pharmacology studies: 1) Relative bioavailability (BA) study (055-BE-2013), comparing the pharmacokinetics (PK) of valsartan from PREXXARTAN, 4 mg/mL (80 mL) to the listed drug Diovan tablet, 320 mg; 2) Food effect study of high-fat, high-calorie meal (059-PK-2014) on PREXXARTAN 4 mg/mL (80 mL) PK. The applicant is relying on the relative BA study for bridging to the efficacy and safety of the listed drug.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1(OCP/DCP1) recommends approval of PREXXARTAN for all the approved indications as of the listed drug based on similar total systemic exposure of valsartan (area under the curve, AUC) between PREXXARTAN and Diovan. OCP recommends the following changes to dosing and administration of PREXXARTAN to address the higher peak concentration (C_{max}) of valsartan with PREXXARTAN compared to Diovan:

- For adult and pediatric hypertension indication, change to a twice-daily dosing regimen for PREXXARTAN (b) (4) administration of Diovan maintaining the same total daily dose.

Table 1. Proposed dosing for PREXXARTAN for hypertension indication

Indication	Starting Dose	Dose Range
Hypertension—adults	40 or 80 mg twice daily	40 -160 mg twice daily
Hypertension—age 6 to16 years	0.65 mg/kg twice daily (up to 40 mg total daily dose)	0.65-1.35 mg/kg twice daily (up to 40 mg-160 mg total daily dose)

- For heart failure (HF) and use in post-myocardial infarction (post-MI) patients where Diovan is recommended as a twice-daily regimen, label PREXXARTAN only for use in patients unable to take the solid oral dosage form and to include a Warning and Precaution related to potential risks associated with the higher C_{max} of PREXXARTAN.

1.2 Post-Marketing Requirements and Commitments

None

1.3 Summary of important clinical pharmacology and biopharmaceutics findings

- The results of the pivotal relative BA Study CR-055-BE-2013 indicate that PREXXARTAN (80 mL at 4 mg/mL strength) and the listed drug, Diovan tablet (320 mg), are not bioequivalent. PREXXARTAN has 1.86 (1.69 – 2.05 90% CI) fold higher C_{max} and 1.25 (1.15 – 1.38 90% CI) fold higher AUC_{0-t} compared to Diovan tablet.
- High-fat, high-calorie meal results in 44% lower C_{max} and similar AUC_{0-t} (fed/fasted ratio of 0.92 (0.84 - 1.0 90% CI)) compared to fasted state administration of PREXXARTAN (80 mL at 4 mg/mL strength).

2. QUESTION BASED REVIEW

This is an abridged version of the question-based review. For review of clinical and clinical pharmacology studies supporting the approval of Diovan, refer to the reviews associated with original NDAs 020665 (capsules) and 021283 (tablets).

2.1 General Attributes of the Drug Product

2.1.1 What are the general features of the drug product?

PREXXARTAN, is formulated as an aqueous solution at a concentration of 4 mg/mL. PREXXARTAN is packaged in bottles containing 473 mL, bottles containing 120 mL and unit dose cups containing 20 mL. The inactive ingredients in PREXXARTAN include poloxamer and propylene glycol (b) (4), sodium citrate dehydrate (b) (4), sucralose (b) (4), methyl paraben and potassium sorbate (b) (4), sodium saccharin, grape flavor (b) (4) and purified water.

2.1.2 What is the applicant's rationale in developing this product?

The applicant has developed an oral solution dosage form 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 oral solution product is to eliminate the need for cold storage of the product and extemporaneous preparation (Ref: Type B meeting minutes for PIND 119968 dated: 11/27/2013).

2.1.3 What are the proposed mechanism(s) of action?

Valsartan is an angiotensin II receptor blocker (ARB). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. The primary metabolite of valsartan is essentially inactive with an affinity for the AT1 receptor about one-200th that of valsartan itself.

2.1.4 What are the proposed therapeutic indication(s)?

The proposed therapeutic indications for PREXXARTAN are:

- Treatment of hypertension, to lower blood pressure.
- Treatment of heart failure (NYHA class II-IV); valsartan significantly reduced hospitalization for heart failure.
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

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

The proposed doses are the same as those for the listed drug Diovan (Table 2). PREXXARTAN is a valsartan solution formulation, proposed to be administered orally.

