# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207620Orig1s000

# SUMMARY REVIEW

# Cross-Discipline Team Leader Review

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| **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:<br>24 mg sacubitril and 26 mg valsartan<br>49 mg sacubitril and 51 mg valsartan<br>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:

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| **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: (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.

(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 (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.

[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

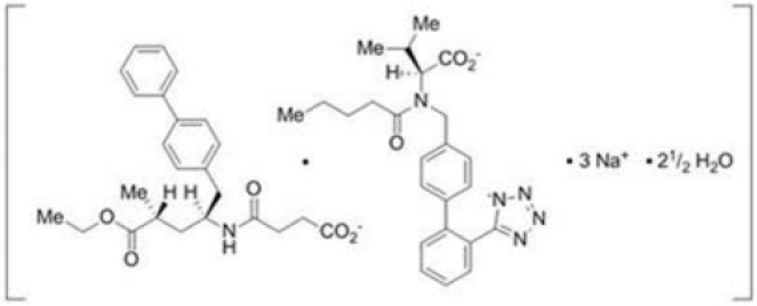


**Figure 1: Structural Formula of Sacubitril Valsartan Sodium hydrate**

*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.

# 4. Nonclinical Pharmacology/Toxicology

According to Dr. Link's review, the preclinical toxicology program was well-conducted and thorough and the application can be approved from a pharmacology/toxicology perspective.

*Toxicology:*[3] Target organs for LCZ696 and/or sacubitril toxicity included the kidney, red blood cells, heart and gastrointestinal tract. In brief, findings included: renal juxtaglomerular hypertrophy/hyperplasia in the rat and monkey and renal tubular changes (tubular basophilia, cytoplasmic vacuolation and single cell necrosis) in the monkey; reversible changes in hematology parameters (e.g., decreases in red blood cell count, hemoglobin concentration, hematocrit, and reticulocytes); decreased heart weights without histopathological findings; and reversible microscopic changes of focal glandular stomach mucosal erosion and mixed cell inflammation in rats and emesis and diarrhea without histologic correlates in the cynomolgus monkey. According to Dr. Link, these findings reflected adaptive responses or resulted from exaggerated pharmacodynamic responses to high doses and do not raise concern for safe use in humans. See pages 240 to 242 of Dr. Link's review for further discussion of these findings.

*Genotoxicity and carcinogenicity:* According to the Carcinogenicity study review, sacubitril had no effect on survival or tumor incidence in mice or rats. In genetic toxicity studies of LCZ696, sacubitril, and the active metabolite LBQ657, there was no evidence of genotoxic potential.

*Reproductive toxicology:* LCZ696 had no effect on fertility in rats. In embryo-fetal development studies in rats and rabbits, treatment with LCZ696 during organogenesis resulted in increased embryo-fetal lethality at clinically relevant doses. Teratogenicity (i.e., a low but dose-dependent increase in the incidence of hydrocephaly) occurred in rabbits administered maternally toxic doses of LCZ696. Pre- and postnatal development studies with valsartan and sacubitril indicate that exposure to LCZ696 during these periods could impair fetal development and survival.

*Other notable issues:* NEP is a major beta amyloid-degrading enzyme in the brain. Hence, there is a theoretical risk that NEP inhibition by LCZ696 could lead to accumulation of beta amyloid in the brain. To address this issue, the applicant assessed the effects of LCZ696 on amyloid-β concentrations in cerebrospinal fluid (CSF) and brain tissue in cynomolgus monkeys treated with a clinically relevant dose (50 mg/kg/day) of LCZ696 for 2 weeks. Treatment was associated with increases in Aβ 1-40, 1-42, and 1-38 levels in the CSF, without corresponding increases in Aβ levels in the brain. In a toxicology study in which cynomolgus monkeys were treated with 300 mg/kg/day of LCZ696 for 39 weeks (AUC exposure ~2X the maximum recommended human dose), there was no amyloid-β accumulation in the brain.

# 5. Clinical Pharmacology/Biopharmaceutics

According to the Clinical Pharmacology Review, the application can be approved from a clinical pharmacology perspective.

[3] Per Dr. Link's review, the pharmacologic targets of LCZ696 (the AT1 receptor and neprilysin) are evolutionarily conserved across mammalian species. Although there are some species differences in the rate of hydrolysis of sacubitril to LBQ657, all species are exposed to the same major compounds delivered by LCZ696.

*Mechanism of action:* LCZ696 inhibits neprilysin via LBQ657, the active metabolite of sacubitril, and blocks the angiotensin II type-1 receptor via valsartan. Effects of the renin-angiotensin-aldosterone system include vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling. Neprilysin inhibition blocks neprilysin-dependent proteolytic degradation of natriuretic peptides, thus enhancing the effects of natriuretic peptides. Effects of natriuretic peptides include promoting vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

*Pharmacokinetics:*
Absorption: Following oral administration, LCZ696 dissociates into sacubitril and valsartan. Absolute bioavailability of sacubitril from LCZ696 is estimated to be ≥ 60%. The absolute bioavailability of valsartan from LCZ696 is about 50% higher than the bioavailability of valsartan administered alone. Food does not have a clinically significant impact on systemic exposure.

Metabolism: Sacubitril undergoes metabolism via esterases to form the active moiety, LBQ657. LBQ657 is not metabolized further into any major metabolites. Valsartan does not undergo significant metabolism.

Distribution: Sacubitril, LBQ657, and valsartan are highly bound to plasma proteins (94-97%).

Elimination: Approximately 52% to 68% of sacubitril is excreted in the urine (primarily as LBQ657), with the remainder excreted in the feces. Approximately 83% and 13% of valsartan is excreted in the feces and urine, respectively.

Intrinsic factors affecting elimination: Age, sex, and body weight do not have a significant impact on exposure or efficacy outcomes. The effect of renal and hepatic impairment is discussed below.

- Renal impairment: Steady state pharmacokinetic parameters of sacubitril and valsartan were similar in patients with mild, moderate, and severe renal impairment and matched healthy subjects. In subjects with mild (CrCl 50 to < 80 mL/min), moderate (CrCl 30 to < 50 mL/min), and severe renal impairment (CrCl < 30 mL/min), steady state exposure of LBQ657 was 2.1 times, 2.2 times, and 2.7 times, respectively, that seen in healthy subjects. No study was conducted in patients undergoing dialysis. LBQ657 and valsartan are unlikely to be removed by dialysis as they are highly bound to plasma protein.
- Hepatic impairment: The exposures (AUC) of sacubitril, LBQ657 and valsartan increased by ~53%, 48%, and 19%, respectively in mild hepatic impairment relative to healthy subjects. The exposures (AUC) of sacubitril, LBQ657 and valsartan increased by ~245%, 90%, and 109% respectively in moderate hepatic impairment relative to healthy subjects. No study was conducted in patients with severe hepatic impairment.

Drug-drug interactions: CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, hence drugs that impact CYP450 enzymes are not expected to impact LCZ696 exposure. From a safety perspective, the main concern is for a pharmacodynamic as opposed to a pharmacokinetic interaction (i.e., angioedema with concomitant or proximate administration of an ACE inhibitor). Angiotensin converting enzyme degrades bradykinin and elevated bradykinin activity is thought to play a role in ACE inhibitor-induced angioedema.

Although not the major pathway for bradykinin degradation, neprilysin also degrades bradykinin. As discussed elsewhere in the review, the current label contains a contraindication against concomitant use with an ACE inhibitor or within 36 hours of switching from or to an ACE inhibitor.

*Pharmacodynamic effects:*
β-Amyloid concentrations: In healthy subjects, administration of LCZ696 400 mg once a day for 2 weeks was associated with a 42% increase in CSF β-Amyloid 1-38 relative to baseline and a 50% increase in plasma β-Amyloid 1-40. As noted in the clinical review, the clinical significance of these findings is not known.

QT effects: No significant QTc prolongation was observed with LCZ696 (400 mg and 1200 mg) in a thorough QT study.

