# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

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# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**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

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| Date: | May 22, 2015 |
| Reviewer(s): | Somya Dunn, M.D.<br>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]

- 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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# 3 REVIEW OF SAFETY CONCERNS

## 3.1 OVERVIEW OF CLINICAL PROGRAM

The clinical program evaluated safety of LCZ696 at doses up to the target dose of 200 mg twice daily in HF patients treated for up to 4.3 years. The safety data came primarily on PARADIGM-HF (study CLCZ696B2314) which had 8442 randomized patients with chronic HF, NYHA functional class II – IV, and systolic dysfunction HFrEF. From this study, a total of 10,513 patients were exposed to enalapril and 9419 patients were exposed to LCZ696 during the run-in period. After the run-in period, a total of 8442 patients were randomized to either LCZ696 or enalapril during the double-blind phase in a 1:1 ratio.

Additional safety data was compiled from two phase 2 studies, CLCZ696B2214 (PARAMOUNT-HF) and CLCZ696B2228 (TITRATION). Six supportive studies in patients with hypertension were also used to give additional safety data.

The consolidated safety database for LCZ696 includes approximately 15,000 patients (10106 (pivotal study) + 3874 (phase 2 studies) + 1117 (supportive studies)). All these patients have been exposed to LCZ696 at varying doses and for varying treatment durations.

Heart failure is the most common cause of hospital admission in this patient population. Cardiovascular death and HF hospitalization are both closely related to progressive worsening of HF and both are thought to be modifiable by treatments that improve HF. This rationale led to the disease-specific composite efficacy endpoint of time to CV death or HF hospitalization used in the pivotal trial in this clinical program.

## 3.2 EFFICACY

PARADIGM-HF was terminated early based on efficacy results evaluated at the third interim analysis. This was due to a recommendation of the trial's independent data monitoring committee. LCZ696 reduced the risk of the primary composite endpoint based on a time-to-event analysis (HR 0.80; 95% CI 0.73, 0.87; 1-sided p=0.0000002). LCZ696 treated subjects experienced both fewer first heart failure hospitalizations (537 [12.8%] vs. 658 [15.6%]) and fewer cardiovascular deaths as the first event (377 [9.0%] vs. 459 [10.9%]) compared with enalapril subjects.[iii]

## 3.3 SAFETY CONCERNS

PARADIGM-HF served as the main safety database. The Sponsor's analysis showed that the incidence of AEs by system organ class (SOC) was comparable between the LCZ696 and enalapril groups (81.4% vs. 82.8%, respectively). Some of the most frequently occurring primary SOC events (occurring in ≥10% of patients in either treatment group) were cardiac disorders, infections and infestations, metabolism and nutrition disorders.

During the randomization phase of PARADIGM-HF, there were more deaths over all in the enalapril arm. Of the deaths, the most common was fatal myocardial infarction (3.5%



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of cardiovascular deaths in the LCZ696 group versus 3.94% in the enalapril group). Additionally, serious adverse events (SAEs) during the double blind period were lower in the LCZ696 group compared to the enalapril group (46.1% vs. 50.7%, respectively). SAEs were predominantly cardiac disorder events. Overall the two treatment arms in the pivotal study had similar patterns for drop outs and discontinuations. Cardiac failure was the most common AE leading to study discontinuation in both groups (2.6% in enalapril group and 2.4% in the LCZ696 group).

**AEs of Special Interest**

The AE of special interest with LCZ696 are hypotension, renal impairment, hyperkalemia, angioedema, accumulation of amyloid and teratogenicity.

*Hypotension, renal impairment and hyperkalemia*

These concerns are due to class effects associated with renin–angiotensin–aldosterone system (RAAS) inhibitors. The Sponsor has proposed that these AEs be addressed with labeling for LCZ696. Hypotension, renal impairment and hyperkalemia are proposed for the AE and Warnings and Precautions section of the label. DCRP reports that these rates in the clinical trial for LCZ696 compared to enalapril during the treatment period were hypotension 24.4% vs. 18.6%, renal impairment 11.9% vs. 14.3% and hyperkalemia 16.2% vs. 17.6% respectively.[iii] These labeling proposals are acceptable to the Agency. Of note, in the Diovan label, hypotension is also a Warning and Precaution; and hyperkalemia is listed as an AE.

*Angioedema*

Another class effect associated with renin–angiotensin–aldosterone system (RAAS) inhibitors is angioedema. This risk is of concern with LCZ696 due to the Agency history of omapatrilat, a vasopeptidase inhibitor that inhibits ACE and neutral endopeptidase (NEP) that was under review from 2000-2002. Omapatrilat could not be approved due to the unacceptable high rate of angioedema (in the clinical program the rate was 2.2% versus 0.7% in patients in the comparator--enalapril). In the case of omapatrilat, there were two mechanisms of action that cause significant angioedema contributing to the high rates. LCZ696 contains one component known to cause angioedema, NEP. Of note, although, angioedema has been seen in patients treated with ARBs, it was not an AE significant enough to be classified as a Warning and Precaution. For example, for Diovan, it is mentioned in the label only as a hypersensitivity reaction seen postmarketing.

