



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for sacubitril / valsartan salt complex

Proprietary Product Name: Entresto / Novartis
sacubitril/valsartan

Sponsor: Novartis Pharmaceuticals Australia Pty
Ltd

September 2016

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

| Abbreviation | Meaning |
|----------------------|---|
| ACE | angiotensin converting enzyme |
| ACSOM | Advisory Committee on the Safety of Medicines |
| ACPM | Advisory Committee on Prescription Medicines |
| ADR | adverse drug reaction |
| AE | adverse event |
| AF | atrial fibrillation |
| ARB | angiotensin II receptor blocker |
| ARTG | Australian Register of Therapeutic Goods |
| ASA | Australian Specific Annex |
| AUC | area under the plasma drug concentration-time curve |
| AUC _{t1-t2} | area under the plasma drug concentration-time curve from t1 to t2 |
| BID | bis in die (twice daily) |
| C _{max} | maximum serum concentration of drug |
| CHMP | Committee for Medicinal Products for Human Use |
| CMI | Consumer Medicines Information |
| CSF | clinical service formulation |
| CV | cardiovascular |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration (US) |
| FDC | fixed dose combination |
| FMI | final market image |
| HF | heart failure |
| HFpEF | heart failure with preserved ejection fraction |
| HFrEF | heart failure with reduced ejection fraction |
| HTN | hypertension |

| Abbreviation | Meaning |
|------------------|--|
| IC50 | inhibitory concentration 50% |
| ICH | International Conference on Harmonisation |
| IV | intravenous |
| LCZ696 | Entresto (sacubitril/valsartan) |
| MI | myocardial infarction |
| NEP | neprilysin |
| NP | natriuretic peptide |
| NT pro BNP | N-terminal pro brain natriuretic peptide |
| NYHA | New York Heart Association |
| PD | pharmacodynamic(s) |
| PI | Product Information |
| PK | pharmacokinetic(s) |
| PO | per os (oral administration) |
| RAAS | renin-angiotensin-aldosterone system |
| RMP | Risk Management Plan |
| SAE | serious adverse event |
| t _{1/2} | elimination half life |
| Tmax | Time taken to reach the maximum concentration (Cmax) |

I. Introduction to product submission

Submission details

| | |
|------------------------------------|--|
| <i>Type of submission:</i> | New combination product |
| <i>Decision:</i> | Approved |
| <i>Date of decision:</i> | 15 January 2016 |
| <i>Date of entry onto ARTG</i> | 20 January 2016 |
| | |
| <i>Active ingredient:</i> | Sacubitril / valsartan salt complex |
| <i>Product name:</i> | Entresto / Novartis sacubitril/valsartan |
| <i>Sponsor's name and address:</i> | Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Rd Macquarie Park NSW 2113 |
| <i>Dose form:</i> | Fixed dose combination film-coated tablets |
| <i>Strengths:</i> | 24.3/25.7 mg, 48.6/51.4 mg and 97.2/102.8 mg |
| <i>Container:</i> | PA/Al/PVC/Al blister packs |
| <i>Pack sizes:</i> | 14 (sample packs) and 28, 30, 56 and 60 tablets |
| <i>Approved therapeutic use:</i> | Entresto or Novartis Sacubitril/Valsartan is indicated in adult patients for the treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction. |
| <i>Route of administration:</i> | Oral |
| <i>ARTG numbers:</i> | 234218, 234219, 234220, 234221, 234222, 234223 |

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd to register Entresto as a new combination product. Entresto (sacubitril/valsartan) is sodium salt complex of two components (sacubitril and valsartan) which dissociates when taken orally. The first component, sacubitril, a new chemical entity, is a pro drug which is metabolised to the active metabolite sacubitrilat, a novel neutral endopeptidase (neprilysin) inhibitor. The second component is valsartan, an angiotensin II receptor blocker (ARB), which is currently approved for the treatment of heart failure (HF) and hypertension. The product is considered a fixed dose combination and therefore has been expressed as having two components or strengths. It is a tablet proposed in three strengths of 24/26 mg, 49/51 mg and 97/103 mg for the treatment of chronic HF. These strengths are sometimes expressed as 50 mg, 100 mg and 200 mg. The sponsor is requesting two trade names; however, for convenience only, the Entresto name will be

used in this document. The combination product of the two active ingredients is also known as LCZ696.

HF is associated with overstimulation of the renin-angiotensin-aldosterone system (RAAS) which promotes vasoconstriction and fluid overload mediated by angiotensin II and aldosterone. Angiotensin converting enzyme (ACE) inhibitors block the deleterious effects of angiotensin II and are usually combined with a diuretic for treatment. Additional complementary therapies include β blockers and aldosterone antagonists. ACE inhibitors are recommended as first line treatment as they have been shown to reduce mortality compared with placebo. Two early, placebo controlled studies of enalapril supported its use: CONSENSUS, 1987 and SOLVD, 1991. In the CONSENSUS study, there was a 27% reduction in overall mortality, and a 50% reduction in deaths due to progressive HF in patients with severe chronic HF (New York Heart Association [NYHA] class IV). In the SOLVD study, there was a 16% reduction in overall mortality and a 22% reduction in deaths due to progressive HF in patients with CHF and ejection fractions $\leq 35\%$. ARBs are an alternative treatment used when ACE inhibitors are not tolerated, particularly in the event of angioedema. In the Val-HeFT study in patients with NYHA class II-IV, valsartan was not superior to placebo for reduction in all cause mortality or cardiovascular deaths.

LCZ696 acts as an angiotensin receptor neprilysin inhibitor (ARNI). Sacubitril inhibits neprilysin (neutral endopeptidase) via its active metabolite, sacubitrilat. By inhibiting neprilysin, this inhibits the degradation of atrial natriuretic peptide (ANP) and other endogenous vasoactive peptides including bradykinin leading to an enhancement of ANP and thus potentially diuresis and natriuresis. Valsartan is an angiotensin II receptor blocker which is designed to block the compensatory stimulation from angiotensin II.

LCZ696 and sacubitril have not been previously considered by the Advisory Committee on Prescription Medicines (ACPM); however, valsartan has been considered. Valsartan is currently approved for use in Australia and listed on the Australian Register of Therapeutic Goods (ARTG). Valsartan is available in four strengths of 40, 80, 160 and 320 mg and is approved for the following indications, one of which is in the treatment of HF:

Valsartan indications

- *Treatment of hypertension.*
- *Treatment of heart failure (NYHA class II-IV) in patients receiving usual therapy (e.g. diuretics, digitalis) who are intolerant to ACE inhibitors.*
- *To improve survival following myocardial infarction in clinically stable patients with clinical or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction (see "CLINICAL TRIALS").*

For background, enalapril, an ACE inhibitor that was used as an active comparator in the pivotal study, has the following indications:

Enalapril indications

- Hypertension
Renitec is indicated in the treatment of:
 - *All grades of essential hypertension*
 - *Renovascular hypertension*
- *Congestive heart failure*
Renitec is indicated for the treatment of all degrees of symptomatic heart failure. In such patients, it is recommended that Renitec be administered together with a diuretic.
- *Left ventricular dysfunction*

All degrees of left ventricular dysfunction where the left ventricular ejection fraction is less than 35%, irrespective of the presence or severity of obvious symptoms of heart failure.

There is one specific EU guideline adopted by the TGA relevant to this submission, besides the general guidelines.¹

Regulatory status

At the time of this submission, Entresto had been approved in the USA (Jul 2015), Switzerland (Sep 2015), and Canada (Oct 2015), and had received a positive opinion from the CHMP in Europe. The approved indications are as follows:

USA

Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

Europe (CHMP positive opinion)

Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1).

Canada

Entresto (sacubitril/valsartan) is indicated for the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with NYHA Class II or III, to reduce the incidence of cardiovascular death and heart failure hospitalisation (see DOSAGE AND ADMINISTRATION).

Entresto should be administered in combination with other heart failure therapies, in place of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS).

Entresto should be initiated, and up-titration conducted, by a physician experienced with the treatment of heart failure.

Switzerland

Entresto is indicated to reduce the risk of cardiovascular mortality and morbidity in adult patients with systolic heart failure (NYHA class II-IV, LVEF \leq 40%).