*Proposed dosing regimen and dosing rationale:*
The proposed dosing regimen (starting dose of 49 mg/51 mg twice-daily doubled after 2 to 4 weeks to the target maintenance dose of 97 mg/103 mg) is based on the dosing regimen used in the LCZ696 run-in phase of the applicant's phase 3 trial. The maximum dose in the phase 3 trial was chosen based on an Emax model that showed no additional neprilysin inhibition (seen as an increase in cGMP) when the dose of LCZ696 was increased beyond 97 mg/103 mg per day; a twice-daily regimen was adopted to prolong the duration of cGMP elevation to 24 hours. The proposed target dose also provides systemic exposure to valsartan similar to that from 160 mg valsartan BID, the approved target maintenance dose of valsartan for heart failure. As discussed in the Clinical Pharmacology Review, a dose/exposure response analysis of the phase 3 trial was not feasible because pharmacokinetic data were collected in only 7% of subjects and the trial employed dose titration based on tolerability.

A lower starting dose (24 mg/26 mg twice-daily) is being recommended for patients not currently taking an ACE inhibitor or ARB and for patients on low doses of these agents. These populations were not included in the phase 3 trial as entry criteria specified a protocol-defined minimum dose of these agents, and entry into the LCZ696 run-in period required successful completion of the enalapril run-in phase. The recommendation to initiate these patients on a lower starting dose is based in part on the findings in a 12-week study in patients with HFrEF. The trial included a 5-day run in period in which all subjects were treated with 24 mg/26 mg of LCZ696 twice-daily. Following the run-in phase, subjects were randomized to 49 mg/51 mg twice-daily titrated to 97 mg/103 mg twice-daily or 24 mg/26 mg twice daily titrated to 49 mg/51 mg twice-daily then 97 mg/103 mg twice-daily (see Figure 5 of the Clinical Pharmacology Review). In this study more subjects who were naïve to previous ACE inhibitor or ARB therapy or on low dose therapy were able to achieve and maintain the target dose when LCZ696 was up-titrated using the more gradual regimen.

Based on pharmacokinetic and/or safety considerations, a lower starting dose (24 mg/26 mg twice-daily) is also being recommended in patients with severe renal impairment and moderate hepatic impairment. Since the dose can be titrated based on tolerability and because the effect of renal impairment differs by component, the target maintenance dose will remain 97 mg/103 mg in these populations.

# 6. Clinical Microbiology

The product is not an antimicrobial. According to the Quality Review, the tests and proposed acceptance criteria for microbial burden are adequate for assuring the microbial quality of the drug product.

# 7. Clinical/Statistical- Efficacy

*Overview of PARADIGM-HF*

In support of the proposed indication, the applicant conducted a single phase 3 trial, PARADIGM-HF. PARADIGM-HF was an international, randomized, double-blind, double-dummy, parallel group, event-driven, active-controlled trial comparing LCZ696 with enalapril in 8,442 patients age ≥ 18 with NYHA class II to IV chronic heart failure and an LVEF ≤ 40% (≤ 35% per protocol amendment 1). The trial's primary endpoint was the time to first heart failure hospitalization or CV death. Secondary endpoints included:

- time from randomization to all-cause death;
- change from baseline (randomization visit) in the clinical summary score for heart failure symptoms and physical limitations (as assessed by KCCQ) at 8 months;
- time from randomization to new onset of atrial fibrillation[4];
- time from randomization to first occurrence of: a 50% decline in eGFR relative to baseline; a >30 mL/min/1.73 m2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73 m2; or ESRD.

To be eligible for enrollment, patients had to have been on an ACE inhibitor or ARB at a stable dose of at least 10 mg/day of enalapril or a protocol-defined equivalent agent and on a stable dose of a beta-blocker (unless contraindicated or poorly tolerated) for at least four weeks before screening. After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril (10 mg twice-daily), followed by LCZ696 100 mg (equivalent to 49 mg sacubitril/51 mg valsartan) twice-daily, increasing to 200 mg (equivalent to 97 mg sacubitril/103 mg valsartan) twice-daily. Subjects who successfully completed the sequential run-in periods were randomized to receive either LCZ696 or enalapril 10 mg twice-daily (see figure below).

[4] Time from randomization to new onset of atrial fibrillation was added as a secondary endpoint in Protocol Amendment 3. Although somewhat of a late addition to the protocol (at the time of the amendment, ~64% of primary endpoint events had accrued), as discussed later in the review, no effect was seen on this endpoint.

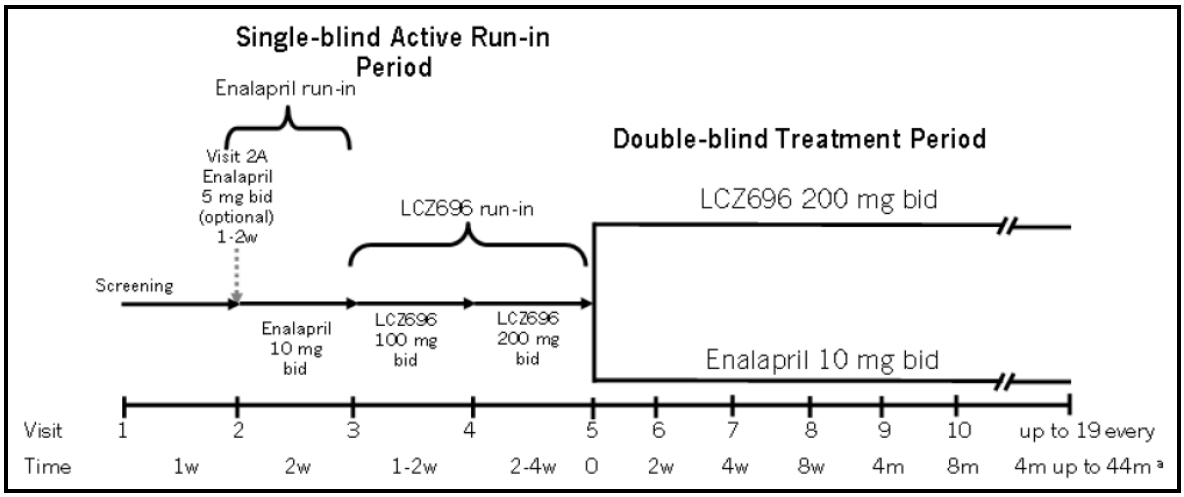


**Figure 2: Paradigm HF Study Design**
Source: Figure 9-1, Clinical Study Report for PARADIGM HF

PARADIGM-HF was designed to have 80% power to detect a 15% reduction in cardiovascular mortality based on the following assumptions: a 7% annual cardiovascular death rate in the enalapril arm, an enrollment period of 18 to 22 months, and a minimum follow-up duration of 21 months. Based on the projected sample size (7980 patients to obtain 1,229 cardiovascular deaths) and assuming a 14.5% event rate for the primary composite endpoint in the enalapril arm, 2410 composite endpoint events were expected, giving the trial 97% power to detect a 15% reduction in the primary composite endpoint.

The statistical analysis plan specified three interim analyses to assess for efficacy at 1/3, 1/2, and 2/3 of primary endpoint events (approximately 804, 1205 and 1607 patients, respectively, with a primary endpoint event). The Haybittle-Peto type of boundary was used to assess superiority with an alpha of 0.0001 (one-sided) spent at the first interim analysis and 0.001 (one-sided) at the second and third interim analyses. Both the primary composite endpoint and the cardiovascular death component would need to meet the boundary to terminate the trial early for efficacy.

According to the statistical analysis plan, the primary composite endpoint would be analyzed using a Cox regression model with terms for treatment and region and that the primary efficacy analysis was to include all positively adjudicated events occurring between randomization and March 31, 2014 (the date the trial was terminated early for efficacy). The analysis would be based on the full analysis set, which was defined as all randomized patients excluding misrandomized patients who did not qualify for randomization but were inadvertently randomized and did not receive study drug. [5]

If the primary endpoint was statistically significant, then the secondary endpoints would be tested using the same alpha as used for the primary endpoint at whatever time point the study was stopped. Testing of the four secondary endpoints would be done using a sequentially

[5] The statistical analysis plan also stated that "Further exclusions could be justified in exceptional circumstances (e.g., serious GCP violations)," and ultimately, additional subjects were excluded for such violations.

rejective multiple test procedure. As shown in Figure 1 of Dr. Lawrence's review, the alpha was initially split between the first two secondary endpoints, with 0.8α allocated to all-cause mortality and 0.2α allocated to the KCCQ. If both hypotheses were rejected, the full alpha was to be allocated to the next secondary endpoint on the testing chain; if only one of the initial hypotheses was rejected, the alpha allocated to the rejected hypothesis would then be allocated to the next secondary endpoint.

