CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s000

OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memo

Date	July 7, 2015
From	Ellis F. Unger, MD, Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	207620
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	December 17, 2014
PDUFA Goal Date	August 17, 2015
Proprietary Name/ Established (USAN) Name	Entresto sacubitril and valsartan
Dosage Forms/ Strengths	24 mg sacubitril and 26 mg valsartan; film-coated tablets 49 mg sacubitril and 51 mg valsartan; film-coated tablets 97 mg sacubitril and 103 mg valsartan; film-coated tablets
Indication originally sought by applicant (see page 29 for final)	(b) (4)
Action:	Approval

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Alexis Childers, RAC
Medical Officer Clinical Review	Kimberly Smith, MD (Efficacy), Tzu-Yun McDowell, PhD (Safety)
Clinical Pharmacology/Pharmacometrics	Luning Zhuang PhD, Sreedharan Sabarinath, PhD
Statistical Review	John Lawrence, PhD; James Hung, PhD
Pharmacology Toxicology	William Link, PhD, Al De Felice, PhD
Executive Cancer Assessment Committee	Paul Brown, PhD (acting chair)
Office of New Drug Quality Assessment	Wendy Wilson-Lee, PhD (technical lead), Anamitro Banerjee, PhD (drug substance), Sherita McLamore-Hines, PhD (drug product), Bogdan Kurtyka, PhD (process), Zhong Li, PhD (facility)
Office of Scientific Investigations	Sharon K. Gershon, PharmD
Division of Pediatric and Maternal Health	Miriam Dinatale, DO
Biopharmaceutics Review	Salaheldin Hamed, PhD
Carcinogenicity Study	Mohammad Rahman, PhD; Karl Lin, PhD
Division of Medication Error Prevention and Analysis	Janine Stewart, PharmD; Alice Tu, PharmD
Risk Management Review	Danny Gonzales, PharmD, MS, Kim Lehrfeld, PharmD
Cross-Discipline Team Leader	Aliza Thompson, MD
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge, MD, PhD

1. Introduction

Novartis is seeking approval of LCZ696 for the proposed indication: (b) (4)

With a number of changes to the label, including changes to the indication statement (see Summary/Conclusions), the review team endorses approval, and I agree with their recommendation.

2. Background

Description:

LCZ696 is a (b) (4), a type of sodium salt complex, consisting of valsartan and sacubitril anions, sodium cations, and water. These 4 individual components are present in a 2:2:6:5 molar ratio, and are not ionically bound. The drug product contains the LCZ696 (b) (4) as the active ingredient. The active moieties in the LCZ696 (b) (4) are sacubitril and valsartan.

The description of the chemical nature of the active ingredient was an important issue that had to be negotiated with the applicant. The Office of Pharmaceutical Quality (OPQ) initially recommended use of the term (b) (4)" to describe the tablet's active ingredient in Section 11 of labeling, whereas the applicant had proposed the term (b) (4)

In an addendum to the Quality review, OPQ noted that both descriptions correctly represent the chemical nature of the active ingredient and are scientifically valid. The structural X-ray diffraction data submitted demonstrate that the active ingredient meets the criteria delineated in FDA Guidance (b) (4) The active ingredient can also be considered a complex, however, based on the IUPAC Gold Book definition: a molecular entity formed by loose association involving two or more molecular entities (ionic or neutral); bonding is normally non-covalent.

(b) (4) the applicant's preferred description of the active ingredient, (b) (4) is correct, OPQ noted that the term (b) (4) OPQ is recommending use of the term "complex" be used to refer to the active ingredient in Section 11 of labeling, and the applicant has agreed.

Valsartan is a previously approved molecular entity, an angiotensin II receptor blocker (ARB), which is widely marketed for hypertension and heart failure as Diovan and generics. Sacubitril is a neprilysin inhibitor, a first-in-class new molecular entity (NME), although there is some experience with this class of agents, as discussed later in this memo.

Although the active ingredient in the tablet is a [redacted], it dissociates *in vivo* to the active moieties valsartan and sacubitril, and so it has been consistently viewed as a combination product from a regulatory perspective.