Entresto is administered in combination with other heart failure therapies (e.g. beta blockers, diuretics and mineralocorticoid antagonists) as appropriate, in place of an ACE inhibitor or ARB (see "Properties/Actions").

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

¹ European Medicines Agency, "Guideline on clinical investigation of medicinal products for the treatment of acute heart failure (CPMP/EWP/2986/03 Rev. 1)", 21 May 2015.

II. Quality findings

Introduction

The sponsor has applied to register new fixed combination film coated tablets containing sacubitril and valsartan (combined as sodium salt hydrate complex). The tablets will be available in 24.3/25.7 mg, 48.6/51.4 mg, and 97.2/102.8 mg strengths of sacubitril/valsartan and will be marketed under the trade names:

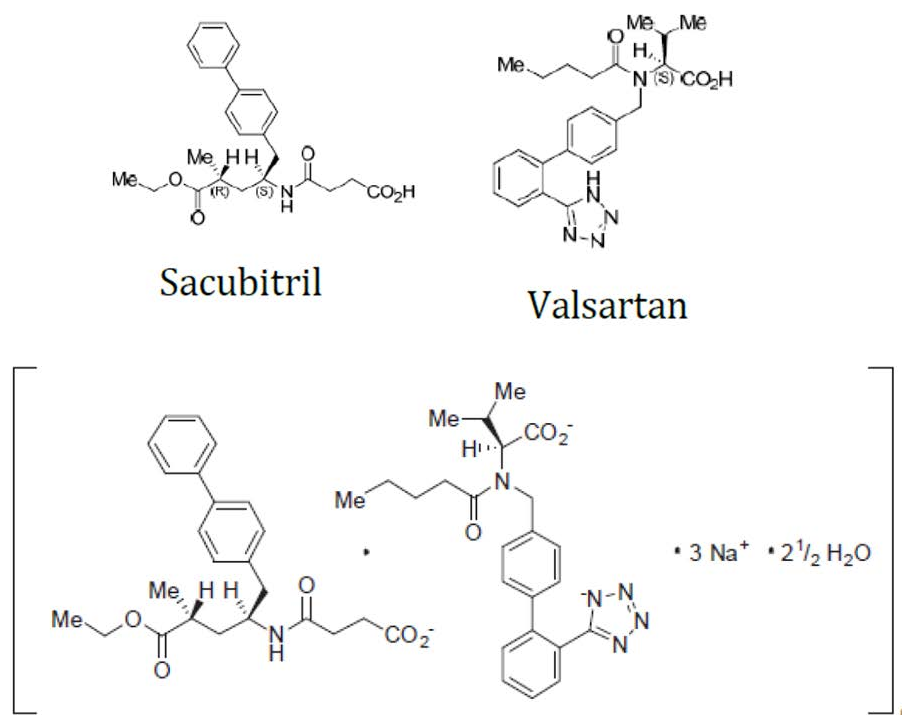
- ENTRESTO 24/26; ENTRESTO 49/51 and ENTRESTO 97/103
- NOVARTIS SACUBITRIL/VALSARTAN 24/26; NOVARTIS SACUBITRIL/VALSARTAN 49/51 and NOVARTIS SACUBITRIL/VALSARTAN 97/103

Novartis Pharmaceuticals Australia Pty Ltd and other sponsors already have registered other monotherapy and other combination products containing 40 mg, 80 mg, 160 mg and 320 mg valsartan.

The company states that equivalent valsartan exposure (AUC) needs to be from higher doses of the monotherapy Diovan (or generics), as the proposed '50 mg' product containing 26 mg (25.7 mg) valsartan is equivalent in vivo with a 'Diovan' dose for AUC of 40 mg, the proposed '100 mg' product containing 51 mg (51.4 mg) valsartan is equivalent in vivo with a 'Diovan' dose for AUC of 80 mg and the proposed '200 mg' product containing 103 mg (102.8 mg) valsartan is equivalent in vivo with a 'Diovan' dose for AUC of 160 mg. The company states that systemic valsartan exposure ($t_{1/2}$ 11.7 h) AUC140-160% versus Diovan.

Drug substance (active ingredient)

The active pharmaceutical ingredients (APIs) exist as a crystalline salt complex with a molar ratio of 1 sacubitril anion: 1 valsartan anion: 3 sodium cations: 2.5 water molecules. The structures of the drug substances sacubitril, valsartan and the complex are presented below in Figure 1.

Figure 1. Chemical structures of sacubitril, valsartan and the complex.

Sodium salt hydrate complex of both sacubitril and valsartan

Sacubitril is a pro drug that is rapidly metabolised ($t_{1/2}$ 1.1 h) to sacubitrilat ($t_{1/2}$ 11.1 h). The active metabolite inhibits neprilysin (neutral endopeptidase), allowing enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides which exert their effects by activating membrane bound guanylyl cyclase coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), thereby 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. Sustained activation of the RAAS results in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

Sacubitril has two chiral centres and is isolated in the complex (and precursor calcium salt) as a single isomer with (1S,3R)-configuration.

Valsartan is a nonpeptide specific angiotensin II receptor antagonist, blocking angiotensin II type 1 (AT1) and also inhibits angiotensin II dependent aldosterone release.

Valsartan contains one chiral centre, as the S-enantiomer.

The valsartan prior to complexation is controlled in a similar manner as the valsartan 'Diovan' products currently registered to Novartis Pharmaceuticals Australia.

The salt hydrate complex cannot be separated by physical means into its molecular moieties, but dissociates at the right pH and chemical conditions, e.g. after oral ingestion and absorption.

The sacubitril, valsartan and salt hydrate complex are manufactured by chemical synthesis. The salt complex comprises the anionic molecular moieties of sacubitril and valsartan, sodium cations and water molecules in the molar ratio of 1:1:3:2.5, respectively (ratio of 6:6:18:15 in the asymmetric unit cell of the solid state crystal). Thermoanalytical

(TGA-DSC) and X-ray Powder Diffraction (XRPD) analyses show that the complex is crystalline form: form A.

The complex (referred to the sponsor also as LCZ696-ABA and LCZ696) is a white to almost white powder with melting point $\sim 136^{\circ}\text{C}$ (onset). It is freely soluble in water. The complex pH is 8.2. The pKa for sacubitril is 4.6 and the pKas for valsartan are 3.9 for the carboxylic group, and 4.7 for the tetrazole-NH group. The partition coefficients are: sacubitril: $\log D = 1.29$ (n-octanol/phosphate buffer pH 6.8) and valsartan: $\log D = -1.49$ (n-octanol/phosphate buffer pH 7.4).

PAMPA artificial membrane permeability (with Liquid Chromatography Mass Spectrometry [LC-MS] detection) effective permeability and Caco-2 apparent permeability studies indicate medium permeability for both valsartan and sacubitril.

The drug substance complex specification includes tests and limits for stereoisomers and one identified related substance. The limits for the each unspecified impurity are in line with the International Conference on Harmonisation (ICH) identification threshold.

The limits for each impurity in valsartan prior to complexation are the same as those applied to valsartan used in the registered Diovan products.

The limits for each specified and unspecified impurity in the sacubitril calcium precursor prior to complexation additionally are in line with the ICH identification threshold and ensure adequate control of impurities in the complex.

Drug product

The proposed immediate release tablets are distinguished by colour, size and debossing:

- **‘Tradename 24/26’ (24.3/25.7 mg):** ‘Violet white ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with ‘NVR’ on one side and ‘LZ’ on the other side’
- **‘Tradename 49/51’ (48.6/51.4 mg):** ‘Pale yellow ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with ‘NVR’ on one side and ‘L1’ on the other side’
- **‘Tradename 97/103’ (97.2/102.8 mg):** ‘Light pink ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with ‘NVR’ on one side and ‘L11’ on the other side’

The tablets are not scored.

The tablet manufacturing process uses standard dry granulation, blending, compression, compaction, coating and packaging. The process has been validated and in-process controls are adequate for the dose form.

The excipients are conventional and include: microcrystalline cellulose, low substituted hydroxypropylcellulose, crospovidone, magnesium stearate, purified talc, colloidal anhydrous silica, hypromellose, macrogol 4000, titanium dioxide, iron oxide red (all strengths) and iron oxide black (24.3/25.7 mg and 97.2/102.8 mg tablets) and iron oxide yellow (48.6/51.4 mg tablets).