*Results*

Demographics

The baseline demographics of subjects who were randomized into the double-blind treatment period are shown in Tables 9-12 of the Clinical Review. As a whole, the two treatment arms were well-matched with regard to baseline characteristics. The mean age was 64 years and the majority of subjects were male (78%). Approximately 5% of subjects were enrolled at sites in the United States and approximately 5% of randomized subjects were black.

Most subjects (70%) were NYHA Class II, 24% were NYHA Class III and fewer than 1% were NYHA Class IV. Mean ejection fraction was ~29%, mean baseline eGFR was 68 mL/min/1.73m$^2$, mean systolic blood pressure was in the low 120's and mean heart rate was in the low 70's. The majority of subjects were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%) at baseline. Overall, only 15% of subjects had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D); however device use was reported in 60% of subjects enrolled at sites in the United States.

Disposition

A total of 10,521 subjects entered the run-in period. Of these, 1,102 subjects failed the enalapril run-in period and 982 failed the LCZ696 run-in period (10.5% and 10.4% of subjects entering the respective run-in periods). As shown in Table 15 of the Clinical Review, the most common reason for failing the enalapril and LCZ696 run-in periods was an adverse event, most often related to renal dysfunction, hyperkalemia, or hypotension.

The disposition of subjects in the double-blind treatment period is shown in the table below. Overall, follow-up was adequate to assess the key efficacy findings. Approximately 17% of subjects prematurely discontinued therapy in the LCZ696 arm as compared with 19% in the enalapril arm. Vital status was unknown in 20 (0.2%) subjects. The most common reason for treatment discontinuation during the double-blind treatment period was an adverse event (12.1% of subjects randomized to enalapril and 10.4% of subjects randomized to LCZ696).

**Table 1: Subject disposition during the randomized double-blind period**

| | **Enalapril n (%)** | **LCZ696 n (%)** |
|---|---|---|
| Randomized | 4233 (100) | 4209 (100) |
| Not treated | 4 (0.1) | 6 (0.1) |
| Primary efficacy population (full analysis set) | 4212 (99.5) | 4187 (99.5) |
| Excluded | 21 (0.5) | 22 (0.5) |
| Misrandomized[1] | 2 (0.1) | 4 (0.1) |
| Site excluded for GCP violations | 19 (0.5) | 18 (0.4) |
| Completed study on treatment | 3379 (79.8) | 3441 (81.8) |
| Alive at study termination | 2869 (67.8) | 3011 (71.5) |
| Prematurely discontinued study treatment | 815 (19.3) | 729 (17.3) |
| Did not complete study | 18 (0.4) | 17 (0.4) |
| Withdrew consent | 13 (0.3) | 15 (0.4) |
| Vital status unknown | 4 (0.1) | 9 (0.2) |
| Lost to follow-up (vital status unknown) | 5 (0.1) | 2 (0.1) |

[1]Subjects who failed the run-in period for whom IVRS randomization calls were erroneously performed but who never received study medication.
Source: Table 16, Clinical Review.

Primary endpoint findings

The trial was stopped for efficacy at the third interim analysis. As of the analysis cut-off date, the primary endpoint (death from cardiovascular causes or hospitalization for heart failure) had occurred in 914 subjects (21.8%) in the LCZ696 arm and 1117 patients (26.5%) in the enalapril arm (HR of 0.80; 95% CI 0.73; 0.87; 1-sided p=0.0000002). The Kaplan-Meier plot of the time to first event showed continued separation of the curves over time. As shown in the table below, the treatment effect reflected a reduction in both components of the composite. The results for the primary composite endpoint were for the most part consistent across the subgroups examined.

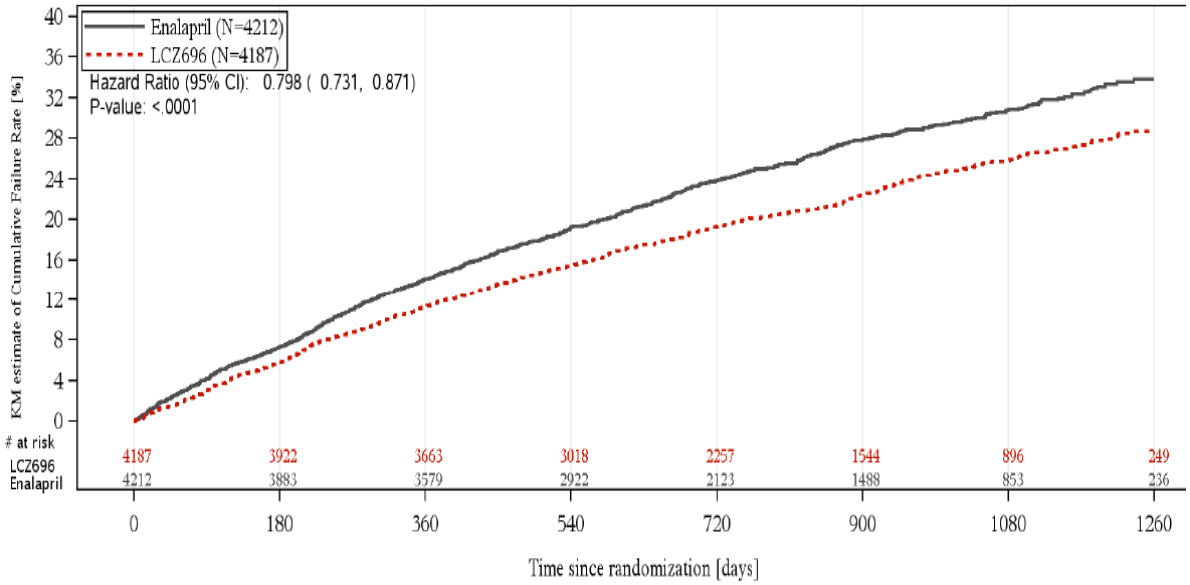


**Figure 3: Kaplan-Meier plot for the primary composite endpoint (CV death or HF hospitalization)**
Source: Figure14.2-1.2, Clinical Study Report for PARADIGM HF

**Table 2: Primary Composite Endpoint (CV death or HF Hospitalization)**

| | **Enalapril (N=4212) n (%)** | **LCZ696 (N=4187) n (%)** | **Hazard Ratio (95% CI; 1-sided p-value)** |
|---|---|---|---|
| **Primary Composite Endpoint*** | 1117 (26.5) | 914 (21.8) | 0.80 (0.73, 0.87; 0.0000002) |
| CV Death | 459 (10.9) | 377 (9.0) | |
| HF Hospitalization | 658 (15.6) | 537 (12.8) | |
| **Subjects with events at any time**** | 693 (16.5) | 558 (13.3) | 0.80 (0.71, 0.89) |
| CV Death | 658 (15.6) | 537 (12.8) | 0.79 (0.71, 0.89) |
| HF Hospitalization | | | |

*Analysis shows time to first component; ** Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.
Source: Tables 18 and 19, Clinical Review

Secondary efficacy endpoints

*Mortality:*

Since the trial met its primary endpoint, all-cause mortality was tested at the allotted alpha level (0.8 of the alpha used to test the primary endpoint). As shown in the table below, there were fewer deaths in the LCZ696 arm (HR of 0.84; 95% CI 0.76, 0.93; 2-sided p=0.0009). This finding was driven entirely by a lower incidence of cardiovascular mortality in subjects randomized to LCZ696.

**Table 3: All-cause death**

| | Enalapril (N=4212) n (%) | LCZ696 (N=4187) n (%) | Hazard Ratio (95% CI; 2-sided p-value) |
|---|---|---|---|
| All-cause death | 835 (19.8) | 711 (17.0) | 0.84 (0.76, 0.93; 0.0009) |
| Cardiovascular death | 693 (16.5) | 558 (13.3) | |
| Non-cardiovascular death | 109 (2.6) | 120 (2.9) | |
| Unknown | 33 (0.8) | 33 (0.8) | |

Source: Table 24, Clinical Review and Figure 5, Statistical Review

*KCCQ Clinical Summary Score:*

The change in the KCCQ Clinical Summary Score from baseline (randomization) to month 8 was also tested at its allocated alpha level (0.2 of the alpha used to test the primary endpoint).[6] At month 8, there was less of a decline in the Clinical Summary Score in the LCZ696 treatment arm, as compared to the enalapril arm, however the treatment effect was small- the least square mean of the difference was 1.6 (95% CI 0.6, 2.7) in subjects with a mean baseline score of ~76 (on a scale of 0 to 100). Although the p-value for this analysis was quite low, the endpoint did not meet its pre-specified alpha threshold.

