CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207620Orig1s000

Trade Name:	ENTRESTO Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.
Generic Name:	sacubitril/valsartan
Sponsor:	Novartis Pharmaceuticals Corp.
Approval Date:	July 7, 2015
Indication:	Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an angiotensin converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207620

NDA APPROVAL

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Global Program Regulatory Director
One Health Plaza
Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated December 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ENTRESTO (sacubitril/valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

We acknowledge receipt of your amendments dated January 15, 16 (two), 20, 22, 28 (two), 30, February 2, 5, 11, 18, 20, 24, 26, March 3, 10, 12, 13, 17, April 2, 3, 8, 15 (two), 16, 20, 21, 24, 29, May 1, 4, 6, 7, 13, 15 (two), 22, 26, June 2, 3, 4, 11, 12, 15, 19, 25, 26, and July 1, 2, and 6, 2015.

This new drug application provides for the use of ENTRESTO (sacubitril/valsartan) Tablets, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an angiotensin converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).

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.

In addition, the revised comparability protocols for 1) drug product manufacturing site, control, batch size, and process and 2) (b) (4) intermediate manufacturing site, control, batch size, and process as included in Submission 0000 dated September 30, 2014 are approved. Regulatory notification of changes to the approved protocols must be made via a prior approval supplement.

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 and text for the patient 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

We acknowledge your June 11, 2015, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for ENTRESTO was not referred to an FDA advisory committee because:

- The safety profile is acceptable for ENTRESTO to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

  ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.
- The application did not raise significant safety or efficacy issues that were unexpected for a drug of these classes
- The application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease
- Outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. The causes and mechanisms of heart failure are different in children compared to adults. Heart failure in children is most commonly caused by congenital heart malformations and cardiomyopathy whereas the primary etiology of adult heart failure is ischemic heart disease due to atherosclerotic coronary artery disease. The form of heart failure seen in adults is rare in children; hence conducting a trial is highly impractical.

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