The finished product specifications include tests for appearance (visual), identification (HPLC, IR), assay (HPLC), average mass (EP), chiral purity (HPLC), impurities (HPLC), uniformity of dosage units (EP), dissolution (HPLC) and microbial quality (EP). Assay limits comply with TGO 78. Impurity limits have been qualified.

The stability data provided supports a shelf life of 18 months when stored below 30°C , protect from moisture in PA/Al/PVC/Al blister packs containing 14 (sample), 28, 30, 56 and 60 film coated tablets.

Biopharmaceutics

The following two biopharmaceutic studies provided were reviewed by the evaluator. The studies' findings are summarised below.

Study CLCZ696B2114 compared the bioequivalence of clinical service formulation (CSF2) with the final market image (FMI) tablet. The study title in the report is:

- A randomized, open-label, single-dose, two-treatment, two-sequence, three-period, replicate, crossover study to determine the bioequivalence of 50 mg LCZ696 final market image (FMI) tablet and the 50 mg LCZ696 clinical service form (CSF) in healthy volunteers

This study was to show that LCZ696 clinical service formulation (CSF) form (50 mg tablet 6002752.001 batch AEUS/2010-0342) was equivalent to the FMI (final marketed image batch) formulation (50 mg tablet 6002752.007 batch H941CI). The CSF form used in phase III had formulation differences to the FMI. The formulation and process of 50 mg film coated tablet, which was used in Phase III trial, was further modified to increase the bulk and change the shape to ovaloid and is intended for the market (FMI). Hence, 50 mg film coated tablet administered in Phase III trial was considered as clinical service formulation (CSF2). Bio equivalence was established between the 50 mg formulation used in pivotal Phase III study (50 mg film coated, CSF2) versus 50 mg ovaloid FMI formulation.

The study concluded that following administration of the single 50 mg dose, three analytes of LCZ696 (sacubitril, sacubitrilat, and valsartan) showed similar pharmacokinetic (PK) profiles for CSF and FMI tablets. The mean AUC_{last} , AUC_{inf} and C_{max} values were similar for both formulations as well. The geometric mean ratio and the 90% confidence interval (CI) for AUC and C_{max} for LCZ696 were within 80-125% range, indicating that the FMI tablet is bioequivalent to the CSF tablet.

Table 1. Assessment of bioequivalence of LCZ696 analytes between 50 mg FMI tablet (test) compared to 50 mg tablets used in Phase III study (CSF).

| Parameter | Sacubitril | LBQ657 | Valsartan |
|---|------------------------|------------------------|------------------------|
| AUC_{inf} | 97.65 (94.97 – 100.41) | 98.79 (97.61 – 99.99) | 95.62 (90.13 – 101.45) |
| AUC_{last} | 97.38 (94.62 – 100.23) | 98.85 (97.63 – 100.08) | 95.70 (90.05 – 101.70) |
| C_{max} | 96.18 (86.61 – 106.80) | 99.71 (97.35 – 102.14) | 95.76 (89.46 – 102.50) |
| Data is presented as geometric mean ratio (90% CI) for test (FMI)/reference (CSF) | | | |

Conclusions:

- The rate (C_{max}) and extent (AUC) of LCZ696 analytes following administration of ovaloid 50 mg FMI tablets proposed for commercialization are bioequivalent to 50 mg tablets administered in the pivotal Phase III trial.

The proposed FMI formulation 50 mg tablet was considered bioequivalent to the CSF formulation 50 mg tablet.

Study CLCZ696B2107 compared the effect of fed and fasted states for 400 mg tablets. The study title is:

- A randomized, open-label, three-period crossover study to determine the effect of food on the pharmacokinetics of a single 400 mg oral dose of LCZ696 in healthy volunteers

This study was a randomised, open label, three period, six sequence crossover study in healthy volunteers that consists of 21 day screening period, 3 baseline periods, 3 treatment periods, and 2 washout periods that lasted 5 to 10 days.

This study compared the dosage of a single oral dose of 400 mg LCZ696 tablets (6002386.008, batch H909HH). Although similar to the FMI formulations, the 400 mg strength is not proposed for registration. The composition of the 400 mg tablet is proportional to the 200 mg FMI and 100 mg FMI; therefore, the study results are relevant

to the proposed products. The 50 mg FMI tablet is not proportional to the 400 mg CSF, but the excipients are the same, and this is unlikely to impact on food effect.

Table 2. Summary of pharmacokinetic parameters from Study LCZ696B2107.

| Study ref.no. | Product ID Batch # (NME) | Study objective (Primary) | Study design; Subjects entered/ completed; M/F | HV/P Age: mean (SD) (range) | Treatments (dose, dosage form, route) | Study report location | | |
|---------------|---------------------------------|--|--|---|---------------------------------------|-----------------------|-------------------|-------------------|
| LCZ696B2107 | LCZ696 400 mg tablets: H909HH | Effect of a high fat and low fat meal on the PK of a single 400 mg oral dose of LCZ696 in healthy volunteers | Randomized, open-label, three-period crossover food effect study in healthy volunteers Enrolled: 38; Completed: 33 M: 25; F: 11 | HV; Age: 43.2 (7.67) (26 - 55) years | Single dose of LCZ696 400 mg. | | | |
| LCZ696 PK | Arithmetic mean parameters (SD) | | | | Geometric means ratio (90% CI) | | | |
| AHU377 | AUCinf (hr*ng/mL) | AUClast (hr*ng/mL) | Cmax (ng/mL) | Tmax (h)* | AUCinf (hr*ng/mL) | AUClast (hr*ng/mL) | Cmax (ng/mL) | |
| Fasting | 4820 (1840) | 4810 (1840) | 3610 (1590) | 1.0 (0.5,2.0) | - | - | - | |
| Low Fat Meal | 4340 (1760) | 4360 (1790) | 2110 (1190) | 2.0 (0.5,4.0) | - | - | - | |
| High Fat Meal | 4700 (1760) | 5140 (2150) | 1670 (1050) | 3.0 (0.5,12.0) | - | - | - | |
| LBQ657 | AUCinf (hr*ng/mL) | AUClast (hr*ng/mL) | Cmax (ng/mL) | Tmax (h)* | Geometric means ratio (90% CI) | | | |
| Fasting | 184000 (36600) | 183000 (36200) | 17800 (3910) | 2.0 (1.5,6.0) | Low Fat Meal/ Fasted | 1.00 [0.97, 1.02] | 0.91 [0.80, 1.03] | 0.81 [0.70, 0.92] |
| Low Fat Meal | 185000 (36300) | 179000 (46700) | 15500 (3930) | 4.0 (2.0, 6.0) | High Fat Meal/ Fasted | 1.04 [1.01, 1.06] | 1.04 [0.92, 1.18] | 0.72 [0.63, 0.82] |
| High Fat Meal | 193000 (42900) | 192000 (42700) | 12800 (2620) | 6.0 (2.0,12.0) | | | | |
| Valsartan | AUCinf (hr*ng/mL) | AUClast (hr*ng/mL) | Cmax (ng/mL) | Tmax (h)* | Geometric means ratio (90% CI) | | | |
| Fasting | 37000 (17800) | 36500 (17500) | 5680 (2450) | 1.75 (1.5,4.0) | Low Fat Meal/ Fasted | 0.66 [0.57, 0.75] | 0.67 [0.58, 0.76] | 0.61 [0.51, 0.71] |
| Low Fat Meal | 25900 (13900) | 25000 (13600) | 3710 (2000) | 4.0 (1.5, 6.0) | High Fat Meal/ Fasted | 0.91 [0.79, 1.04] | 0.91 [0.79, 1.04] | 0.60 [0.51, 0.70] |
| High Fat Meal | 32900 (13200) | 32000 (13000) | 3260 (1050) | 4.0 (1.5,8.0) | | | | |

The effect of a low and a high fat meal (as per FDA/EMA guidance) was evaluated following administration of 400 mg LCZ696. The 400 mg LCZ696 formulation is compositionally proportional to 200 mg LCZ696 tablets and involves a similar manufacturing process. No significant changes in sacubitrilat AUC was observed. However, the Cmax of sacubitrilat decreased by 19% and 28%, respectively, and time to reach maximum concentrations was delayed from 2 h to 4 and 6 h, respectively, with low fat and high fat meal. Low and high fat meal reduced valsartan AUC by 34% and 9%; and Cmax by 39% and 40%, respectively. The median Tmax of valsartan increased from 1.75 h to 4.0 h suggesting potential delay in absorption in the presence of low fat or high fat meal.