**Table 4: KCCQ Clinical Summary Score**

| | Enalapril | | LCZ696 | | LSM of difference[1] (95% CI; 2-sided p-value) |
|---|---|---|---|---|---|
| | n (%) | LSM of CFB[2] (SE) | n (%) | LSM of CFB[2] (SE) | |
| Clinical Summary Score[3] | 3638 (94) | -4.6 (0.4) | 3643 (95) | -3.0 (0.4) | 1.6 (0.6, 2.7; 0.001[4]) |
| Physical Limitation | 3586 (93) | -4.1 (0.4) | 3588 (94) | -2.6 (0.4) | 1.5 (0.5, 2.6; 0.005) |
| Total Symptom | 3635 (94) | -5.2 (0.4) | 3640 (95) | -3.3 (0.4) | 1.9 (0.8, 3.0; 0.001) |
| Symptom Frequency | 3632 (94) | -5.2 (0.4) | 3637 (95) | -3.0 (0.4) | 2.2 (1.1, 3.3; <0.001) |
| Symptom Burden | 3635 (94) | -5.3 (0.4) | 3640 (95) | -3.6 (0.4) | 1.7 (0.6, 2.8; 0.003) |

[1]LSM of difference = LSM of (CFB [LCZ696] - CFB [Enalapril]); [2]CFB=change from baseline; [3]Subject numbers represent subjects in the full analysis set with a KCCQ CSS score at both baseline and month 8 and subjects who died. An additional 171 subjects with data available at month 4 but not month 8 are included in the secondary endpoint analysis. [4]One-sided p-value = 0.0007.
Source: Table 23, Clinical Review

In the prespecified analysis, subjects who died were assigned a Clinical Summary Score of zero for all subsequent visits. In the analysis shown below, subjects who died were treated as missing. The size of the treatment effect is smaller in this analysis (0.98; 95% CI 0.30, 1.66), suggesting that the difference between treatment arms is driven in part by the treatment effect on mortality.

[6] As discussed in the clinical review, a subject's KCCQ item responses were used to calculate Physical Limitation, Symptom Frequency, and Symptom Burden domain scores, which were then combined to produce the Total Symptom score (mean of the Symptom Frequency and Symptom Burden scores) and CSS (mean of Total Symptom and Physical Limitation scores).

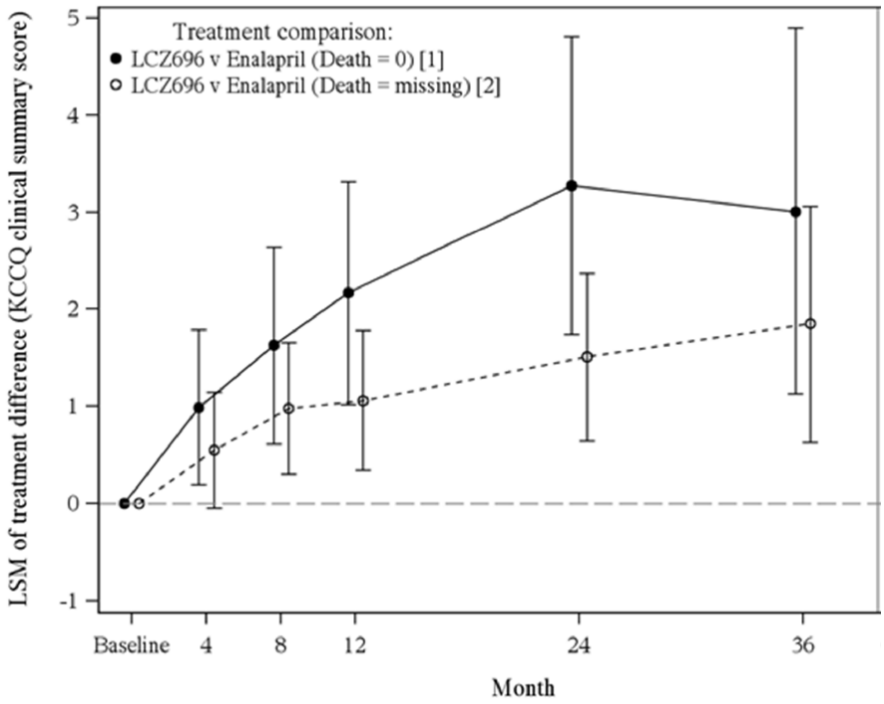


**Figure 4: LSM of treatment difference (KCCQ Clinical Summary Score) with different assumptions for death**
Source: Figure 11-5, Clinical Study Report for PARADIGM-HF

As discussed in the Clinical Review, the applicant also conducted responder analyses based on the number of subjects with at least a 5-point deterioration or improvement in the Clinical Summary Score from baseline to month 8, since according to the applicant a 5-point change represents a clinically meaningful change in score. Fewer LCZ696 subjects deteriorated by ≥5 points on the clinical summary score compared with enalapril subjects; however there was no difference in the number of subjects with a ≥ 5 point improvement (see table below). A plot of the cumulative distribution of the change in Clinical Summary Score from baseline to month 8 did not suggest a subpopulation with a more marked treatment response (see Figures below).

**Table 5: Proportion of subjects with a ≥ 5 point deterioration or improvement from baseline in KCCQ Clinical Summary Score at month 8**

| | **Enalapril n/N (%)** | **LCZ696 n/N (%)** | **Odds Ratio (95% CI)** |
|---|---|---|---|
| ≥ 5 point deterioration | 1283/3638 (35.3) | 1124/3643 (30.9) | 0.82 (0.74, 0.90) |
| ≥ 5 point improvement | 1113/3638 (30.6) | 1132/3643 (31.1) | 1.02 (0.93, 1.13) |

*Analysis assigns a score of zero following death. In an analysis in which subjects who died before month 8 were counted as missing, 31% of subjects on enalapril as compared to 27% of subjects on LCZ696 had a ≥ 5 point deterioration.
Source: Tables 38 and 39, Clinical Review, and Applicant's June 8, 2015 response to an FDA Information Request

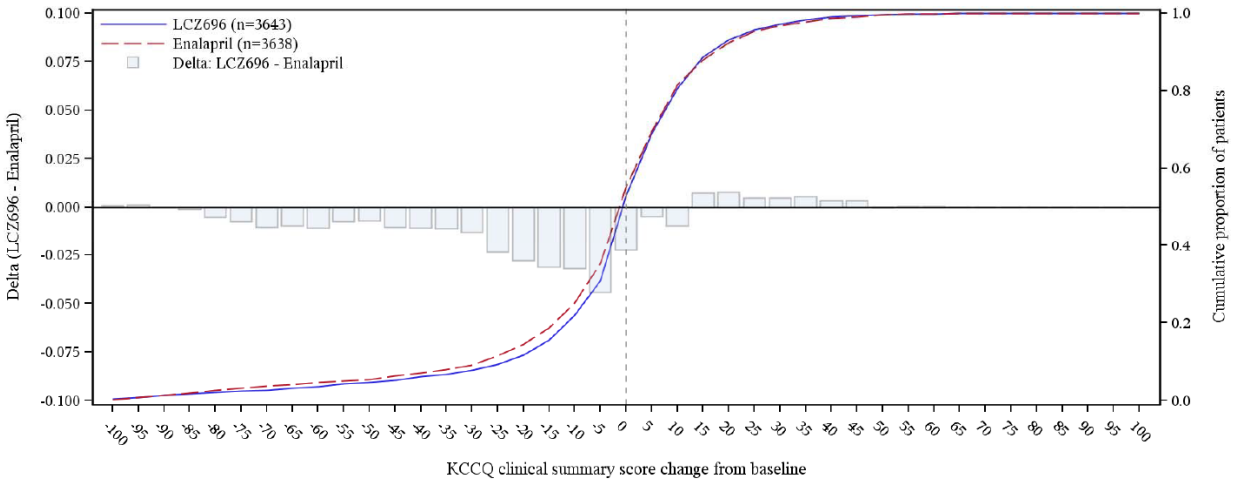


**Figure 5: Cumulative distribution of change from baseline in KCCQ at month 8, assigning a score of zero following death**
Source: Figure 14.2-2.4.post.02b, Clinical Study Report for Paradigm HF