Table 2. Proposed dosing for PREXXARTAN

Indication	Starting Dose	Dose Range	Target Maintenance Dose*
Adult Hypertension	(b) (4)		---
Pediatric Hypertension (6 to 16 years of age)			---
Heart Failure	40 mg twice daily	40 mg-160 mg twice daily	160 mg twice daily
Post-Myocardial Infarction	20 mg twice daily	20 mg-160 mg twice daily	160 mg twice daily

*as tolerated by patient

Please refer to Section 2.3 for dosing recommendation and instructions proposed by the reviewer for PREXXARTAN based on the relative bioavailability of valsartan with PREXXARTAN compared to Diovan tablets.

2.2 Comprehensive Clinical Pharmacology Review

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

The applicant submitted two clinical pharmacology studies to support proposed dosing and labelling (Table 3). The pivotal relative bioavailability study (CR-055-BE-2013) compared the bioavailability of valsartan from PREXXARTAN and Diovan tablets for the highest approved dose of 320 mg following single oral dose administration. Study 059-PK-2014 evaluated the effect of high-fat, high-calorie meal on the bioavailability of valsartan from PREXXARTAN. The studies have been summarized in Table 3. Please refer Appendix for the individual study reviews.

Table 3. Summary of clinical pharmacology studies

Study	Type	Design	Subjects
055-BE-2013	Relative Bioavailability study	An open label, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose comparative bioavailability study under fasting conditions	**Enrolled**: 72 **Completed**: 66 (66 males) Healthy adult, male subjects **Age(years):** **Mean** 28.15 **Range** (18-43)
059-PK-2014	Food effect study	Open-label, balanced, randomized, two-period (fasting versus fed), cross-over, single-dose food effect study in healthy, adult, human subjects	**Enrolled**: 18 **Completed**: 18 (18 males) Healthy adult, male subjects **Age(years):** **Mean** 30.94 **Range** (24-39)

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

The active moiety analyzed was valsartan. High performance liquid chromatography mass spectrometric method in positive ion mode was used for the estimation of valsartan in human plasma using valsartan d9 as internal standard. Sample preparation was done by solid-phase extraction technique. The method was validated over a concentration range of 50 ng/mL to 12000 ng/mL for valsartan (MV Report No.: VR-3 14-VALS-2015 Version-01. Dated: 11/27/15). Quality control samples at four different concentrations were analyzed along with the study samples. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Greater than two-thirds (67%) of the incurred samples concentration results were within 20% of the original concentration of the respective samples and meeting the acceptance criteria for incurred samples reanalysis. Analytical methods were validated and performed within acceptable limits as shown in Table 4.

Table 4. Summary of bioanalytical sample analysis and method validation

Study Number Validation report	Matrix Analyte	Total No. of samples analyzed	Range and QCs	Accuracy	Precision
055-BE-2013 Method validation VR-314-VALS-2015	Matrix K_2-EDTA Plasma Analyte Valsartan	3389 samples from 72 subjects	LLOQ 0.050 µg/mL ULOQ 12.00 µg/mL QCs (µg/mL) 0.146, 2.526, 6.014, 9.017	CSs 95.45% to 107.23% QCs 93.89% to 99.14%.	CSs 1.14% to 2.90% QCs 5.24% to 8.34%
059-PK-2014 Method validation VR-314-VALS-2015	Matrix K_2-EDTA Plasma Analyte Valsartan	900 samples from 18 subjects	LLOQ 0.050 µg/mL ULOQ 12.00 µg/mL QCs (µg/mL) 0.146, 2.527, 6.017, 9.022	CSs 92.60% to 106.50% QCs 95.05% to 101.77%	CSs 1.06% to 4.87% QCs 0.55% to 3.27%

CSs: Calibration Standards, QCs: Quality Control Samples, LLOQ: Lower Limit of Quantification, ULOQ: Upper Limit of Quantification

