CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 12, 2015
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 207620
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	December 17, 2015
PDUFA Goal Date	August 15, 2015
Proprietary Name / Established (USAN) names	Entresto / sacubitril and valsartan
Dosage forms / Strength	Film-coated tablets / strengths: 24 mg sacubitril and 26 mg valsartan 49 mg sacubitril and 51 mg valsartan 97 mg sacubitril and 103 mg valsartan
Proposed Indication(s)	(b) (4)
Recommended:	*Approval for the treatment of heart failure pending resolution of the outstanding product quality issues and agreement on labeling*

This secondary review is based on the following reviews:

Quality (5/15/15)	Wendy Wilson-Lee (Application Technical Lead), Anamitro Banerjee (Drug Substance), Sherita McLamore-Hines (Drug Product), Bogdan Kurtyka (Process), Robert Mello (Microbiology), Zhong Li (Facility), Salaheldin Hamed (Biopharmaceutics)
Pharmacology Toxicology (5/15/15)	William Link
Clinical Pharmacology (5/15/15)	Sreedharan Sabarinath, Luning Zhuang
Clinical (5/15/15)	Kimberly Smith (Efficacy), Tzu-Yun McDowell (Safety)
Statistical (5/20/15)	John Lawrence
Risk Evaluation and Mitigation Strategy (5/22/15)	Somya Dunn
Division of Pediatric and Maternal Health (5/26/15)	Miriam Dinatale
Division of Medication Error Prevention and Analysis (6/1/15 and 6/11/15)	Janine Stewart
Patient Labeling (6/4/15)	Karen Dowdy, Zarna Patel
Office of Prescription Drug Promotion (6/8/15)	Zarna Patel
Office of Scientific Investigations (6/8/15)	Sharon Gershon

1. Introduction

LCZ696 is a fixed-dose combination of valsartan and sacubitril. The proposed indication is as follows: [redacted] (b) (4)

There is widespread agreement among members of the review team that the submitted data support the efficacy and safety of the product for its intended use. There are, however, outstanding CMC issues and agreement needs to be reached with the applicant on labeling. In addition, Dr. Lawrence, the statistical reviewer, has raised concern that the application does not adequately address the Agency's combination policy.

2. Background

Heart failure affects over 5 million patients in the United States; approximately half of these patients have heart failure with a reduced ejection fraction (HFrEF). HFrEF is associated with significant morbidity and mortality. Although a number of agents have been approved to treat HFrEF (most based on their effect on cardiovascular mortality and/or heart failure hospitalizations), there is still significant unmet need for therapies that can improve outcomes in these patients.

LCZ696 is a fixed-dose combination of valsartan, an ARB, and sacubitril, a neprilysin inhibitor. Valsartan, as monotherapy, is indicated for the treatment of heart failure (NYHA class II-IV). According to the label, valsartan significantly reduced hospitalizations for heart failure in this population. Sacubitril is an NME. Although at present there is no approved neprilysin inhibitor, as discussed later in the review, there is some experience with this class of agents.

[redacted] (b) (4) the IND to develop LCZ696 as a treatment for chronic heart failure followed in October 2009. There were a number of discussions with Novartis over the course of the product's development. Topics included the active comparator in the applicant's phase 3 trial (choice of active comparator and dose), what the applicant would need to do to address the combination policy, and the use of [redacted] (b) (4). These same topics have also generated discussion during the review of the applicant's NDA and hence are discussed in greater detail below.

- *The combination policy and the proposed active comparator.* In June 2009, Novartis submitted a request for Special Protocol Assessment of their multi-center, randomized, double-blind phase 3 trial to evaluate the efficacy and safety of LCZ696 compared to enalapril in treating patients with chronic heart failure; the Agency responded with a No-Agreement Letter. In that letter, the Agency indicated that the trial would need to assess whether one of the components of the combination was sufficient for the entirety of the benefit. As an alternative to the proposed comparison with enalapril, the Division suggested an add-on study to evaluate whether sacubitril added to the benefit of valsartan.