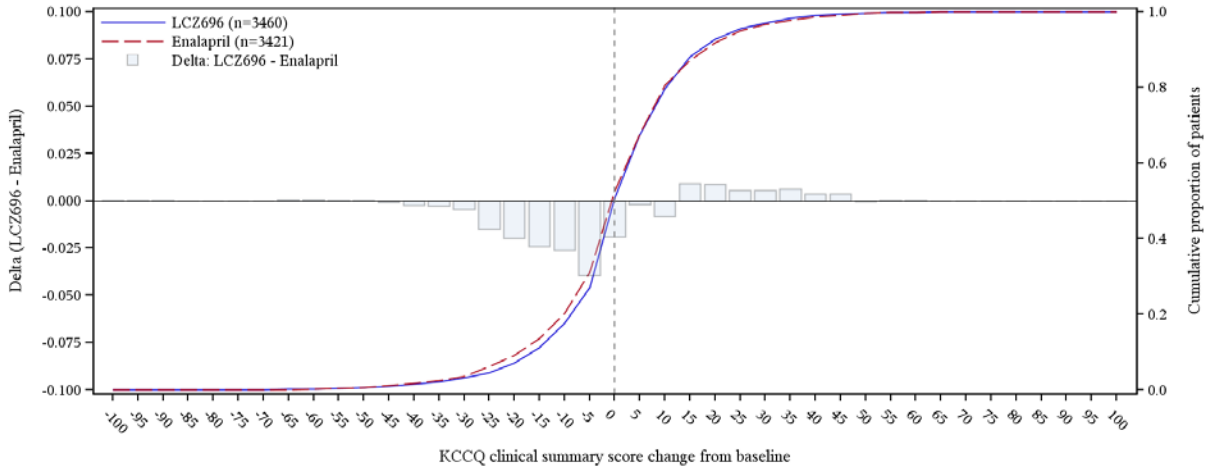


**Figure 6: Cumulative distribution of change from baseline in KCCQ at month 8 with deaths prior to month 8 counted as missing**
Analysis performed on subjects with KCCQ data at Month 8. For subjects who died prior to month 8, their KCCQ data at month 8 is treated as missing. These subjects are excluded from the analysis.
Source: Applicant's June 8, 2015 response to an FDA Information Request

*New onset atrial fibrillation and progression of renal disease:*
The results for the remaining secondary endpoints, new onset atrial fibrillation and the renal composite endpoint, are shown in the table below. There was no treatment effect on either endpoint.

**Table 6: Time to new onset atrial fibrillation and renal composite endpoint**

| | Enalapril n (%) | LCZ696 n (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Time to first new onset atrial fibrillation*** | 83 (3.2) | 84 (3.2) | 0.97 (0.72, 1.31) |
| **Time to renal composite endpoint** | 108 (2.6) | 94 (2.3) | 0.86 (0.65, 1.13) |
| 50% decline in eGFR | 42 (1.0) | 32 (0.76) | |
| >30 mL/min/1.73m$^2$ decline in eGFR to value <60 mL/min/1.73m$^2$ | 69 (1.6) | 77 (1.8) | |
| ESRD | 16 (0.4) | 8 (0.2) | |

*Analysis based on subset of FAS without a history of atrial fibrillation before randomization.
Source: Tables 25 and 26, Clinical Review

# 8. Safety

A total of 4,203 subjects received one or more doses of LCZ696 in the double-blind period of PARADIGM-HF; the median duration of exposure in trial was ~24 months. Based on the mechanism of action of the components of LCZ696 and the clinical experience with the pharmacologic classes, safety topics of interest included angioedema, hypotension, renal impairment, hyperkalemia and cognitive impairment. Each of these topics is discussed below; beyond these issues, there were no obvious safety signals.

*Angioedema*
Angioedema was a safety topic of interest in part because of the experience with omapatrilat, a combination ACE inhibitor and neprilysin inhibitor. In OCTAVE, an approximately 25,000 patient, 24-week, double-blind, randomized, active controlled trial in patients with hypertension, angioedema occurred in 2.2% of subjects treated with omapatrilat as compared with 0.7% of subjects treated with enalapril. Among black subjects, the incidence was 5.5% and 1.6% on omapatrilat and enalapril, respectively.[7]

In the LCZ696 development program, potential angioedema events were adjudicated by a blinded angioedema adjudication committee. In PARADIGM-HF, there were 54 confirmed cases of angioedema. Of these cases, 15 occurred during the enalapril run-in period (0.1% of subjects) and 13 occurred in the LCZ696 run-in period (0.1% of subjects). During the double-blind period, confirmed cases of angioedema occurred in 0.5% of subjects treated with LCZ696 and 0.2% of subjects treated with enalapril. No subject who developed angioedema required mechanical airway protection or died from airway compromise.

Because blacks are more susceptible to angioedema secondary to ACE inhibitors and agents that inhibit both neprilysin and ACE, Dr. McDowell examined the incidence of angioedema by race (blacks vs. non-blacks) and among black subjects enrolled at sites in the U.S. Approximately 5% of subjects entering each of the study periods (enalapril and LCZ696 run-in periods and double-blind treatment period) were black. In each run-in period, 2 black subjects (0.4%) developed angioedema. During the double-blind phase of the trial, the incidence of

[7] Source: FDA Advisory Committee Briefing Book For OMAPATRILAT Tablets NDA 21-188, Cardiovascular and Renal Drugs FDA Advisory Committee Meeting July 19, 2002

angioedema in black subjects in the enalapril arm was similar to that reported during the run-in phase (1 out of 214 subjects, or 0.5%). In contrast, 5 out of 213 black subjects (2.4%) randomized to LCZ696 had a confirmed case of angioedema. Among the subset of black subjects enrolled at sites in the U.S. (57 in the enalapril arm and 54 in the LCZ696 arm), there were three cases of confirmed angioedema in the LCZ696 arm (5.6% of subjects) as compared to no cases in the enalapril arm.

*Hypotension*
Treatment with LCZ696, as compared to enalapril, was associated with a higher risk of hypotension. The vast majority of cases appeared to be manageable, with fewer than 1% of subjects permanently discontinuing LCZ696 during the double-blind period because of a possible hypotension-related adverse event. In contrast, dose adjustment or temporary interruption of study medication was not uncommon (~11% of subjects in the LCZ696 arm during the double-blind period). During the enalapril and LCZ696 run-in periods, 1.4% and 1.7% of subjects, respectively, permanently discontinued study medication because of a hypotension-related adverse event. Falls were also reported at a slightly higher incidence in the LCZ696 arm as compared to the enalapril arm (80/4203, 2% vs. 54/4229, 1.3%) during the double-blind period.

**Table 7: Actions taken for potential hypotension-related AEs during the double-blind period in PARADIGM-HF**

| | **Enalapril N =4,229 n (%)** | **LCZ696 N=4,203 n (%)** |
|---|---|---|
| Hypotension-related AE[a] | 786 (18.6%) | 1027 (24.4%) |
| - No action taken | 384 (9.1%) | 504 (12.0%) |
| - Study dose adjusted/temporary interruption | 327 (7.7%) | 475 (11.3%) |
| - Study drug permanently discontinued | 29 (0.7%) | 36 (0.9%) |
| - Concomitant medication taken[b] | 128 (3.0%) | 175 (4.2%) |
| - Non-drug therapy given | 23 (0.5%) | 38 (0.9%) |
| - Hospitalization/prolonged hospitalization | 121 (2.9%) | 104 (2.5%) |

[a] Subjects could have more than one hypotension-related AE thus the number for actions taken for each event did not sum up as number of subjects with hypotension AEs; [b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications
Source: Table 65, Clinical Review

Analyses based on vital sign data, shown below, were consistent with the adverse event findings.