2.2.3 What are the PK characteristics of the drug product? Do they support the proposed dosing and label claims?

The systemic exposure (AUC_{0-t}) of valsartan following administration of PREXXARTAN is 1.25 fold higher than Diovan (90% CI for Test/Reference ratio: 1.15 – 1.38). Compared to Diovan, valsartan reaches its peak plasma concentration faster following PREXXARTAN administration (median T_{max} = 1.00 h (0.7 h-2.7 h) for PREXXARTAN vs 4.0 h (1.3 h-5.5 h) for Diovan). Peak plasma concentration for PREXXARTAN is 1.86 fold higher compared to that for Diovan (90% CI for Test/Reference ratio: 1.69 – 2.05). AUC and C_{max} values of valsartan increase approximately dose proportionally with increasing dose over the dose range of 40 mg to 320 mg following single and multiple dose

administration. Given the dose proportionality of valsartan across the clinical dose range and the proportional similarity of the formulations across all strengths of Diovan tablets, the relative BA findings established for the 320 mg dose level should be applicable across all the lower dose levels of PREXXARTAN.

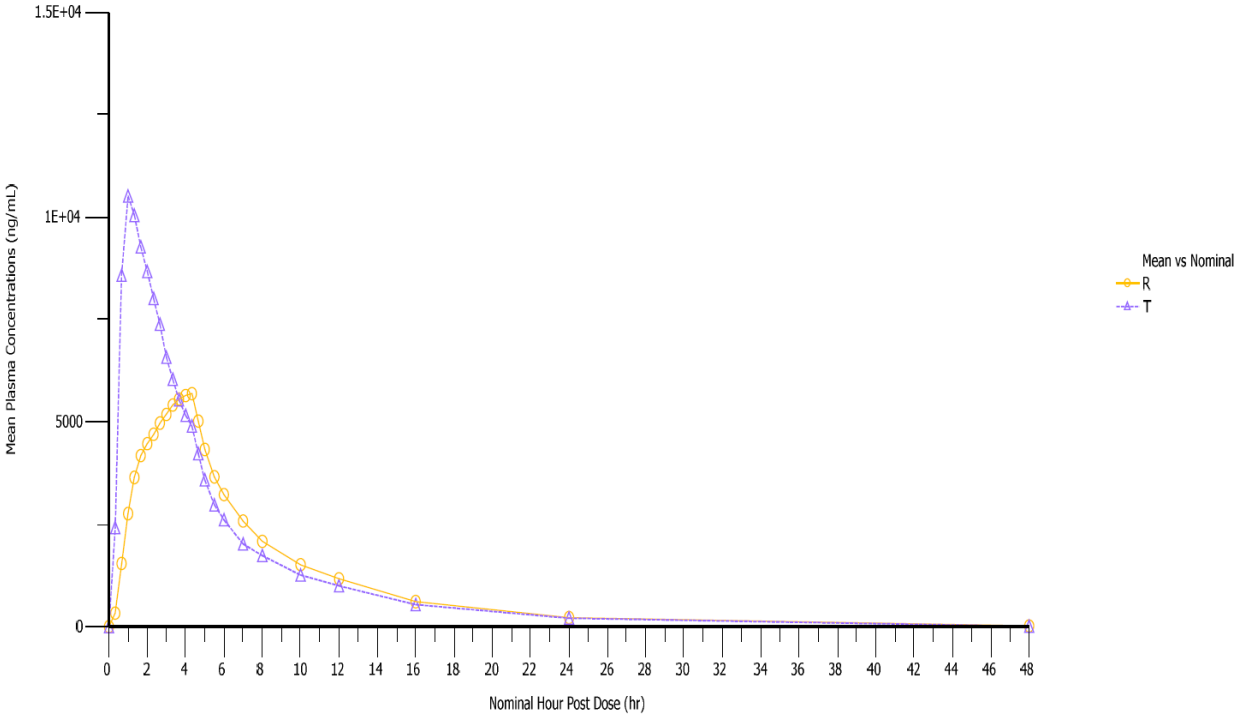


Figure 1. Valsartan mean plasma concentration profile in healthy adults following administration of single oral dose of (T) PREXXARTAN (80 mL) and (R) Diovan (320 mg)

Valsartan has an elimination half-life of ~6 h. Between-subject variability of valsartan PK following PREXXARTAN is similar to that following Diovan (30-33% for PREXXARTAN and 25-30% for Diovan). The relative BA study was not of a replicate crossover design to evaluate the intra-subject variability following PREXXARTAN.

