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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207620Orig1s000

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APPLICATION NUMBER:

207620Orig1s000

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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of angioedema in Black patients or to identify an unexpected serious risk of cognitive dysfunction with the use of Entresto (sacubitril/valsartan).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess or identify these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2924-1 Conduct an epidemiologic study using claims or electronic health records data to evaluate the incidence of angioedema in Black patients treated with Entresto compared to a control drug. A target sample size, supported by sample size calculation, should be included in the protocol.

The timetable you submitted on June 19, 2015, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	December 2015
Final Protocol submission	July 2016
Interim Report #1	July 2017
Interim Report #2	July 2018
Final Report Submission:	July 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious risks of cognitive dysfunction with the use of Entresto (sacubitril/valsartan).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2924-2 A multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and PET imaging in patients with chronic heart failure with preserved ejection fraction.

The timetable you submitted on July 6, 2015, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission	November 2015
Final Protocol submission	April 2016
Trial Completion	October 2021
Final Report Submission:	March 2022

Submit the protocols to your IND 104628, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2924-3 Development of a new dissolution method for all the strengths with demonstrated discriminating ability, [redacted] (b) (4) , and setting of the final dissolution acceptance criterion for Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg using the new dissolution method and data from the overall multipoint dissolution profile from a minimum of 12 commercial batches per strength, manufactured under the same conditions as those used for the manufacture of the batches used in pivotal clinical trials. The FDA will be open to providing feedback during the method's development process as needed.

The timetable you submitted on June 25, 2015, states that you will conduct this study according to the following schedule:

Dissolution Method Development Report Submission:	February 2016
Final Report Submission:	July 2016

Submit clinical protocols to your IND 104628 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 to:

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

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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call:

Alexis Childers, RAC
Senior Regulatory Project Manager
(301) 796-0442

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
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/

ELLIS F UNGER
07/07/2015