**Table 8: Changes in systolic blood pressure during the run-in and double-blind periods in PARADIGM-HF**

| Study Period (median drug exposure) | Run-in period (15 days/29 days) | | Double-blind period (24 months) | |
|---|---|---|---|---|
| SBP decrease | Enalapril N=10,004[a] | LCZ696 N=9,158[a] | Enalapril N=4,202[b] | LCZ696 N=4,184[b] |
| SBP < 90 mmHg | 63 (0.1%) | 112 (1.2%) | 205 (4.9%) | 321 (7.7%) |
| ≥ 30 mmHg drop in SBP | 510 (5.1%) | 1078 (11.8%) | 1031 (24.5%) | 1325 (31.7%) |
| Simultaneously SBP <90 mmHg and ≥ 30 mmHg drop in SBP | 22 (0.2%) | 47 (0.5%) | 96 (2.3%) | 194 (4.6%) |
| SBP < 90 mmHg with symptomatic hypotension | 36 (0.4%) | 65 (0.7%) | 62 (1.5%) | 119 (2.8%) |
| ≥ 30 mmHg drop in SBP with symptomatic hypotension | 30 (0.3%) | 65 (0.7%) | 95 (2.3%) | 203 (4.9%) |

[a] SPB at screening was used as the baseline
[b] Number of patients with a non-missing value at screening and post-baseline values in the study period

Source: Table 88, Clinical Review

*Hyperkalemia*

The incidence of hyperkalemia-related adverse events was lower in the LCZ696 arm as compared to the enalapril arm during the double-blind period. Hyperkalemia SAEs were uncommon in the LCZ696 arm.

**Table 9: Hyperkalemia AEs during the double-blind period in PARADIGM-HF**

| | **AE** | | **SAE** | |
|---|---|---|---|---|
| | **Enalapril N =4,229 n (%)** | **LCZ696 N=4,203 n (%)** | **Enalapril N =4,229 n (%)** | **LCZ696 N=4,203 n (%)** |
| **Hyperkalemia-related event** | 605 (14.3%) | 500(11.9%) | 42 (1.0%) | 17 (0.4%) |
| Hyperkalemia | 592 (14.0%) | 488(11.6%) | 42 (1.0%) | 17 (0.4%) |
| Blood potassium increased | 18 (0.4%) | 14 (0.3%) | 0 (0.0%) | 0 (0.0%) |
| Blood potassium abnormal | 1 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

Source: Table 74, Clinical Review

No action was taken with regard to study medication for most of these events. Approximately 3.6% of subjects in the LCZ696 treatment arm had a dose adjustment or temporary interruption of study medication for their hyperkalemia-related event during the double-blind period while only 0.3% subjects had their study medication permanently discontinued. During the enalapril and LCZ696 run-in periods, 1.7% and 1.3% of subjects, respectively, permanently discontinued study medication because of a hyperkalemia adverse event.

**Table 10: Actions taken for hyperkalemia-related AEs during the double-blind period in PARADIGM-HF**

| | Enalapril N =605 n (%) | LCZ696 N=500 n (%) |
|---|---|---|
| **Hyperkalemia-related AE**[a] | 605 (14.3%) | 500(11.9%) |
| No action taken | 357 (8.4%) | 304 (7.2%) |
| Study dose adjusted/temporary interruption | 178 (4.2%) | 151 (3.6%) |
| Study drug permanently discontinued | 15 (0.4%) | 11 (0.3%) |
| Concomitant medication taken[b] | 124 (2.9%) | 88 (2.1%) |
| Non-drug therapy given | 79 (1.9%) | 67 (1.6%) |
| Hospitalization/prolonged hospitalization | 31 (0.7%) | 13 (0.3%) |

[a] Subjects could have more than one hyperkalemia-related AE thus the number for actions taken for each event does not equal the number of subjects with hyperkalemia AEs; [b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications
Source: Table 35, Clinical Review

Consistent with the AE findings, the percentage of subjects with a potassium >5.5 or ≥6 mmol/L was slightly lower in the LCZ696 arm relative to the enalapril arm during the double-blind period.

**Table 11: Potassium > 5.5 or ≥ 6 mmol/L during the run-in and double-blind periods in PARADIGM-HF**

| | Run-in period (15 days/29 days)* | | Double-blind period (24 months)* | |
|---|---|---|---|---|
| | Enalapril N=9,825[b] | LCZ696 N=9,096 [b] | Enalapril N=4,155[b] | LCZ696 N=4,129 [b] |
| **Potassium** | | | | |
| >5.5 mmol/L | 357(3.6%) | 402 (4.4%) | 701 (16.9%) | 649(15.7%) |
| ≥6.0 mmol/L | 94 (1.0%) | 103 (1.1%) | 283 (6.8%) | 231 (5.6%) |

[b] Number of patients with a non-missing value during the study period;*Median duration of drug exposure
Source: Table 87, Clinical Review

*Renal Impairment*
The incidence of renal impairment-related AEs was slightly lower in the LCZ696 arm compared to the enalapril arm during the double-blind period in PARADIGM-HF (see table below).

**Table 12: Renal Impairment AEs during the double-blind period in PARADIGM-HF**

| Safety Topic/MedDRA PT | AE | | SAE | |
|---|---|---|---|---|
| | Enalapril N =4,229 n (%) | LCZ696 N=4,203 n (%) | Enalapril N =4,229 n (%) | LCZ696 N=4,203 n (%) |
| **Renal Impairment-related event[a]** | **746 (17.6%)** | **682 (16.2%)** | **188 (4.4%)** | **161 (3.8%)** |
| Renal impairment | 487 (11.5%) | 426 (10.1%) | 57 (1.3%) | 46 (1.1%) |
| Renal failure | 144 (3.4%) | 111 (2.6%) | 54 (1.3%) | 42 (1.0%) |
| Renal failure acute | 93 (2.2%) | 95 (2.3%) | 79 (1.9%) | 74 (1.8%) |
| Glomerular filtration rate decreased | 48 (1.1%) | 58 (1.4%) | 1 (0.0%) | 2 (0.0%) |
| Blood creatinine increased | 34 (0.8%) | 33 (0.8%) | 2 (0.0%) | 4 (0.1%) |
| Blood urea increased | 23 (0.5%) | 22 (0.5%) | 0 (0.0%) | 0 (0.0%) |
| Azotaemia | 6 (0.1%) | 8 (0.2%) | 0 (0.0%) | 1 (0.0%) |
| Acute prerenal failure | 6 (0.1%) | 4 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Prerenal failure | 6 (0.1%) | 4 (0.1%) | 0 (0.0%) | 0 (0.0%) |

[a] Using MedDRA renal failure broad SMQ. Table only lists preferred terms with ≥ a total of 10 AEs in the study
Source: Table 70, Clinical Review

As was true for hypertension and hyperkalemia related adverse events, few subjects had their medication permanently discontinued for renal impairment-related adverse events during the double blind period, although dose adjustment or temporary interruption of LCZ696 was not uncommon. During the enalapril and LCZ696 run-in periods, 1.7% and 1.8% of subjects, respectively, permanently discontinued study medication because of a renal impairment adverse event.

**Table 13: Actions taken for renal impairment AEs during the double-blind period in PARADIGM-HF**

| | **Enalapril N =4,229 n (%)** | **LCZ696 N=4,203 n (%)** |
|---|---|---|
| **Renal Impairment AE[a]** | **746 (17.6%)** | **682 (16.2%)** |
| - No action taken | 441 (10.4%) | 413 (9.8%) |
| - Study drug dose adjusted/temporary interruption | 236 (5.6%) | 211(5.0%) |
| - Study drug permanently discontinued | 56 (1.3%) | 29 (0.7%) |
| - Concomitant medication taken[b] | 130 (17.6%) | 98 (2.3%) |
| - Non-drug therapy given | 61 (1.4%) | 46 (1.1%) |
| - Hospitalization/prolonged hospitalization | 132 (3.1%) | 115 (2.7%) |

[a] Subjects could have more than one renal impairment AE thus the number of actions taken for each event does not equal the number of subjects with renal impairment AEs; [b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications
Source: Table 71, Clinical Review

As shown in the table below, the percentage of subjects with more marked increases in creatinine or declines in eGFR was similar in the two arms during the double-blind treatment

period. The difference in the length of the run-in periods may explain in part the higher incidence of more marked increases in creatinine and declines in eGFR during the LCZ696 as compared to the enalapril run-in period.