2.2.4 What is the effect of food on the bioavailability of the drug from the drug product?

Taking PREXXARTAN with a high fat meal decreases the systemic exposure (AUC_{0-t}) of valsartan by about 8% (fed/fasted ratio%: 92.1%; 90% CI: 84.8 – 100.1). Peak plasma concentration (C_{max}) following administration of PREXXARTAN with high-fat, high-calorie meal is 44% (Fed/fasted ratio%: 56.1%; 90% CI: 50.1 - 62.8) lower compared to fasted state administration. T_{max} is delayed by 1 hour (Median T_{max}: 2.17 vs 1 h) in fed state. Since the AUC of valsartan following PREXXARTAN administration is similar between fed and fasted states, PREXXARTAN can be taken without regards to food.

2.2.5 What are the safety findings from the clinical pharmacology studies?

In the relative BA study, safety adverse event (AE) data was available for 71 and 69 healthy adults following test drug (PREXXARTAN) and reference drug (Diovan) administration, respectively. Compared to Diovan, subjects had more AEs (2.90 % vs 22.53%) following PREXXARTAN administration. Itching was the only reported adverse effect following Diovan administration. Of note, incidences of headache (5.63%) and vomiting (5.63%) headache and vomiting occurred 0.5 to 1.5 hours following PREXXARTAN administration. Time of occurrence headache and vomiting is around the time for peak plasma concentration of valsartan. Eighteen healthy adults participated in the food effect study. No AEs were reported in the food effect study.

2.3. Dosing and Therapeutic Individualization

2.3.1 Can the submission rely on the FDA's previous finding of efficacy and safety for the listed drug Diovan tablets for the proposed indications and dosing regimens?

The total systemic exposure to valsartan (AUC) is on average 25% higher and the peak concentration (C_{max}) is 86% higher with the PREXXARTAN compared to Diovan tablets. Given the AUC of valsartan is similar or slightly greater, this submission can rely on the efficacy findings of the listed drug, Diovan, for all proposed indications.

To assess whether this submission can rely on the safety findings of Diovan, the reviewer gathered safety information from the reviews of the clinical studies conducted with Diovan. The integrated safety findings for Diovan for adult hypertension, heart failure and post-MI indications (reference: Medical review for NDA 020665 and Clinical Pharmacology-Biopharmaceutics reviews for NDA 020665 /SE1-016, 21-283 /SE1- 001) note that the most common reasons for discontinuation of therapy in hypertension controlled studies with Diovan were headache and dizziness. There was a dose-related increase in the incidence of dizziness in hypertension and heart failure controlled trials for Diovan (NDA 020665). Incidence of dizziness was 2-4% in the 10 to 160 mg dose group and 8% in 320 mg dose groups for hypertension controlled trials. For HF, the incidence of dizziness increased from 2.3% in 0 mg, 7.7% in 80 mg, 7.4% in 160 mg and 9.0% in 320 mg total daily dose groups. Integrated analysis of 5 double-blind short-term heart failure trials reported hypotension incidence of 7% vs 2 % in the valsartan and placebo treated patients, respectively. These findings suggest a trend for dose-dependent AEs such as headache, dizziness and hypotension which are more closely associated with the peak concentration of valsartan. As described earlier (section 2.2.53), there was a higher incidence of AEs reported for the PREXXARTAN compared to Diovan in the healthy volunteer relative BA study and the timing of these events seem to correspond with the T_{max} of valsartan. Also, as stated in the clinical review (NDA 209139, DARRTS date: 07/31/2017), patients with heart failure and patients post-MI are more vulnerable than hypertensive patients to the risk for hypotension. It is possible that a potentially

greater risk for hypotension and tolerability with the PREXXARTAN could effectively hinder titration to the optimal dose required for therapy in these patients. Therefore, feasible solution(s) to the dosing and administration of PREXXARTAN should be considered to address the potential risks associated with a higher C_{max}.

