DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209139

NDA APPROVAL

Carmel Biosciences, Inc.
Attention: Bobby V. Khan, M.D., Ph.D.
Executive Director
5673 Peachtree Dunwoody Road
Suite 440
Atlanta, GA 30342

Dear Dr. Khan:

Please refer to your New Drug Application (NDA) dated and received on December 30, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Prexxartan (valsartan) Oral Solution, 4 mg/mL.

We acknowledge receipt of your amendment dated November 2, 2017, which constituted a complete response to our October 30, 2017 action letter.

This new drug application provides for the use of Prexxartan (valsartan) Oral Solution for the following indications:

- Treatment of hypertension in adults and children six years and older, to lower blood pressure.
- Treatment of heart failure (NYHA class II-IV) to reduce the risk of hospitalization for heart failure in patients who are unable to swallow valsartan tablets.
- To reduce the risk of cardiovascular death in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction who are unable to swallow valsartan tablets.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton label submitted on October 2, 2017 and immediate container labels submitted on August 4, 2017 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 209139**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

For the hypertension indication:
We are waiving the pediatric study requirement for ages 0 to <2 years because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group. It is unclear whether use of RAAS inhibitors before renal maturation is complete has long-term deleterious effects on the kidney and feasible clinical studies are unlikely to resolve this issue.

We are deferring submission of your pediatric studies for ages 2 to 5 years for this application in this indication because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3319-1 Conduct a pharmacokinetic bridging study in adults to determine the exposure of valsartan with both the current and revised formulations of Valsartan Oral Solution prior to the conduct of studies in children. A revised formulation (b) (4) is proposed for use in the clinical study for the 2 to 5 year old age group with hypertension.

The timetable you submitted on October 6, 2017 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/2019
Trial Completion:	09/2019
Final Report Submission:	01/2020

3319-2 Conduct an efficacy and safety study of Valsartan Oral Solution in pediatric patients 2 to 5 years of age with hypertension.

The timetable you submitted on October 17, 2017 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/2020
Trial Completion:	01/2023
Final Report Submission:	01/2024

Submit the protocol(s) to your IND 119968, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

This product is appropriately labeled for use in ages 6 to <17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

For the heart failure indication:
We are waiving the pediatric study requirement for this application in this indication because necessary studies are impossible or highly impracticable. The causes and mechanisms of heart failure in children and adults are different.

For the post-myocardial infarction indication:
We are waiving the pediatric study requirement for this application in this indication because necessary studies are impossible or highly impracticable. Atherosclerotic cardiovascular disease rarely or never occurs in pediatrics.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
12/19/2017