**Table 14: Changes in creatinine and eGFR**

| Study period (median drug exposure) | Run-in Period (15 days/29 days) | | Double-blind period (24 months) | |
|---|---|---|---|---|
| Criteria | Enalapril N=9,798[a] | LCZ696 N=9,086[a] | Enalapril N=4,159[b] | LCZ696 N=4,136[b] |
| **eGFR decline** | | | | |
| > 25% decrease from baseline | 536 (5.5%) | 811 (8.9%) | 1497(36.0%) | 1484(35.9%) |
| > 50% decrease from baseline | 36 (0.4%) | 42 (0.5%) | 282(6.8%) | 244(5.9%) |
| > 30 mL/min/1.73m$^2$ | 114 (1.2%) | 188 (2.1%) | 490(11.8%) | 480(11.6%) |
| **Serum creatinine increase** | | | | |
| > 50% increase from baseline | 142 (1.4%) | 198 (2.2%) | 675(16.2%) | 644(15.6%) |

[a] eGFR and serum creatinine at screening was used as the baseline;[b] Number of patients with a non-missing value at screening and during the study period
Source: Table 86, Clinical Review

*Cognitive Impairment*
As discussed in Section 4, neprilysin is a beta amyloid-degrading enzyme in the brain. Hence, there is a theoretical risk that inhibition of neprilysin by LCZ696 could accentuate accumulation of beta amyloid in the brain, thus increasing the risk of Alzheimer's disease.

To evaluate this issue, Dr. McDowell looked at the incidence of potential dementia-related AEs in PARADIGM-HF. According to the clinical review, there was no obvious safety signal for cognitive impairment/Alzheimer's disease. The incidence of potential dementia-related AEs (as defined using the broad SMQ) was similar in the two treatment arms during the double-blind period-- 2% in both arms (see Table 77 of the Clinical Review). A similar result was observed when the narrow SMQ was used to identify potential dementia-related adverse events.

# 9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There are no significant safety and/or efficacy issues that require the input of an Advisory Committee.

# 10. Pediatrics

The applicant's request for a waiver for all pediatric age groups should be granted. The causes and mechanisms of heart failure in children and adults are different and studies would be impossibly or highly impracticable. PeRC review of the waiver request is pending. (b) (4)

## 11. Other Relevant Regulatory Issues

*Financial disclosures:* The applicant has adequately disclosed financial arrangements with clinical investigators in PARADIGM-HF (see pages 21 through 23 of the Clinical Review). These arrangements do not raise concern about the integrity of the data.

*DSI audits:* Four foreign and a sponsor inspection were conducted. The final EIRs for three of the sites are pending and so observations for these sites were based on the preliminary EIRs or email communications with the field investigator.

According to Dr. Gershon's review, no regulatory violations were observed during the sponsor inspection or during inspections at two of the sites (site 665 in India and site 117 in Bulgaria). Two sites received a classification of VAI for minor regulatory violations. At one site (site 98 in Brazil), a one-item FDA 483 was issued for failure to follow the investigational plan. One subject experienced an AE (abdominal cramping and diarrhea) that was documented in the source record by not listed in the eCRF/data submitted to the sponsor and eight of twenty-two subject records reviewed had at least one concomitant medication documented in the source records but not listed in the eCRF/data submitted to the sponsor. At the other site (site 217 in China), a one observational FDA 483 was issued for failure to prepare and maintain accurate records. Specifically, data listing/records of AEs submitted to the sponsor did not include four AEs documented in source records and observed during the conduct of the study. These events (a TIA, bronchitis, palpitation and edema) occurred in subjects in the enalapril arm.

OSI believes the observed issues are unlikely to significantly impact the quality or the integrity of the data submitted in the NDA. OSI recommends the data be accepted. I concur with their assessment.

## 12. Labeling

*Proprietary name:* According to DMEPA, the proposed proprietary name, Entresto, is acceptable from both a promotional and safety perspective.

*Physician labeling:* Labeling negotiations with the applicant are ongoing. Agreement has not yet been reached with the applicant on:

- how to describe the indicated population in Section 1 ( (b) (4) .
- claims that will be included in Section 14 (b) (4) .

There is general consensus about the information that will be included on safety findings and measures to mitigate risk (e.g., Warnings and Precautions, Contraindications). Agreement has also been reached on how to describe the dosage strength in the label. Labeling will refer to the strength of the product by the dosage of the strengths of the individual components, with the exception of Section 14 which will describe how the dosage strengths reported in the label

relate to the dosage strengths reported in the publication describing the findings in PARADIGM-HF.

The Division of Pediatric and Maternal Health (DPMH) was consulted to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule (PLLR) formatting requirements. The PLLR will take effect on June 30, 2015. Since the approach taken here could be precedent setting for ACE inhibitor and ARB labels, Mary Ross Southworth, Deputy Director for Safety, and Michael Monteleone, Associate Director for Labeling, have been involved in the discussion with DPMH and have also provided input on language that should be included in the Pregnancy and Lactation subsections of labeling.

*Carton and immediate container labels:* DMEPA has recommended changes to the carton and container labels to mitigate confusion and promote the safe use of the product. OPDP has also recommended changes to the carton and container labeling for a proposed starter kit. These recommendations have been conveyed to the applicant.

*Patient labeling* (b) (4) The Patient Labeling Team has recommended revisions to the Patient Package Insert to reduce redundancy, make patient information more consistent and concise, and include the information necessary for patients to safely take their medication. Mary Ross Southworth, Deputy Division Director for Safety, has also reviewed the document and made further edits.

Of note, the applicant initially proposed (b) (4) . DRISK believes that the risk of this drug-drug interaction will best be mitigated through prescriber labeling and drug-drug interaction screening at pharmacies for contraindicated medications. I agree with their assessment. (b) (4) .

# 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Approval for the treatment of heart failure pending resolution of the outstanding product quality issues and agreement on labeling.

- **Risk Benefit Assessment**

*Benefit*
In support of the proposed indication, the applicant conducted an international, randomized, double-blind, active-controlled trial comparing LCZ696 with enalapril in 8,442 patients with chronic heart failure (NYHA class II to IV) and a reduced EF. The trial met its primary endpoint, the time to first heart failure hospitalization or CV death, with a highly persuasive p-value. As of the analysis cut-off date, 914 subjects (21.8%) in the LCZ696 arm and 1117 subjects (26.5%) in the enalapril arm had reached the primary endpoint (HR of 0.80; 95% CI 0.73; 0.87; 1-sided p=0.0000002). Of note, both components of the composite contributed to the effect. All-cause mortality, a prespecified secondary endpoint, was also lower in the LCZ696 arm as compared to the enalapril arm (HR of 0.84; 95% CI 0.76, 0.93; 2-sided p= 0.0009), a finding that was driven entirely by a lower incidence of cardiovascular deaths in subjects randomized to LCZ696.

*Risk*
From a safety perspective, key risks include fetal toxicity, angioedema, hypotension, renal impairment, and hyperkalemia. These risks, with the exception of fetal toxicity, are discussed below; none represents a barrier to approval.

Angioedema: Confirmed cases of angioedema occurred in 0.1% of subjects in both the enalapril and LCZ696 run-in periods. During the double-blind period, confirmed cases of angioedema occurred in 0.5% of subjects on LCZ696 as compared to 0.2% of subjects on enalapril. No subject who developed angioedema on LCZ696 required mechanical airway protection or died from airway compromise. The review team believes that the risk of serious angioedema can be adequately managed with prescriber labeling. Specifically, the current label indicates that LCZ696 is contraindicated in patients with hypersensitivity to either component and in those with a history of angioedema related to previous ACE inhibitor or ARB therapy. Concomitant use with an ACE inhibitor or within 36 hours of switching from or to an ACE inhibitor is also contraindicated. Finally, the label contains a Warning and Precaution related to the risk of angioedema. Based on the available data, I agree that the proposed prescriber labeling should be adequate to address this risk.

Consistent with the experience with ACE inhibitors and omapatrilat, a combined neprilysin and angiotensin converting enzyme inhibitor, the incidence of angioedema was higher in black subjects than in caucasian subjects treated with LCZ696. The incidence of angioedema was also higher in black subjects treated with LCZ696 than in black subjects treated with enalapril (2.4% and 0.5%, respectively). Because of the small number of blacks enrolled in the trial, and in particular at U.S. sites, there is considerable uncertainty about the risk of serious events of angioedema in this population. The review team has recommended a PMR to evaluate the risk of serious angioedema events in black patients treated with LCZ696. I agree with their recommendation. Some have questioned why a more precise estimate is needed since the experience in PARADIGM-HF, as well as the experience with ACE inhibitors and omapatrilat, indicates that the incidence of angioedema will likely be a few-fold higher in blacks patients than in caucasian patients and if a serious angioedema event occurs, it will likely be reported. My concern is that, in the absence of a reliable estimate of the risk, isolated

reports of serious cases of angioedema in black patients may inappropriately discourage use of a drug that provides a mortality benefit.