In the PARADIGM-HF trial double-blind period, the incidence of angioedema was low in the overall population (19 events, rate of 0.2%), and compared to an enalapril rate of 0.5%. None of these events involved airway compromise or death. Most events were non-serious and did not require treatment or were treated with antihistamines. Most angioedema cases occurred within 180 days after randomization. The incidence of angioedema was higher in black patients treated with LCZ696 than enalapril in the double-blind period (2.4% and 0.5%, respectively); however the number of black patients overall in the trial was very low (54 patients) limiting the interpretation of this finding. The higher rate of angioedema in black patients is seen as part of the class effect of ACE-I and currently in labeling for ACE-I. The Sponsor proposes to include this information



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in the label in the Warnings and Precautions as well as Adverse Reactions sections. The Agency is discussing a post marketing study to better characterize this risk.

*Drug-Drug Interaction and Angioedema*

There were three confirmed cases of angioedema in PARADIGM-HF that occurred in subjects given ACE inhibitor within < 36 hours of discontinuing LCZ696 or vice versa. The Sponsor proposed a labeling contraindication to address this, stating not to coadminister LCZ696 with ACE-I.

The Sponsor proposed a (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) The risk of this drug-drug interaction will best be mitigated through labeling (Warning and Contraindications) to inform prescribers and through drug-drug interaction screening at pharmacies for contraindicated medications.

DCRP requested that the Sponsor include a Patient Package Insert (PPI) with labeling to address this drug-drug interaction risk. There are PPIs for ARBs for the risk of teratogenicity; Diovan has a PPI for this (the risk of teratogenicity is discussed below). For LCZ696, the risk of the drug-drug interaction will be stated in the PPI, followed by the risk of teratogenicity. DRISK does not have any issues with the inclusion of a PPI for labeling.



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*Teratogenicity*

LCZ696 is considered a teratogen due to a class effect of drugs that act directly on the renin-angiotensin system. Valsartan carries a boxed warning for potential injury or death to a developing fetus. The proposed label for LCZ696 also carries this warning.

Patient labeling for other medications that treat HF that are in the same class as valsartan with a teratogenicity risk include a PPI, i.e. Edarbi (an angiotensin II receptor blocker with a PPI for risk to unborn baby). However, the Sponsor proposed (b) (4) . For LCZ696, this risk can be mitigated sufficiently with a PPI, as it is for ACE-Iand ARBs. The expected patient population (chronic HF patients) would include few females of reproductive potential as this condition is not commonly seen in patients younger than age 50.[iv] Additionally, likely prescribers (cardiologists and internists managing HF) are aware of the risk as a class effect and would be expected to counsel FRP patients. Therefore, the Sponsor was asked to submit a PPI to align with labeling of other products in the same class. The Sponsor submitted the requested labeling, which is under review by DCRP.

*Accumulation of Amyloid*

DCRP selected cognitive impairment as an AE of interest based the theory that inhibition of NEP could accentuate accumulation of beta amyloid in the brain increasing the risk of Alzheimer's disease. NEP is believed to be a major beta amyloid-degrading enzyme in the brain. Therefore, inhibition of NEP could accentuate accumulation of beta amyloid and theoretically increase the risk of Alzheimer's disease. In preclinical studies with LCZ696, monkeys had an increased accumulation of beta amyloid (β-Amyloid 1-38, 1-40 & 1-41) in the cerebrospinal fluid (CSF), but not in the brain tissue. In addition, administration of LCZ696 400 mg daily for two weeks in healthy subjects was associated with a 42% increase in CSF β-Amyloid 1-38 and a 50% increase in plasma β-Amyloid 1-40. DCRP asserts that the clinical significance of these findings is not known. In the clinical program, there were very few cognitive impairment related AEs. At this time the Sponsor proposes labeling in the Clinical Pharmacology section of the label that addresses this data and mentions that the clinical significance is unknown. The Division acknowledges that they will be working with the Sponsor on how to better assess this risk in the development program.

## 4 DISCUSSION

LCZ696 is a novel therapy with two active components: valsartan, an approved ARB, and sacubitril, an ARNI which inhibits NEP. It is proposed to be indicated for the treatment of heart failure NYHA class II–IV (b) (4) . Based on the currently available data, no AEs of concern were identified that would warrant a REMS. AEs that are consistent with other inhibitors of the RAAS were seen. The Sponsor has included a boxed warning and a PPI to address teratogenicity and appropriate labeling to address angioedema, hypotension, renal impairment, hyperkalemia and elevated amyloid levels that were identified during the drug



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development program. They have also addressed the need to discontinue ACE-I at least 36 hours prior to starting LCZ696 in the label as well as the PPI.

## 5 CONCLUSION/RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling and a PPI are not warranted for LCZ696. Based on currently available data, no safety concerns have been identified that cannot be discussed and communicated in the label.

Should DCRP raise concerns with risks discussed in this review, or identify additional risks associated with LCZ696 warranting more extensive risk mitigation or a formal REMS please send a consult to DRISK.

This serves as the primary DRISK review for LCZ696 under NDA 207-620. Please notify DRISK if you have any questions.

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[i] Turner, A.J. et al The neprilysin (NEP) family of zinc metalloendopeptidases: genomics and function. Bioessays. 2001 Mar;23(3):261-9.

[ii] Yancy et al, Circulation. 2013;128:e240-e327

[iii] Smith, Kimberly. LCZ696 Clinical Efficacy Review, DCRP, FDA submitted May 15, 2015.

[iv] Redfield M. et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA: 2003; 289,194–202.



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/s/

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SOMYA V DUNN
05/22/2015

REEMA J MEHTA
05/22/2015
I concur.