For all analytes, Cmax decreased upon LCZ696 administration with food (low fat and high fat meals) in comparison to the fasting state. Similarly, for all the analytes, the Tmax was delayed in the presence of food (low fat and high fat meals).

Food effects were referred to the Delegate. The clinical evaluator stated:

Administration of LCZ696 with food has no significant impact on the systemic exposures of sacubitril and sacubitrilat, while valsartan exposure decreased by about 40%. The observed changes in LCZ696 analyte exposure are not clinically relevant and hence no dosage adjustment is required when administered with food.

A summary of biopharmaceutic studies was provided. The other studies considered by the Clinical evaluator included:

- An absolute biostudy for valsartan, Protocol 15 (HPH 9305, bioavailability study). Study title 'Absolute bioavailability of an oral capsule formulation and an oral solution (of CCGP48933 valsartan) in healthy volunteers'. The study compared a single 80 mg oral capsule dose of valsartan (CGP48933, batch 1052/1) with an 80 mg single dose as 10 mg/mL buffered solution for injection (batch 16/309/1) and a 20 mg single dose as

10 mg/mL IV bolus injection (batch 16/309/1). This report was previously submitted during registration of Diovan.

- An absolute biostudy for sacubitril or sacubitrilat (the ester hydrolysis metabolite), Study LCZ696B2105 (PK study with BA estimated from levels detected in urine and faeces). The LCZ696 sodium salt complex is a highly soluble compound that rapidly and completely dissociates on oral administration, resulting in systemic exposure of sacubitril, its active metabolite sacubitrilat, and valsartan. The pharmacokinetic properties of LCZ696 were investigated in this study, wherein the sacubitril component of the salt complex was [¹⁴C] radiolabelled. 100% of administered radioactivity was recovered in the excreta of all subjects, primarily as sacubitrilat (the ester hydrolysis metabolite). The absorption, distribution, metabolism and elimination (ADME) characteristics suggest rapid absorption of the LCZ696 analytes (sacubitril, sacubitrilat and valsartan). The intact LCZ696 sodium salt complex has not been detected in any studies. The study title is:

- An open-label, single dose study to investigate the ADM&E of 200mg [¹⁴C]LCZ696 and its metabolites in healthy male subjects

The 200 mg dose was administered as 2 x 100 mg capsules (formulation 09-0567US; B# AEUS/2009-0225).

- Relative bioavailability study for valsartan from LCZ696 400 mg (CSF) versus Diovan 320 mg, Study CLCZ696A2103 (bioavailability study). The study title is:
 - Study to determine the relative BA of valsartan following administration of 400mg LCZ696 compared to 320mg Diovan in healthy volunteers

The study compared dosing of 400 mg [2 x 50 mg tablets (clinical service form, batch AEUS/2007-0036) + 1 x 300 mg tablet (clinical service form, batch AEUS/2007-0035)] with 320 mg (as 2 x 160 mg Diovan capsules, batch H108EB), each in fasted state (10 h).

- Relative bioavailability: valsartan from LCZ696 5, 20 and 50 mg doses versus Diovan 40 mg, Study CLCZ696A2101 (pharmacokinetic study with relative bioavailability objective). The study title is:
 - Study to assess the pharmacokinetics, safety and tolerability of LCZ696 compared to valsartan in healthy volunteers

The study compared dosing of a single 80 mg LCZ696 dose [6 x 5 mg LCZ696 tablets (batch AEUS/2006-0352) + 1 x 50 mg LCZ696 tablet (batch AEUS/2006-0315), subjects from cohort C, relative BA, n = 8) and a single 40 mg Diovan (valsartan batch S0015) tablet.

- Relative bioavailability study for LCZ696 200 mg (FMI) versus granules (bioavailability study), CLCZ696B2126. The study title is:
 - Study to determine the relative bioavailability of the 200mg LCZ696 granules compared to the 200mg LCZ696 FMI under fasted condition

This study compared dosage of a single LCZ696 200 mg (FMI) tablet (6002385.006, batch H875CH) with a single oral dose of 64 x 3.125 mg LCZ696 granules (7008721.004, B# VMLK/2014-0373). The granules appear to be for paediatrics and are not proposed for registration in Australia.

- Food effect study for valsartan 160 mg capsule, Protocol 06 (report UK R7/1993, pharmacokinetic study). This report was previously submitted during registration of Diovan. The study title is:

- Open, single-dose, single centre, 2-way balanced cross-over trial in 12 healthy volunteers to determine the effect of food on PK of CGP48933

The study compared the dosage of a single oral dose of 160 mg valsartan (2 x 80 mg capsules CGO48933, batch 1052/1) in the fed (standard breakfast) and fasted (overnight) states.

- Food effect study for sacubitril 100 mg capsule, VNP489A2102 (FiH PK/PD and safety study - cohort C). The study title is:

- An ascending single oral dose study of AHU377 to assess PK, safety, tolerability and PD in mildly hypertensive subjects

The study compared dosing of sacubitril (AHU377) as a single 100 mg oral dose (6001513.001, batch AEUS/2004-0126) in the fed and fasted states (cohort C only for BA objective).

- Food effect study for LCZ696 200 mg tablet (CSF), CLCZ696A1101 (pharmacokinetic study). The study title is:

- Ascending single oral dose study to assess safety, tolerability and PK of LCZ696 in Japanese healthy male subjects

The study compared the effect of food on a single oral 200 mg dose (4 x 50 mg LCZ696 tablets (6002189.001 batch AEUS/2006-0315, cohort 3 fasted versus fed only).

The pivotal Phase III clinical study was administered without regard to meals.

Advisory committee considerations

The application was not considered by the Pharmaceutical Subcommittee (PSC) of the ACPM.

Quality summary and conclusions

The sponsor has provided satisfactory responses to the issues raised by the evaluator.

Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical studies was reasonable. The range of studies was consistent with ICH guidelines. Pivotal studies examining repeat dose toxicity and reproduction/development were conducted under Good Laboratory Practice (GLP) conditions. The exposure ratios for the sacubitril metabolite sacubitrilat, the neprilysin inhibitor, following sacubitril/valsartan complex treatment are low due to dose limiting gastritis seen in both rats and monkey; however, the exposure ratios for sacubitrilat following sacubitril treatment are adequate to address the clinical relevance of the observed toxicities.

This report has evaluated the studies conducted with the sacubitril/valsartan complex and with sacubitril alone. The studies on valsartan alone were evaluated in a previous application.

The application contained reports of combination studies involving sacubitril or valsartan with other drugs. These studies were not considered relevant to this application and have not been evaluated.

Pharmacology

Mechanism of action

Sacubitril is an inhibitor of neprilysin (neutral endopeptidase; NEP) and thus enhances the level of natriuretic peptides (NPs), which are reported to have beneficial cardiovascular and renal effects. Valsartan blocks the angiotensin II type-1 (AT1) receptor, thus inhibiting the vasoconstrictive actions of angiotensin II, inhibiting aldosterone release, reducing sodium and water retention, and inhibiting cardiovascular hypertrophy and remodelling. Together, sacubitril and valsartan are reported to enhance the beneficial cardiovascular and renal effects of NPs, as well as reducing other detrimental cardiovascular and renal effects observed in HF patients.