Disease Background:

Over 5 million people in the US have heart failure, about half of whom have reduced left ventricular ejection fraction or systolic heart failure. (Many patients with heart failure have preserved left ventricular systolic function, so-called "diastolic heart failure," for which there are no approved treatments.) According to the 2013 American College of Cardiology Foundation/American Heart Association "Guideline for the Management of Heart Failure," the lifetime risk of developing heart failure is 20% for the U.S. population ≥ 40 years of age, with over 650,000 new cases diagnosed annually (*J Am Coll Cardiol* 2013;e147-239). The incidence of heart failure increases with age: from ~2 per 100 individuals at age 65 to 69 to over 8 per 100 individuals at age 85 and over. As life expectancy increases in the US, the prevalence is anticipated to rise. Moreover, despite improvements in the pharmacologic and non-pharmacologic management of heart failure, 5-year survival rates are still only ~50%.

There is an excellent summary of current therapy for heart failure in the Clinical Review, page 14.

For the regulatory history, refer to the clinical review and the cross-discipline team leader review.

3. Product Quality

OPQ recommends approval from a drug product perspective.

As noted above, the active ingredient in LCZ696 is a [redacted] comprised of two active moieties – sacubitril and valsartan anions – with 1:1 stoichiometry. The other components are sodium cations and water. The [redacted] is synthesized using the drug substances sacubitril [redacted] and valsartan [redacted]. The [redacted] quickly dissociate *in vivo* to release sacubitril and valsartan.

Although designated as regulatory drug substances, it was agreed that the applicant's quality systems and standards control sacubitril [redacted] and valsartan [redacted] to produce the co-crystal. [redacted] specifications for sacubitril [redacted] and valsartan [redacted] include appropriate tests and acceptance criteria to ensure the identity, purity, strength, quality, and bioavailability of these compounds.

A 24-month drug product expiration date has been granted when stored at room temperature and protected from moisture in the intended container closure. The drug product is packaged in bottles and unit dose blister packages.

Based on firm inspectional history and data reviewed during the pre-approval inspections, OPQ found the manufacturing facilities to be acceptable.

Following discussions regarding the expression of strength in the carton and container labels, OPQ agreed on a compromise to allow use of a "/" between the sacubitril and valsartan in the established name, and found the carton and container labels acceptable.

Post-Marketing Commitment:

It was determined during the review that the dissolution data submitted for the clinical and the registration batches of the (b) (4) mg strength did not support the dissolution acceptance criterion proposed by the applicant (Q = (b) (4) % at (b) (4) minutes). (b) (4)

OPQ recommended that the applicant optimize the dissolution method and acceptance criterion, which would require a post-marketing commitment. It was noted that the control strategy for the current product (e.g., operating closely to the normal operating ranges for the clinical trial batch) would ensure the quality of the drug product.

In the absence of an adequate *in vitro* to *in vivo* relation and proper exposure-response data, FDA recommended establishment of a release specification at Q = (b) (4) % to ensure complete release of the drug substance.

There will be a post-marketing commitment with the following goals: 1) Development of a new dissolution method for all the strengths with demonstrated discriminating ability, (b) (4) and 2) Setting of the final dissolution acceptance criterion for Entresto (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg using the new method and the overall multipoint dissolution profile data from a minimum of 12 commercial batches/strength, manufactured under the same conditions as those used for the manufactured of the batches used in pivotal clinical trials.

The FDA would be open to the possibility of a (b) (4) OPQ reiterated that a justification would need to be provided, supported by data, before agreeing to (b) (4) for the drug product.

The applicant has agreed to this post-marketing commitment, and agreed to submit a development report by February 1, 2016, and the final report by July 1, 2016.

4. Nonclinical Pharmacology/Toxicology:

Salient findings in mice, rats, rabbits, and cynomolgus monkeys included renal juxtaglomerular hypertrophy/hyperplasia, renal tubular changes; decreased hemoglobin/hematocrit and reticulocytes; decreased heart weights (without histopathological findings); reversible focal gastric mucosal erosion, and emesis and diarrhea without histologic correlates. According to Dr. Link, these findings do not raise concerns for human use because they reflect adaptive responses and/or exaggerated pharmacodynamic responses to high doses.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.