2.3.2. Is an alternative dosing regimen and/or management strategy required for patient population for which the indication is being sought?

Yes, an alternative dosing regimen and/or management strategy is required to address the higher C_{max} of valsartan observed with the PREXXARTAN.

Valsartan exhibits linear and dose proportional pharmacokinetics in the dose range of 40-320 mg following single dose administration. A potential solution to address the higher peak concentration and allow for use in hypertensive patients is to halve the total daily dose and administer PREXXARTAN as a twice-daily regimen. Since the peak concentration of valsartan is almost 86% higher, administering PREXXARTAN twice-daily following split dosing (e.g., 160 mg BID) will result in similar C_{max} compared to a QD regimen of Diovan (e.g., 320 mg QD), maintaining the same AUC difference (25% higher) observed for the PREXXARTAN in the relative BA study. Although the reviewer proposed dosing strategy increases the frequency of administration, it nevertheless seems to be a practical solution, as dose reduction is not viable because of different magnitude of changes for AUC and C_{max} for PREXXARTAN compared to Diovan.

Diovan is approved for a twice daily dosing for both, heart failure (40 mg BID to 160 mg BID) and post-MI (20 mg BID to 160 mg BID) indications. Therefore, modification of dosing regimen to further divide the total daily dose seems not viable from a patient compliance perspective. Therefore, as a management strategy, it seems prudent to not allow the use of PREXXARTAN in all patients, but to restrict the use only in patients who are unable to swallow the oral dosage form, as the potential benefit of therapy in reducing the risk for cardiovascular morbidity and mortality events may outweigh the potential risks for hypotension associated with the higher C_{max}.

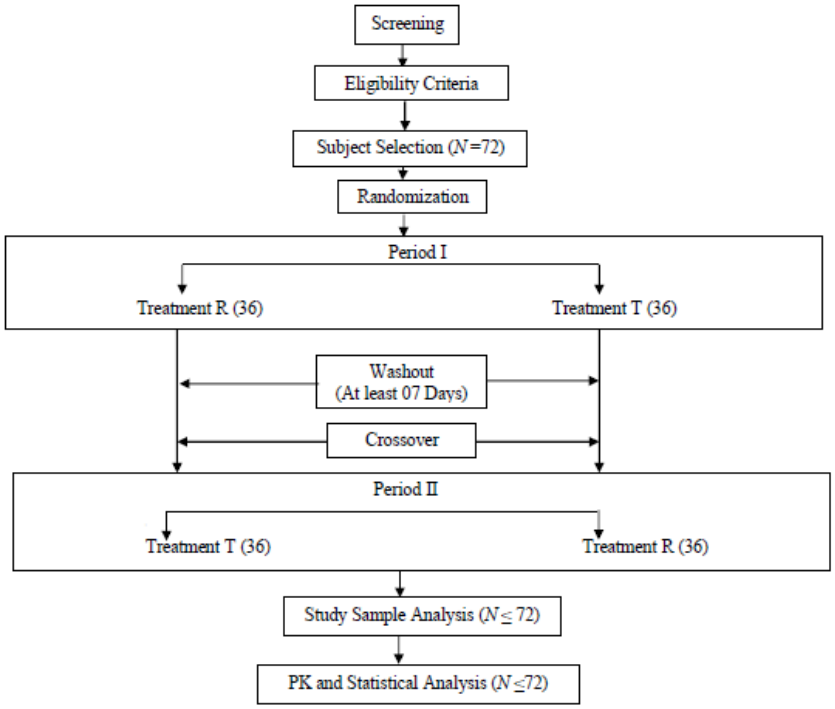
Interestingly, the reviewer also notes that administration of PREXXARTAN with high fat meal decreased the peak concentration of valsartan by 44% without affecting the AUC significantly (8% decrease). However, the food effect following a lower fat/regular diet is not known. If the effect of a regular meal on valsartan PK for the PREXXARTAN were to be available and the results were to be similar as seen with the high fat meal, another potential alternative would be to recommend the use of PREXXARTAN with a meal to address the potential risk associated with a higher C_{max}.