Primary pharmacology

In vitro studies were conducted with sacubitril and its metabolite sacubitrilat since the sacubitril/valsartan complex dissociated in aqueous solution to sacubitril and valsartan. Sacubitril was a weak inhibitor of human NEP activity (IC₅₀ 16700 nM) while sacubitrilat was a potent inhibitor of NEP activity (IC₅₀ 2.3 nM). Both were weak inhibitors of NEP2. Similar IC₅₀ values for sacubitril and sacubitrilat were observed in microsomal preparations of human and rat NEP derived from kidney cortex and in human NEP from human cerebrospinal fluid. In vitro inhibition by sacubitrilat occurred at dose levels well below the clinical exposure (based on C_{max}). Neither sacubitril nor sacubitrilat was shown to inhibit or activate a range of other receptors, transporters or enzymes, including the human AT1 receptor. In rat cardiac fibroblasts, concurrent exposure to sacubitrilat and valsartan reduced angiotensin II-induced collagen synthesis and cardiomyocyte hypertrophy to a greater extent than exposure to either alone.

In vivo studies were conducted mainly in rats with sacubitril/valsartan complex as well as with sacubitril and its metabolite sacubitrilat. Studies were also conducted in dogs and monkeys. Studies directly measured NEP activity, as well as measuring atrial natriuretic peptide (ANP) levels and biological markers of increased ANP levels. NEP activity in rat renal cortex homogenate was inhibited by 73 and 84% at 60 minutes after oral treatment with 30 or 100 mg/kg per os (PO) sacubitril. Similar inhibition of NEP activity was observed in monkeys treated with 10 mg/kg PO (IC₅₀ 0.5 µM), which is a dose level well below the clinical exposure (based on C_{max}). ANP infused rats had increased plasma ANP levels (100%) following treatment with sacubitril/valsartan complex at 16.7 mg/kg PO. ANP infused rats and dogs had dose dependent increased plasma ANP levels after treatment with sacubitril at 10 and 30 mg/kg. Urinary sodium excretion was also increased and potentiated in ANP infused rats and dogs by treatment with sacubitril (30 mg/kg i.d.) or sacubitrilat (10 mg/kg i.e.).

Urinary effects of sacubitril/valsartan and sacubitril were further examined in DSS rats (requiring high blood pressure to maintain sodium excretion). Sacubitril/valsartan complex (68 mg/kg PO) was able to maintain elevated sodium excretion without increased blood pressure, as well as reducing markers of renal injury. This occurred at dose levels below the clinical exposure (based on C_{max}). In a subsequent study in DSS rats, sacubitril/valsartan complex was able to maintain a greater reduction in the increased blood pressure caused by the high salt diet than valsartan alone. In SD rats with induced myocardial infarction, 4 weeks treatment with sacubitril/valsartan complex (68 mg/kg PO) significantly reduced cardiac hypertrophy.

In spontaneously hypertensive stress prone (SHRSP) rats, 10 weeks treatment with sacubitril/valsartan complex (100/10 mg/kg PO), but not sacubitril or valsartan alone, significantly reduced diastolic blood pressure, as well as increasing vascular matrix metalloproteinase-2 activity and decreased tissue inhibitor of metalloproteinase-2. Similarly, sacubitril/valsartan complex or valsartan alone, but not sacubitril alone, decreased the media/lumen ratio and perivascular collagen density of intra myocardial coronary arteries. The effect of sacubitril/valsartan complex (15 or 45 mg/kg PO) or valsartan (60 mg/kg PO) on biomarkers of the RAAS was examined in dogs. Observed changes were consistent with known activities of valsartan on the AT1 receptor and sacubitril metabolite sacubitrilat inhibition of NEP. These effects occurred at dose levels well below the clinical exposure (based on C_{max}).

Secondary pharmacodynamics

In vitro receptor binding assays examined the potential for activity of sacubitril and sacubitrilat against a range of enzymes as well as in screening assays for a broad range of receptors, transporters and ion channels. Sacubitril was only a weak inhibitor of NEP (IC₅₀ 16.7 μM) and not active against other enzymes. sacubitrilat was a potent inhibitor of NEP (IC₅₀ 2.3 nM) and a weak inhibitor of NEP-2 (IC₅₀ 84 μM) and ECE-2 (IC₅₀ 5.5 μM), but not active against other enzymes. Against 57 receptors, transporters and ion channels, neither sacubitril nor sacubitrilat were strongly active. In spontaneously hypertensive rats, sacubitril (100 mg/kg PO), with or without valsartan (30 mg/kg PO), did not potentiate bradykinin induced angioedema. In SD rats, sacubitril (100 mg/kg i.d.), with or without valsartan (30 mg/kg i.d.), had no effect on the haemodynamic response or blood pressure in bradykinin induced hypotensive animals. These dose levels are in the range of the clinical exposure (based on C_{max}). The clinical relevance of this result is uncertain and the potential for clinical angioedema needs to be examined.

Safety pharmacology

Safety pharmacology studies examined the potential acute effects of sacubitril/valsartan complex or sacubitril alone on CNS, cardiovascular and respiratory functions. In Wistar rats, there was no evidence of CNS related effects following treatment with 600 mg/kg PO sacubitril/valsartan complex (equivalent to 0.8 times the clinical exposure, based on C_{max}). In CD mice, there was no evidence of CNS related effects following treatment with 2000 mg/kg PO sacubitril (equivalent to approx. 7 times the clinical exposure, based on C_{max}).

Potential effects on cardiovascular functions were examined in vitro and in vivo. In vitro studies of hERG tail current did not reveal any potential inhibitory effect following treatment with sacubitril/valsartan complex (IC₅₀ >3000 μM) (>500 times the clinical exposure based on C_{max}) or with sacubitril alone at 1 mM (equivalent to approx. 160 times the clinical exposure based on C_{max}).

In vivo studies in monkeys did not reveal any effect on haemodynamic or electrocardiographic parameters following treatment with sacubitril/valsartan complex up to 100 mg/kg PO (equivalent to 3 times the clinical exposure, based on C_{max}), or with sacubitril alone at 250 mg/kg (equivalent to approx. 14 times the clinical exposure based on C_{max}).

In rats, there was no evidence of potential respiratory effects following treatment with sacubitril/valsartan complex at doses up to 600 mg/kg (equivalent to approx. 0.8 times the clinical exposure based on C_{max}), or with sacubitril alone at doses up to 2000 mg/kg (equivalent to 2.3 times the clinical exposure based on C_{max}).

Pharmacokinetics

Nonclinical pharmacology studies with sacubitril/valsartan complex and/or sacubitril alone were conducted in mice, rats, dogs and monkeys.

Absorption

Sacubitril/valsartan complex was well absorbed in all animal species and humans (>60%). Absorption was also rapid, with T_{max} reached in <1 h. Absorption of sacubitril when administered alone was rapid with a T_{max} of <1 h, providing a high bioavailability for both sacubitril and the metabolite sacubitrilat. Clearance was measured only in rats and was high as a result of metabolism of sacubitril to sacubitrilat. The rapid metabolism to sacubitrilat was also reflected in the C_{max} and AUC values for sacubitril and sacubitrilat followings single dose exposure in all species. The terminal half life of metabolite sacubitrilat varied between species, with the lowest value in the mice and the highest value in monkeys (6 h) and humans (12 h). In repeat dose studies with sacubitril/valsartan complex in mice, rats and monkeys, exposure to both sacubitrilat and valsartan was generally dose proportional with no evidence of gender differences. Exposure to both sacubitrilat and valsartan increased with the period of exposure. In repeat dose studies with sacubitril alone in mice, rats and monkeys, exposure to sacubitrilat was generally dose proportional with no evidence of gender differences. Exposure to sacubitrilat increased with the period of exposure.

Distribution

Studies were not conducted on sacubitril/valsartan complex due to its rapid dissociation to sacubitril and valsartan. Plasma protein binding by sacubitrilat was high in both laboratory animals and humans. Both sacubitril and sacubitrilat bound preferentially to human serum albumin rather than to α 1-acid glycoprotein. Uptake of radioactivity derived from ¹⁴C sacubitril into red blood cells was not significant. Tissue distribution of radioactivity derived from ¹⁴C sacubitril extensive, with highest concentrations found in kidney, liver and bile and lowest levels in brain, seminal fluid, eye and spinal cord. There was no evidence of significant penetration of the blood:brain or blood:testes barriers. There was no retention of radioactivity in melanin containing pigmented skin or in the uveal tract of the eye. After 24 h, radioactivity in all tissues was <LOQ except for the small intestine and kidney.