Hypotension, renal impairment and hyperkalemia: Treatment with LCZ696, as compared to enalapril, was associated with a higher incidence of hypotension. The vast majority of cases appeared to be manageable, with <1% of subjects permanently discontinuing LCZ696 during the double-blind period because of a possible hypotension-related adverse event. In contrast, dose adjustment or temporary interruption of study medication was not uncommon (~11% of subjects in the LCZ696 arm during the double-blind period). Falls were also reported at a slightly higher incidence in the LCZ696 arm as compared to the enalapril arm during the double-blind period (80/4203, 2% vs. 54/4229, 1.3%, respectively).

In contrast to the risk of hypotension, analyses of adverse event and laboratory data did not suggest an increased risk of hyperkalemia or renal impairment in the LCZ696 arm as compared to the enalapril arm. As was true for hypotension-related adverse events, few subjects had their medication permanently discontinued during the double blind period for these adverse events, although dose adjustment or temporary interruption of LCZ696 was not uncommon.

Because of the run-in period, as well as the trial entry criteria, the incidence of these adverse events is expected to be greater in the post-marketing setting than what was seen in the clinical trial. The current label contains Warnings and Precautions related to these risks, as is appropriate.

*Theoretical safety concerns*
Beyond these issues, there is a theoretical risk that inhibition of neprilysin by LCZ696 could accentuate accumulation of beta amyloid in the brain and thus increase the risk of Alzheimer's disease. In preclinical studies, treatment with LCZ696 was associated with increases in Aβ levels in the CSF, without corresponding increases in the brain. In a study in healthy subjects changes of unclear significance were seen in CSF β-Amyloid 1-38 and plasma β-Amyloid 1-40 concentrations. Analyses of adverse event data from the phase 3 trial did not reveal an obvious signal. That said, it seems unlikely that the trial would have been able to detect a signal given its duration, the likely timeframe for disease progression, and the tool used to detect a signal (i.e., adverse event data as opposed to a sensitive measure of cognitive decline). There has been internal discussion about whether to include information on this issue in the label, and if so where. At this point, the risk is only theoretical, while the benefit, an effect on survival, is established. There appears to be general agreement that we do not want to discourage use based on a hypothetical risk, particularly in a population with a high competing risk of death. Currently, there is text in Section 12.2 describing the findings in healthy subjects, with the appropriate caveat that the "clinical relevance of the finding is unknown." There is also a cross-reference to text in Section 13.2 describing the findings in animals. I think the proposed approach is reasonable.

There has also been internal discussion about appropriate next steps, if any, to further evaluate this hypothetical risk. The Clinical Reviewer team does not believe a postmarketing study is needed. Given the findings to date as well as the established benefit of the therapy, I do not

think there is sufficient basis for requiring that a study be conducted in the postmarketing setting. That said, as noted in the Clinical Review, the applicant is planning to (1) (b) (4) and (2) conduct a (b) (4) subject trial with more extensive neurocognitive testing in a patient population similar to (b) (4). I agree with the Clinical Reviewers that these studies will likely provide further insight into this hypothetical safety concern.

*Combination Policy*

Dr. Lawrence does not believe the combination should be approved since he does not believe there is evidence that both components contribute to the effect. He believes, however, that a case can be made for approving the sacubitril component with an indication for reducing cardiovascular mortality. From a public health perspective, I find it difficult to sustain an argument that LCZ696 should not be approved because the policy in its current form has not been met.

- The applicant's phase 3 trial established that the combination product provides a mortality benefit. Moreover, there were no serious safety signals in the trial that might lead one to believe that it is critical to determine the contribution of the components at this point in time. Given these findings, I do not think it would be ethical to conduct another study to assess the contribution of the components.
- The trial established a benefit over an active comparator with a better claim than valsartan (i.e., enalapril is indicated to improve symptoms, increase survival, and decrease the frequency of hospitalization in patients with symptomatic heart failure, whereas valsartan is indicated to reduce hospitalizations for heart failure). Hence, I am reasonably satisfied that the combination product provides an advantage over the valsartan component.
- It is true that we do not know whether valsartan provides an added benefit beyond what is provided by sacubitril alone, but the same issues arises whenever sponsors do an add-on study (i.e., they study their therapy on top of "established" background therapy). Moreover, from an ethical perspective, I think it would have been difficult to study the effect of the sacubitril alone on heart failure. ACE inhibitor/ARB therapy represents the standard of care in this population and there was no prior belief or strong basis for believing that sacubitril, in the absence of RAS inhibitor therapy, would have been beneficial in heart failure patients.

*Other outstanding issues*

As noted in Section 12, there are ongoing discussions with the applicant about (b) (4) (b) (4) . (b) (4) (b) (4) Although there was less of a decline in the Clinical Summary Score in the LCZ696 treatment arm, as compared to the enalapril arm, the between-group difference in KCCQ Clinical Summary Score at month 8 was small- 1.6 (95% CI of 0.6 to 2.7) in subjects with a mean baseline score of ~76 (on a scale of 0 to 100). As noted by Dr.

Smith, the observed difference falls within the range of background variation for patients considered clinically stable. As also noted by Dr. Smith, the difference between treatment arms was driven in part by LCZ696's treatment effect on mortality. In the prespecified analysis, subjects who died before month 8 were assigned a Clinical Summary Score of zero for all subsequent visits. In an analysis in which subjects who died were treated as missing, the between-group difference in KCCQ Clinical Summary Score was 0.98 (95% CI of 0.3 to 1.7). A plot of the cumulative distribution of the change in Clinical Summary Score from baseline to month 8 also did not suggest a subpopulation with a more marked treatment response.[8]


[8] While it has also been noted that the p-value did not meet its prespecified threshold, the prespecified threshold was very low (1-sided p= 0.0002). Hence, my main concern is with the size of the treatment effect, not the p-value that was achieved (1-sided p=0.0007).

[redacted] (b) (4)

[redacted] (b) (4) I agree with Dr. Smith's position on these issues and hence do not address them further in this review.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Based on the safety findings to date, DRISK does not think risk mitigation measures beyond professional labeling and a PPI are warranted. I concur with their assessment, as do the clinical reviewers.

- **Recommendation for other Postmarketing Requirements and Commitments**

The Clinical Reviewers have recommended a postmarketing study to characterize the risk of serious cases of angioedema in black patients with heart failure and a reduced EF in the U.S. In the phase 3 trial, the incidence of angioedema was higher in blacks than in whites in both treatment arms. The incidence of angioedema was also higher in black subjects treated with LCZ696 than in black subjects treated with enalapril. Because of the small number of black subjects enrolled in the trial, the risk of serious angioedema events in black patients treated with LCZ696 in the United States remains unclear. I agree with the Clinical Reviewers that a postmarketing study should be conducted to address this issue. The applicant has proposed a cohort study using electronic medical record information and/or administrative claims data. OSE has been consulted on the applicant's proposal and has provided preliminary comments for the applicant.

There is also ongoing discussion about a formal postmarketing commitment related to outstanding dissolution issues.

- **Recommended Comments to Applicant**

1. According to Dr. Wilson, the approval letter should indicate that the comparability protocols supporting post-approval changes are approved. Dr. Wilson recommends that the following language be included in the approval letter:

   *The comparability protocols for 1) drug product manufacturing site, control, batch size, and process and 2)* [redacted] (b) (4) *intermediate manufacturing site, control, batch size, and process as included in Submission 0000 dated September 30, 2014 are approved. Additionally, regulatory notification of changes to the approved protocols must be made via a prior approval supplement.*

2. According to the DPMH review, because the applicant voluntarily complied with the PLLR requirements prior to the June 30, 2015 effective date, language waiving the current labeling requirements should be included in the approval letter. The following approval letter language is suggested by DPMH:

*WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS*
*We are waiving the current requirements of 21CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015.*

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/s/

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ALIZA M THOMPSON
06/12/2015