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APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	May 22, 2015
Reviewer(s):	Somya Dunn, M.D. Division of Risk Management (DRISK)
Team Leader:	Kimberly Lehrfeld, Pharm.D., DRISK
Acting Deputy Division Director	Reema Mehta Pharm.D., M.P.H., DRISK
Drug Name(s):	LCZ696 (sacubitril and valsartan)
Therapeutic Class:	Angiotensin Receptor Neprilysin Inhibitor (ARNI)
Dosage and Route:	97 mg of sacubitril and 103 mg of valsartan twice daily orally
Application Type/Number:	NDA 207-620
Submission Number:	Supporting Document 5
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2014-2615

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1 INTRODUCTION

The purpose of this review is to document DRISK's evaluation of the need for a risk evaluation and mitigation strategy (REMS) for LCZ696 (sacubitril/valsartan) oral tablets, NDA 207-620. It was submitted by Novartis Pharmaceuticals Corporation (Novartis) and received in a three part submission due to the Sponsor being granted Fast Track Rolling Submission status; the submissions were received September 30, 2014, October 29, 2014 and December 17, 2014. The application is currently under review in the Division of Cardiovascular and Renal Products (DCRP). The Sponsor did not include a proposed REMS with the submission.

1.1 PRODUCT BACKGROUND

LCZ696 is a novel therapy that dissociates into valsartan and the pro-drug sacubitril (AHU377). Sacubitril is further metabolized to LBQ656. The LBQ656 component acts as an angiotensin receptor neprilysin inhibitor (ARNI) by inhibiting neprilysin (neutral endopeptidase enzyme: NEP). NEP is a zinc metalloendopeptidase that plays a role in turning off peptide signaling events at the cell surface.[i] The valsartan component blocks the angiotensin II type-1 (AT1) receptor (angiotensin II receptor blocker or ARB). Valsartan (Diovan) is an approved product (NDA 20-665, approved 1996) indicated for treatment of hypertension and heart failure.

The Sponsor formulated and studied three film-coated tablets of LCZ696 in strengths of 50 mg (24 mg of sacubitril / 26 mg of valsartan), 100 mg (49 mg of sacubitril / 51 mg of valsartan) and 200 mg (97 mg of sacubitril / 103 mg of valsartan).The proposed starting dose is (b) (4) twice a day and the dose should be doubled every two to four weeks as tolerated to reach the proposed target dose of 200 mg twice-daily.

LCZ696 is proposed to be indicated for the treatment of heart failure New York Heart Association (NYHA) class II–IV (b) (4)

1.2 DISEASE BACKGROUND

Chronic heart failure (HF) is a common syndrome affecting approximately 2 to 3% of the population in many industrialized countries. Coronary artery disease (CAD) is the cause of approximately two-thirds of cases of systolic HF, although hypertension and diabetes are probable contributing factors in many cases. There are many other causes of systolic HF, which include previous viral infection, alcohol abuse, chemotherapy (e.g. doxorubicin or trastuzumab), and "idiopathic" dilated cardiomyopathy.

HF due to left ventricular dysfunction, also referred to as HF with reduced Ejection Fraction (HFrEF), is substantial and growing medical problem that effects millions of adults in the United states. Class I recommendations in the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for the pharmacologic treatment of HFrEF include:[ii]

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- Angiotensin-converting enzyme inhibitors (ACE-I), or ARB if ACE inhibitors are not tolerated, to reduce morbidity and mortality
- Beta-blockers (bisoprolol, carvedilol, or controlled release/extended release metoprolol succinate) to reduce morbidity and mortality
- Diuretics and a low-sodium diet, if there is evidence of fluid retention to improve symptoms
- Aldosterone antagonists (provided estimated creatinine > 30 mL/min and K+ < 5.0
- Hydralazine/isosorbide dinitrate (for African Americans with persistently symptomatic NYHA class III-IV heart failure) receiving optimal therapy with ACE inhibitors and beta blockers, to reduce morbidity and mortality.

In addition to the indicated pharmacotherapies for HFrEF (i.e., digoxin, ACE inhibitors, beta-blockers, etc.), Class I recommendations for the device treatment of HFrEF, including the implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT), are as follows:

- ICD therapy for primary prevention of sudden cardiac death (SCD) to reduce total mortality in selected patients with nonischemic dilated cardiomyopathy (DCM) or ischemic heart disease at least 40 days post-myocardial infarction (MI) with left ischemic heart disease at least 40 days post-myocardial infarction (MI) with left ventricular ejection fraction (LVEF) of 35% or less and NYHA class II or III symptoms on chronic guideline-directed medical therapy (GDMT), who have reasonable expectation of meaningful survival for more than 1 year
- CRT for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT
- ICD therapy is for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF of 30% or less, and NYHA class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for more than 1 year.

Despite these treatments, which have substantially improved outcomes in the past two decades, HF can severely affect the patient's quality of life and the prognosis continues to be poor. New therapies are continuously sought.

1.3 REGULATORY HISTORY

February 5, 2009: The IND for LCZ696 was submitted

April 22, 2009: Pre-IND Meeting--no major safety issues discussed. Carcinogenicity assessments were discussed.

June 2, 2009: Pre-IND meeting--to discuss the Sponsor's proposed non-clinical and clinical development plan for the HF indication using LCZ696.

May 23, 2014: Novartis requests Fast Track Designation because an independent Data Monitoring Committee unanimously recommended early closure of the PARADIGM-HF study due to observed superior efficacy of LCZ696 versus enalapril.

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June 23, 2014: Novartis is granted Fast Track Designation, allowing a rolling submission of the NDA.

June 25, 2014: Pre NDA meeting. Discussion of REMS was postponed. The Agency requested that the Sponsor address the potential for theoretical safety concerns such as neurological diseases (from amyloid accumulation) and cancer promotion. They also requested an analysis for neurological Adverse Events (AEs) of interest.

September 22, 2014: Type C meeting--Novartis proposed the following labeling:
Contraindication: (b) (4)

Warnings & Precautions: *To include risk of angioedema*

The Agency declined to give advice without specifics of cases for angioedema but did agree to the idea of a (b) (4). DRISK commented that a REMS would likely not be needed.

September 30, October 29 and December 17, 2014: The NDA is submitted in three parts. The initial submission, 9/30/14 requests Priority Review.

February 10, 2015: DCRP and DRISK discuss the need for a REMS at an internal meeting to discuss known safety issues. A preliminary decision was that a REMS would likely not be needed.

February 12, 2015: Submission is filed; Priority Review status is granted.

March 11, 2015: DCRP and DRISK met internally and determined that a REMS would not be needed.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The materials that informed this review were:

- Novartis Pharmaceuticals Corporation *Clinical Overview for LCZ686* received 12/17/14, Seq 0002
- Novartis Pharmaceuticals Corporation *Summary of Clinical Safety for LCZ686* received 12/17/14, Seq 0002
- Novartis Pharmaceuticals Corporation *Draft Labeling for LCZ686* received 12/17/14, Seq 0002
- Novartis Pharmaceuticals Corporation *Summary of Clinical Safety Amendment 120 day update for LCZ686* received 4/15/15, Seq 0029
- Dr. Tzu-Yun McDowell FDA DCRP Safety Review, submitted May 15, 2015.
- Dr. John Lawrence and Dr. Norman Stockbridge, FDA DCRP NDA 21-188 Review for omapatrilat, 6/5/2002.

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