3. APPENDICES

3.1 Individual Study Reviews

3.1.1 Relative bioavailability study

Report No: CR-055-BE-2013	Name of Sponsor / Company: (b) (4) on behalf of Carmel Biosciences	EDR: \\CDSESUB1\evsprod\NDA209139\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\055-be-2013
Title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose comparative bioavailability study of 80 mL of PREXXARTAN (valsartan oral solution) 4 mg / mL (a total of 320 mg) comparing with Diovan Tablets 320 mg (containing valsartan 320 mg) in healthy, adult, human subjects under fasting conditions.		
Study objectives: 1) To assess comparative bioavailability of single oral dose of test product, a 80 mL of PREXXARTAN 4 mg / mL (a total of 320 mg) with reference product (R) Diovan Tablets 320 mg (containing valsartan 320 mg) in healthy, adult, human subjects under fasting conditions. 2) To monitor the safety and tolerability of single dose of PREXXARTAN 4 mg / mL		
Methodology: The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose comparative bioavailability study under fasting conditions. Study design schematic is as follows:		



Reference (R): Diovan® Tablets 320 mg (containing valsartan 320 mg) distributed by Novartis Pharmaceuticals Corp., East Hanover NJ 07936, USA

Test (T): 80 mL of Valsartan Oral solution 4 mg / mL (a total of 320 mg valsartan) of Carmel Biosciences, Atlanta Vascular Research Foundation, 5673 Peachtree Dunwoody Road, Suite 440, Atlanta, Georgia 30342

N: Number of subjects PK: Pharmacokinetic;

Subjects:

72 adult male subjects entered the study and 66 subjects completed both the periods of the study (Participant IDs: (b) (6) withdrawn from the study due to adverse event during period-II). (b) (6) subjects were included in the PK analysis for Reference and Test product, respectively. Statistical analysis was performed on 66 subjects for both, Reference and Test product.

Duration of treatment:

The subjects who completed both the periods of the study received both the study treatments (T and R) as per the randomization schedule. The total duration of the study was 11 days with a washout period of 7 days between two treatment periods.

Bioanalytical Methods:

A validated LC-MS/MS method was employed for the estimation of valsartan in human plasma. During estimation of the analyte, quality control samples were distributed throughout each batch of study samples. Details of the analytical method are reviewed in section 2.2.2.

Statistical Methods:

The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using an ANOVA model with the main effects of sequence, subject nested within sequence, period and 'treatment'. A 5% level of significance was used for with-

in subject comparison (i.e. period, 'treatment') and 10% level of significance was used for between-subject comparison (i.e. sequence). For the pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$), the geometric mean ratio of the test and reference product and the 90% confidence intervals for the ratio were calculated using the ANOVA output from the analysis of the log-transformed data.

Results:

Statistical Summary of Relative BA Data:

Parameter	Geometric Least Squares Mean		T/R Ratio (%)	90% C.I
	Test (T)	Reference (R)		
C_{max} (ng/mL)	11048.23	5934.26	186.18	169.47 - 204.53
AUC_{0-t} (ng.hr/mL)	49151.88	39125.91	125.62	114.81 - 137.46
$AUC_{0-\infty}$ (ng.hr/mL)	50620.63	40567.87	124.78	114.45 - 136.04

Summary of Pharmacokinetic Parameters:

Parameter	Test (T) Arithmetic Mean (SD)	Reference (R) Arithmetic Mean (SD)
C_{max} (ng/mL)	11497.6 (3216.1)	6605.5 (3219.5)
AUC_{0-t} (ng.hr/mL)	52176.5 (18298.3)	43579.5 (21528.3)
$AUC_{0-\infty}$ (ng.hr/mL)	53646.4 (18484.1)	45001.4 (21856.8)
T_{max} (hr)*	1.0 (0.7-2.7)	4 (1.3 – 5.5)
K_{el} (1/hr)	0.13 (0.03)	0.13 (0.03)
$t_{1/2}$ (hr)	5.7 (1.71)	5.7 (2.6)