Metabolism

Sacubitril/valsartan complex salt complex dissociates rapidly in solution to sacubitril and valsartan. Sacubitril undergoes ethyl ether hydrolysis to form sacubitrilat, the major circulating metabolite and the major excretion product in urine and faeces in all species. Other minor metabolites are formed by further hydroxylation, glucuronidation, sulfation, and glycine and taurine conjugation. No human specific metabolites have been identified. In vitro, sacubitril is converted to sacubitrilat in the presence of rat, dog or human liver slices. In the presence of human microsomes or human liver S9, transformation of sacubitril to sacubitrilat occurred by hydrolysis and was independent of NADPH. sacubitrilat was stable in the presence of human liver microsomes. Neither sacubitril nor sacubitrilat was metabolised significantly by cytochrome P450 enzymes.

In CYP450 enzyme inhibition studies using human hepatocytes, sacubitril showed weak inhibition potential against only CYP2C8 and CYP2C19 (IC₅₀ 15-20 μ M). sacubitrilat showed weak inhibition potential against only CYP2C9 (IC₅₀ 40 μ M). Neither inhibition is expected to be clinically relevant given the human C_{max} and high protein binding. In CYP450 enzyme induction studies using human hepatocytes, there was no induction of CYP enzyme mRNA or enzyme activity by sacubitril.

In in vivo studies in mice, rats and monkeys, the two major components of plasma/blood were sacubitrilat and sacubitril. Conversion of sacubitril to sacubitrilat was rapid in the mouse and rat, while conversion was moderate in dog and monkey. In humans, there was rapid conversion of sacubitril to sacubitrilat.

Excretion

The major excretion route in mice, rats and dogs was the faeces, while in monkeys and in humans, excretion was more evenly distributed between urine and faeces. The major excretion component was sacubitrilat.

Conclusion

The pharmacokinetic profiles in rats and monkeys are sufficiently similar to humans for these species to be used as models for the assessment of the toxicity of sacubitril/valsartan complex and sacubitril alone in humans.

Pharmacokinetic drug interactions

In the repeat dose studies with sacubitril/valsartan complex in rats and monkeys, valsartan exposure was generally proportional to dose and increased with the period of exposure, similar to results observed previously with valsartan alone in rats and marmosets (App. No. 97-514-3). There was no evidence of a pharmacokinetic interaction with sacubitril.

In vitro studies in Caco-2 cell monolayer indicated that sacubitril may be a low affinity substrate for P-glycoprotein, but its high permeability suggests that inhibition of P-gp would be unlikely to affect absorption of sacubitril. Transportation of sacubitrilat by OATP1B1 and OATP1B3 in HEK393 cells was significant (K_m 184 μ M for OATP1B3), suggesting a role in systemic clearance of sacubitrilat which could be of clinical relevance. Transportation of sacubitrilat by OAT1 and OAT3 was not significant (K_m 10.6 μ M for OAT3), suggesting a weak contribution to clearance of sacubitrilat which is not clinically relevant. In in vitro studies of transporter inhibition, sacubitril was not a significant inhibitor of BCRP, P-gp or MRP-2, up to 50 μ M. Similarly, sacubitrilat was not a significant inhibitor of BCRP or P-gp up to 50 μ M. In relation to OATP1B1 and OATP1B3, sacubitril (C_{max} 5.9 μ M) showed inhibition at 50 μ M, which is unlikely to be clinically relevant, given its metabolism to sacubitrilat. There was no clinically relevant inhibition by sacubitrilat. In relation to OCT1, OCT2, MATE1 and MATE2-K, there was no clinically relevant inhibition by sacubitril or sacubitrilat.

Toxicology

Acute toxicity

In single dose studies in mouse and rat (PO gavage and intraperitoneal [IP]), sacubitril demonstrated low toxicity. General symptoms of toxicity (decreased activity and abnormal gait) and oedema of the liver were observed only after IP administration. There were no clinical signs or pathological changes after PO administration up to 2000 mg/kg in the mouse or rat. The maximum non lethal oral dose in mice was 2000 mg/kg and in rats was 500 mg/kg (maximum doses tested).

Repeat dose toxicity

Appropriately designed repeat dose studies were conducted in mouse, rat, monkey and marmosets. Sacubitril/valsartan complex was administered in either 0.5%

carboxymethylcellulose, while sacubitril was administered in either 0.5% carboxymethylcellulose or 0.5% hydroxymethylcellulose by the oral route, which is the clinical route. Dosing was once daily which produced adequate exposure to compare with the clinical exposure following twice daily dosing. The cynomolgus monkey was the principal non-rodent species based on homology of NEP and NEP substrates to humans. Pivotal studies were conducted in mouse with sacubitril/valsartan complex and sacubitril alone (up to 13 weeks); in rats with sacubitril/valsartan complex and with sacubitril alone (up to 26 weeks); and in cynomolgus monkeys with sacubitril/valsartan complex (up to 39 weeks), consistent with ICH guidelines. Studies were also conducted with sacubitril alone in marmosets (up to 52 weeks) for comparison with previous valsartan studies in marmosets in order to define the toxicological endpoints.

Relative exposure

The exposure ratios have been calculated based on animal:human plasma AUC, adjusted to account for the clinical 200 mg BID dose. Human reference values are derived from Clinical Studies CLCZ696A2117 and CLCZ696B2223 conducted with stable patients with HF. The NOAEL is shown in bold type.

Table 3. Relative exposure in repeat-dose toxicity studies with sacubitril/valsartan complex.

| Species | Study duration | Dose (mg/kg/day) | AUC _{0-24h} (ng·h/mL) | Exposure ratio [#] |
|------------------|----------------|---------------------|--------------------------------|-----------------------------|
| Mouse (CD-1) | 2 weeks | sacubitrilat | | |
| | | 400 | 192000 | 0.63 |
| | | 800 | 297000 | 0.98 |
| | | Valsartan | | |
| | | 400 | 19550 | 0.24 |
| | | 800 | 710500 | 8.6 |
| | 13 weeks | sacubitrilat | | |
| | | 200 | - | - |
| | | 400 | 67000 | 0.22 |
| | | Valsartan | | |
| 200 | | 9210 | 0.11 | |
| 400 | | 12325 | 0.15 | |
| Rat (Han Wistar) | 2 weeks | sacubitrilat | | |
| | | 50 | 8285 | 0.027 |
| | | 200 | 47750 | 0.15 |
| | | 600 | 157500 | 0.52 |
| | | 1200 | 268500 | 0.88 |
| | | Valsartan | | |
| | | 50 | 20600 | 0.25 |
| | | 200 | 82400 | 1.0 |
| | | 600 | 273000 | 3.3 |
| | | 1200 | 470500 | 5.7 |
| Rat (Han Wistar) | 13 week | sacubitrilat | | |
| | | 30 | 4980 | 0.016 |
| | | 100 | 27800 | 0.09 |
| | | Valsartan | | |
| | | 30 | 10900 | 0.13 |
| | 100 | 43050 | 0.52 | |

| Species | Study duration | Dose (mg/kg/day) | AUC _{0-24h} (ng·h/mL) | Exposure ratio |
|---|----------------|----------------------|-----------------------------------|----------------|
| Rat (Han Wistar) | 26 weeks | sacubitrilat | | |
| | | 30 | 5170 | 0.015 |
| | | 100 | 15200 | 0.05 |
| | | Valsartan | | |
| | | 30 | 8105 | 0.10 |
| | | 100 | 27150 | 0.33 |
| Monkey (Cynomolgus) | 1 week | sacubitrilat | | |
| | | 25 | 30750 | 0.10 |
| | | 100 | 163500 | 0.54 |
| | | Valsartan | | |
| | | 25 | 5500 | 0.07 |
| | | 100 | 17000 | 0.21 |
| | 2 weeks | sacubitrilat | | |
| | | 100 | 258500 | 0.85 |
| | | 300 | 1160000 | 3.85 |
| | | 600 | 3500000 | 11.5 |
| | | Valsartan | | |
| | | 100 | 24700 | 0.30 |
| | 13 weeks | sacubitrilat | | |
| | | 30 | 35900 | 0.12 |
| | | 100 | 161000 | 0.5 |
| | | 300 | 821000 | 2.71 |
| | | Valsartan | | |
| | | 30 | 5285 | 0.06 |
| | 39 weeks | sacubitrilat | | |
| | | 30 | 27200 | 0.18 |
| | | 100 | 152000 | 0.50 |
| | | 300 | 614000 | 2.02 |
| | | Valsartan | | |
| | | 30 | 8500 | 0.10 |
| Human (stable patients with HF) | 7 days | 200 mg BID | sacubitrilat | |
| | | | 151611* | - |
| | | | Valsartan | |
| | | | 41388* | - |
| | | | | |
| | | | | |

*AUC_{0-12h} values: These were multiplied by 2 for comparison with the animal AUC_{0-24h} and calculation of the Exposure Ratio.