The Agency also voiced concern that the proposed dose of the active comparator (10 mg bid of enalapril) was inadequate since labeling recommended titration to a higher dose.

At a follow-up Type A meeting in August 2009, the Division stated that "…the issue of whether or not both components of LCZ696 contribute to the overall effect may or may not matter" and indicated that it would not matter if Novartis showed an effect on nonreversible events, such as mortality, myocardial infarctions, or strokes. During the meeting, Novartis asserted that a NEP inhibitor alone study would be ethically impossible and that there was evidence that NEP inhibitors alone would not be effective. The Division asked the sponsor to submit for review any data or literature supporting their assertion that sacubitril alone could not be the sole contributor to the effect of the combination product. The Division also indicated that if sacubitril (vs. placebo) was studied on top of background therapy, (b) (4) but would not approve a combination product. Several months after the Type A meeting, Novartis opened their IND with their phase 3 trial, a randomized, double-blind trial comparing LCZ696 to enalapril.

- (b) (4) In January 2010, members of the review Division and the Study Endpoints and Label Development Team met with Novartis to discuss the use of (b) (4) The Agency encouraged the sponsor to develop a measure that captured the important symptom concepts that define chronic heart failure for the target population. The Agency also noted that, based on the submitted qualitative study data, the most important symptom concepts appeared to be shortness of breath, tiredness, swelling, and pain.

  According to the minutes, the Agency stated that the (b) (4)

In April 2014, Novartis notified the Agency that the Data Monitoring Committee for their phase 3 trial had recommended early closure for compelling efficacy. The Agency subsequently granted fast track designation, rolling review and priority review.

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1 (b) (4)

3. CMC

According to Dr. Wilson, at this time, the overall product quality recommendation is pending completion of facilities inspections and evaluations. Agreement also needs to be reached on the dissolution specification.

Drug Substance: Sacubitril (b) (4) and valsartan are designated as the regulatory drug substance but are (b) (4) under the applicant's quality system.

Chemical names and structure:
Sacubitril: 4-{[(1*S*,3*R*)-1-([1,1'-Biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoic acid.
Valsartan: *N*-Pentanoyl-*N*-{[2'-(1*H*tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl}-L-valine

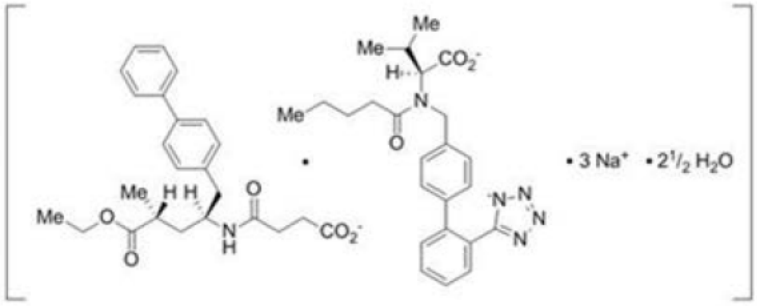

Figure 1: Structural Formula of Sacubitril Valsartan Sodium hydrate

Drug Product: The drug product is a fixed-dose combination available in the following strengths: 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan.[2] Inactive ingredients include microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate, talc, and colloidal silicon dioxide.

Expiration Date and Storage Conditions: A 24-month drug product expiration date has been granted when stored at a controlled room temperature and protected from moisture in the intended container closure. The drug product is packaged in bottles and unit dose blister packages as described on pages 6 and 7 of the Quality Review.

Facilities review/inspection: As noted above, facilities inspections have not been completed.

Post-marketing agreements: The applicant has submitted comparability protocols supporting post-approval changes to 1) the drug product manufacturing site, control, batch size and process and 2) the (b) (4) intermediate manufacturing site, control, batch size and process. According to the Quality Review, these protocols are acceptable.

[2] During the product's development and in the published trials, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg was referred to as LCZ696 50 mg, 100 mg and 200 mg, respectively.

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