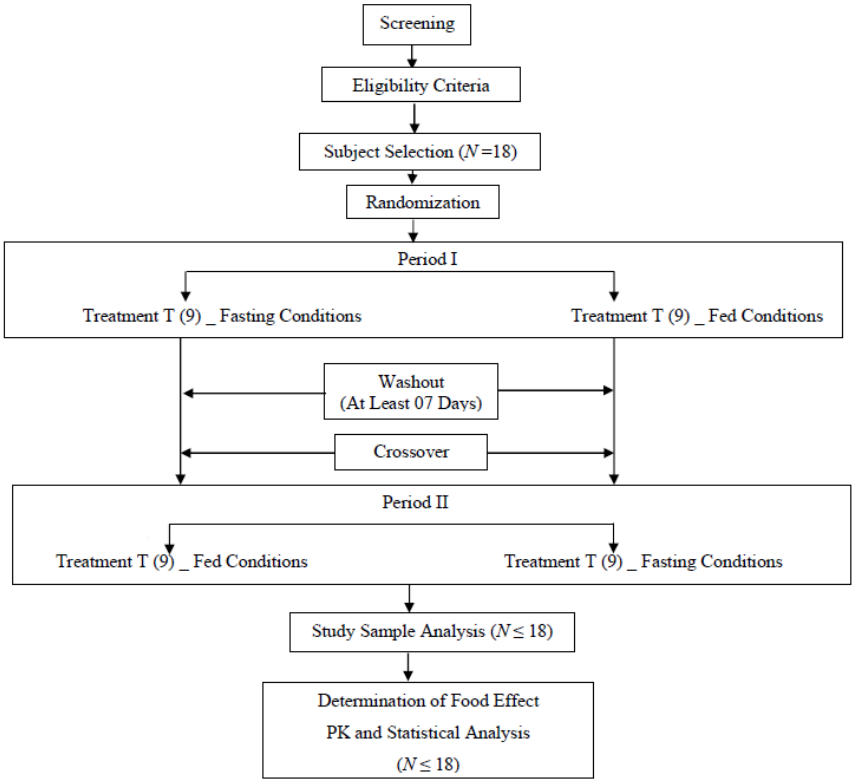
* Median (minimum-maximum), SD standard deviation

Conclusions:

- The Test product, 80 mL of PREXXARTAN 4 mg / mL (a total of 320 mg) is not bioequivalent to the Reference product, Diovan Tablets 320 mg in healthy, adult, male subjects under fasting conditions.
- The peak concentration of valsartan is 86% higher and area under the curve is 25% higher for PREXXARTAN compared to Diovan tablets.
- Peak plasma concentrations of valsartan were attained earlier following PREXXARTAN administration (1 h) compared to Diovan tablets (4 h).
- Higher incidence of headache and vomiting was observed in the Test group (5.63%) compared to the Reference group (0%). The time of occurrence of the events was around the time of peak plasma levels (0.5 – 1.5 hours post dose) of valsartan

3.1.2 Food effect study

Report No: CR-059-PK-2014	Name of Sponsor / Company: (b) (4) on behalf of Carmel Biosciences	EDR: \\CDSESUB1\evsprod\NDA209139\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\059-pk-2014
Title: An open label, balanced, randomized, single-treatment, two-period (fasting versus fed), crossover, single oral dose food-effect study of 80 mL of PREXXARTAN, (valsartan oral solution) 4 mg / mL (a total of 320 mg valsartan) in healthy, adult, human subjects.		
Study objectives: 1) To determine the effect of food on pharmacokinetics PREXXARTAN 4 mg / mL (a total of 320 mg) in healthy subjects by comparing the pharmacokinetics in two periods (fasted versus fed). 2) To determine the safety and tolerability of PREXXARTAN 4 mg / mL in healthy subjects.		
Methodology: The study was an open-label, balanced, randomized, two-period (fasting versus fed), cross-over, single-dose food effect study in healthy, adults designed to evaluate the effect of a high-fat, high calorie meal on the oral absorption of valsartan from PREXXARTAN. Total eighteen subjects completed both the periods of the study. Data from all 18 subjects were considered for PK and statistical analysis. A single oral dose of 80 mL of PREXXARTAN 4 mg / mL was administered under fasting/fed conditions as per the randomization schedule. Study design schematic is as follows:		



Test (T): 80 mL of Valsartan Oral Solution 4 mg / mL (a total of 320 mg) of Carmel Biosciences, Atlanta Vascular Research Foundation, 5673 Peachtree Dunwoody Road, Suite 440, Atlanta, Georgia 30342.