Table 4. Relative exposure in repeat-dose toxicity studies with sacubitril.

| Species | Study duration | Dose (mg/kg/day) | AUC _{0-24h} (ng·h/mL) | Exposure ratio [#] |
|---|-----------------------------|----------------------------|-----------------------------------|--------------------------------|
| sacubitrilat | | | | |
| Mouse (CD-1) | 13 weeks | 400 | 108500 | 0.35 |
| | | 800 | 257500 | 0.85 |
| | | 1200 | 634500 | 2.09 |
| | 104 week carcinogenicity | 1200 M^{\$} | 759000 | 2.5 |
| | | 1200 F^{\$} | 510000 | 1.7 |
| Rat (Han Wistar) | 2 weeks | 50 | 22150 | 0.07 |
| | | 150 | 81900 | 0.27 |
| | 2 weeks | 250 | 102550 | 0.34 |
| | | 500 | 138000 | 0.46 |
| | | 1000 | 182000 | 0.60 |
| | | 2000 | 393000 | 1.30 |
| | 13 weeks | 50 | 19550 | 0.06 |
| | | 100 | 61100 | 0.20 |
| | | 200 | 167500 | 0.55 |
| | | 400 | 299500 | 0.99 |
| | 13 weeks | 400 | 240000 | 0.80 |
| | | 800 | 389500 | 1.30 |
| | | 1200 | 773000 | 2.55 |
| | 26 weeks | 50 | 31500 | 0.10 |
| | | 150 | 156500 | 0.52 |
| | | 600 | 344000 | 1.13 |
| | 104 week ^{\$} | 400 M^{\$} | 266000 | 0.88 |
| 400 F^{\$} | | 510000 | 0.71 | |
| Marmosets (<i>Callithrix jacchus</i>) | 1 week | 50 | 56500 | 0.19 |
| | | 250 | 242500 | 0.80 |
| | | 500 | 250500 | 0.83 |
| | 52 weeks | 25 | 30400 | 0.10 |
| | | 100 | 220000 | 0.73 |
| | | 200 | 441500 | 1.46 |
| Human (stable patients with HF) | 7 days | 200 mg BID | 151611 | - |

= based on animal:human AUC values. Clinical plasma AUC_{0-12h} multiplied by 2 to compare with the animal AUC_{0-24h} values; \$ AUC_{0-24h} values obtained from CTD.

Major toxicities

Sacubitril/valsartan complex was well tolerated in repeat dose studies in rat and monkey with little evidence of adverse effects. Target organs were identified as the gastrointestinal tract and the kidney. Changes were also noted in the heart. Sacubitril alone was well tolerated in repeat dose studies in mouse, rat and marmoset. The target organ in both rats and marmosets was the glandular stomach.

Renal effects

Juxtaglomerular hypertrophy/hyperplasia was observed following treatment with sacubitril/valsartan complex in all the monkey studies at ≥ 100 mg/kg/day and in the 2 week rat study at ≥ 200 mg/kg/day. The effect was still present in monkeys after the recovery period. The effect was not observed in longer rat studies which were conducted at ≤ 100 mg/kg/day. Juxtaglomerular hypertrophy/hyperplasia is considered to be related to the pharmacology of AT1 receptor blockage and has been reported in studies with

valsartan in marmosets at ≥ 200 mg/kg/day. There were no reports of similar effects in rats or marmosets treated with sacubitril alone. A dose of 200 mg/kg/day in rats is equivalent to the clinical exposure to valsartan resulting from treatment with sacubitril/valsartan complex. A dose of 100 mg/kg/day in monkeys is equivalent to 0.45 times the clinical exposure to valsartan resulting from treatment with sacubitril/valsartan complex. In monkeys, renal tubular changes were only observed at 600 mg/kg/day, equivalent to 4.6 times the clinical exposure to valsartan resulting from treatment with sacubitril/valsartan complex. The potential for juxtaglomerular hypertrophy/hyperplasia is considered clinically relevant, but unlikely to lead to a decline in renal function.

Gastrointestinal effects

Gastrointestinal changes were observed following treatment with sacubitril/valsartan complex in rat studies at ≥ 50 mg/kg/day and in monkey studies at ≥ 30 mg/kg/day. The changes were characterised by reversible mixed cell inflammation and focal erosion in the glandular stomach in rats, and by emesis and diarrhoea in the monkey, but without microscopic findings. Previous studies with valsartan also reported gastritis, but only at high dose levels where ulcerative gastritis occurred. In the current studies, the gastritis was attributed to local irritancy effects associated with the sacubitril treatment, since similar microscopic changes were observed in sacubitril treated rats at ≥ 50 mg/kg/day, and emesis in marmosets at ≥ 100 mg/kg/day. This conclusion is also supported by the tolerability study which compared the inflammatory effects of subcutaneous and oral administration of sacubitril/valsartan complex. Subcutaneous administration produced higher systemic exposure and skin inflammation, but did not result in gastric inflammation. Based on these results, a dose based exposure ratio is more relevant to determine the safety margin. The NOAEL for gastritis in rats was 30 mg/kg, which is 9 times the human dose of 200 mg BID (3.3 mg/kg). On this basis, the observed gastrointestinal effects are unlikely to be clinically relevant.

Haematology changes

Small decreases in red blood cell count, haemoglobin concentration and haematocrit were observed in rats occurred at ≥ 200 mg/kg/day in a 2 week study. In longer studies at lower dose levels, these changes were not observed. Similar decreases in red blood cell parameters were observed previously in rat studies with valsartan at ≥ 60 mg/kg/day. No changes were observed in rat and marmoset studies with sacubitril. The observed changes are attributed to the pharmacological effects of valsartan on the AT1 receptor. A dose of 200 mg/kg/day in rats is equivalent to the clinical exposure to valsartan resulting from treatment with sacubitril/valsartan complex. The observed changes should be considered clinically relevant.

Heart weight changes

Heart weights were decreased in mice treated with sacubitril/valsartan complex at ≥ 400 mg/kg/day and in rats at ≥ 100 mg/kg/day. Heart weights were also decreased in rats in one 13-week study with sacubitril alone at ≥ 400 mg/kg/day. This effect on heart weight was not consistently observed in all studies with sacubitril and was not accompanied by any pathological changes. In previous studies with valsartan, heart weights were consistently decreased in rats treated at ≥ 60 mg/kg/day. This observation is likely to be related to the pharmacological effects of valsartan on the AT1 receptor, but may also be related to the pharmacological effects of sacubitril. The observed changes are not considered to be clinically relevant.

Genotoxicity

The genotoxic potential of sacubitril/valsartan complex was examined in vitro in a bacterial reverse mutation assay and in a test for chromosomal aberrations in human blood lymphocytes, and in vivo in a rat micronucleus assay. The genotoxic potential of

sacubitril alone and its metabolite sacubitrilat were further examined in vitro in a bacterial reverse mutation assay (sacubitril) and in a test for chromosome aberrations in human blood lymphocytes (sacubitril and sacubitrilat). All assays complied with guidelines and had appropriate positive controls. In all studies, the results were negative and no further testing was considered necessary. Previous studies with valsartan alone did not demonstrate any genotoxic potential. Neither sacubitril (alone or in complex with valsartan) nor its metabolite sacubitrilat are considered to have genotoxic potential.