N: Number of subjects PK: Pharmacokinetic;

Meal Plan and High fat calories break-up:

Meal Plan:

For Fasting Conditions:

Day	Break fast	Lunch	Snacks	Dinner
D-0	-	-	-	11.00 hrs prior to the dose
Dosing day (D-1)	-	4.00 hrs post dose	8.00 hrs post dose	13.00 hrs post dose

For Fed Conditions:

Day	Break fast	Lunch	Snacks	Dinner
D-0	-	-	-	11.00 hrs prior to the dose
Dosing day (D-1)	0.50 hrs prior to the dose	4.00 hrs post dose	8.00 hrs post dose	13.00 hrs post dose

High Fat Calories Break-Up:

Food Item	Amount	k. cal
Bread + Butter	20 gm of Bread + 20 gm of Butter	281.84
Egg Omelette+ Butter	45 gm of Omelette + 5 gm of Butter	97.65
French Fries	25 gm of Potatoes	145.72
Milk (Whole) + Sugar	240 ml + 2.5 gm	240.90
Chicken Tikka (fried in oil) + Garnished with Ginger, Garlic and Masala for Taste	55 gm	151.30
Total	-	**917.41**

Bioanalytical Methods:

A validated LC-MS/MS method was employed for the estimation of valsartan in human plasma. During estimation of the analyte, quality control samples were

distributed throughout each batch of study samples. Details of the analytical method are reviewed in section 2.2.2.

Statistical Methods:

The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using an ANOVA model with the main effects of sequence, subject nested within sequence, period and 'treatment condition'. A separate ANOVA model was used to analyze each of the parameters. A 5% level of significance was used for within subject comparison (i.e., period, 'treatment condition') and 10% level of significance was used for between-subject comparison (i.e., sequence). For the pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$), the geometric mean ratio of the test and reference product and the 90% confidence intervals for the ratio were calculated using the ANOVA output from the analysis of the log-transformed data.

Results:

Statistical Summary of Relative BA Data:

Parameter	Geometric Least Squares Mean		Fed/fasted Ratio (%)	90% C. I
	Fed	Fasted		
C_{max} (ng/mL)	6398.0	11402.4	56.1	50.1 - 62.8
AUC_{0-t} (ng.hr/mL)	51708.0	56137.5	92.1	84.8 – 100.1
$AUC_{0-\infty}$ (ng.hr/mL)	53600.9	57895.2	92.6	84.3 – 101.7

Summary of Pharmacokinetic Parameters:

Parameter	Fed Arithmetic Mean (SD)	Fasted Arithmetic Mean (SD)
C_{max} (ng/mL)	6505.4 (3023.3)	11747.5 (1226.1)
AUC_{0-t} (ng.hr/mL)	53205.5 (13339.7)	57398.3 (12883.8)
$AUC_{0-\infty}$ (ng.hr/mL)	55048.5 (13232.5)	59153.3 (13120.7)
T_{max} (hr)*	2.2 (1.3-4.7)	1.0 (0.7-2.0)
K_{el} (1/hr)	0.12 (0.02)	0.12 (0.03)
$t_{1/2}$ (hr)	6.9 (4.0)	6.2 (1.5)

* Median (minimum-maximum), SD standard deviation

Conclusion:

- Administration of PREXXARTAN with a high-fat, high-calorie meal decreased the C_{max} of valsartan by 8% and AUC of valsartan by 44%.
- The time to attain peak plasma concentration of valsartan was delayed by about 1 hour following administration of PREXXARTAN in the fed state.
- In general, the safety profile of test product under both fasting and fed conditions was similar.

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10/24/2017

SUDHARSHAN HARIHARAN
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