Carcinogenicity

Carcinogenicity studies were conducted in 2 year studies in mice and rats with sacubitril and with valsartan since higher exposure ratios could be achieved with the separate components than with sacubitril/valsartan complex. Studies with valsartan were considered in a previous application. Dose selection, route of administration and selection of vehicle were determined in preliminary short term studies in mice and rats, and considered appropriate. Studies were conducted in compliance with ICH guidelines, however, there were insufficient blood sample time point were taken to determine pharmacokinetic parameters, and parameters from comparable 13 week studies in mice and rats were used to determine relative exposure.

In mice, sacubitril was administered in 0.5% hydroxypropylcellulose at dose levels up to 1200 mg/kg/day, which was the maximum dose based on solubility of sacubitril and dosing volume. There was no evidence of a treatment related increase in the incidence of neoplastic lesions leading to early death. After 2 years, neoplastic and non neoplastic changes were evident in a range of tissues in males and females, but none were considered to be treatment related. The maximum dose was equivalent to 2.09 times the clinical exposure based on AUC (Study 0770896).

In rats, sacubitril was administered in 0.5% hydroxypropylcellulose at dose levels up to 400 mg/kg/day, based evidence of toxicity at higher dose levels. There was no evidence of a treatment related increase in the incidence of neoplastic lesions leading to early death. After 2 years, there was no treatment related increase in the incidence of neoplastic lesions in males or females. The maximum dose was equivalent to 0.8 times the clinical exposure based on AUC (Study 0770711).

Reproductive toxicity

The reproductive and developmental toxicity of sacubitril/valsartan complex and sacubitril alone was examined in rats and rabbits. Studies included fertility and early embryonic development, embryofoetal development, pre and postnatal development, and a study of juvenile development. All studies were considered to be appropriately designed.

In all of studies with sacubitril/valsartan complex, the exposure ratios were low at the NOAEL due to maternal toxicity; however, in studies with sacubitril alone, the exposure ratios at the NOAEL were adequate.

Relative exposure

The exposure ratios have been calculated based on animal:human plasma AUC, adjusted to account for the clinical 200 mg BID dose. Human reference values are derived from Clinical Studies CLCZ696A2117 and CLCZ696B2223. The NOAEL is shown in bold type.

Table 5. Relative exposure in reproductive and developmental toxicity studies with sacubitril/valsartan complex.

| Species & strain | Study type | Dose mg/kg/day | AUC _{0-24h} ng·h/mL | ER [#] |
|---|---|---------------------|---------------------------------|-----------------|
| Rat (Han Wistar) | Fertility and early embryonic development | sacubitrilat | | |
| | | 150 | 41700^a | 0.13 |
| Rat (Han Wistar) | Embryofoetal development | sacubitrilat | | |
| | | 30 | 5950 | 0.02 |
| | | 100 | 19200 | 0.06 |
| | | 200 | 29400 | 0.10 |
| | | Valsartan | | |
| | | 30 | 13400 | 0.16 |
| | | 100 | 60000 | 0.72 |
| | | 200 | 119000 | 1.44 |
| Rabbit (NZW) | Embryofoetal development | sacubitrilat | | |
| | | 3 | 1930 | 0.02 |
| | | 10 | 8920 | 0.03 |
| | | 30 | 102000 | 0.34 |
| | | Valsartan | | |
| | | 3 | 41100 | 0.50 |
| | | 10 | 169000 | 2.04 |
| | | 30 | 400000 | 4.83 |
| Human (stable patients with HF) | Treatment for 7 days | 200 mg BID | sacubitrilat | |
| | | | 151611* | - |
| | | | Valsartan | |
| 41388* | - | | | |

*AUC_{0-12h}; # = based on animal:human AUC values. Clinical plasma AUC_{0-12h} multiplied by 2 to compare with the animal AUC_{0-24h} values; ^a AUC value based on linear extrapolation from 100 mg/kg/day exposure on day 76 in rat study (0670283).

Table 6. Relative exposure in reproductive and developmental toxicity studies with sacubitril.

| Species & strain | Study type | Dose mg/kg/day | AUC _{0-24h} ng·h/mL | ER# |
|------------------------------------|---|---------------------|------------------------------|------|
| Rat (Han Wistar) | Fertility and early embryonic development | sacubitrilat | | |
| | | 750 | 365150 ^a | 1.20 |
| | Embryofoetal development | sacubitrilat | | |
| | | 75 | 60300 | 0.20 |
| | | 250 | 58700 | 0.19 |
| | | 750 | 659000 | 2.17 |
| | Pre- post-natal development | sacubitrilat | | |
| | | 250 | 87187 ^b | 0.29 |
| | | 750 | 325500 ^b | 1.07 |
| | Juvenile development | 100 | 41950 | 0.12 |
| | | 400 | 182000 | 0.60 |
| | | 800 | 633500 | 2.09 |
| Rabbit (NZW) | Embryofoetal development | sacubitrilat | | |
| | | 15 | 35100 | 0.12 |
| | | 50 | 129000 | 0.43 |
| | | 200 | 679000 | 2.24 |
| | | 500 | 1730000 | 5.56 |
| Human (stable patients with HF) | Treatment for 7 days | 200 mg BID | 151611* | - |

*AUC_{0-12h}:# = based on animal:human AUC values. Clinical plasma AUC_{0-12h} multiplied by 2 to compare with the animal AUC_{0-24h} values; ^aAUC value based on linear extrapolation from 800 mg/kg/day exposure on day 72 in rat study (0770711); ^bAUC value based on linear extrapolation from 400 or 800 mg/kg/day exposure on day 27 in rat study (0770711).

Placental transfer of radioactivity associated with 14C-sacubitril/valsartan complex was examined in pregnant rats. Transfer of radioactivity to fetal tissue was low, with a fetus-to-maternal blood ratio of 0.246-0.509. In pregnant rabbits treated with sacubitril/valsartan complex, transfer of sacubitrilat to foetal tissue was low with a foetus to maternal blood ratio of 0.06-0.21. Excretion into milk was examined in pregnant rats treated with 14C sacubitril/valsartan complex. There was ready transfer of radioactivity with a milk:plasma ratio of 0.91, based on AUC. The radioactivity was associated with LBQ675, with no detection of sacubitril. On this basis, the breast fed infant intake of sacubitrilat is estimated to be <1% adult clinical exposure, based on an intake of 1 L milk per day.

There was no effect on fertility in rats following treatment with sacubitril/valsartan complex up to 150 mg/kg/day (equivalent to 0.13 times the clinical exposure based on

AUC) or following treatment with sacubitril alone up to 750 mg/kg/day (equivalent to 1.1 times the clinical exposure, based on AUC). Maternal toxicity was evident at lower dose levels in both studies.

In the embryofoetal development study in rats with sacubitril/valsartan complex, there was an increase in post implantation loss at 100 mg/kg/day (equivalent to 0.06 times the clinical exposure based on AUC) which was likely to be related to maternal toxicity. In the rat study with sacubitril alone, there was maternal toxicity but no evidence of embryofoetal toxicity at 750 mg/kg/day (equivalent to 2.17 times the clinical exposure). In both studies, there was no evidence of treatment-related skeletal or visceral findings. In the embryofoetal development study in rabbits, the sacubitril/valsartan complex was embryotoxic at maternally toxic doses (low incidence of foetal hydrocephaly malformations at ≥ 10 mg/kg/day; equivalent to 0.03 times [sacubitrilat] and 2 times [valsartan] the clinical exposure based on AUC) and embryo lethal at 30 mg/kg/day, effects attributed to the angiotensin receptor antagonist activity of valsartan.

In the rabbit embryofoetal development study with sacubitril alone, there was maternal toxicity at ≥ 50 mg/kg/day and embryofoetal toxicity at 500 mg/kg/day (equivalent to 5.56 times the clinical exposure, based on AUC). There was also a small increase in skeletal malformation and delayed ossification at 500 mg/kg/day (equivalent to 5.56 times the clinical exposure based on AUC). The effect observed in pups is unlikely to be clinically relevant.

Pre and postnatal development studies were not conducted with the sacubitril/valsartan complex, but were conducted separately with sacubitril and valsartan in order to obtain an adequate exposure ratio to the clinical exposure.

In the pre and postnatal development study in rats with sacubitril alone, there was no evidence of maternal toxicity or effects on reproductive parameters. There was slight evidence of toxicity in F1 pups (reduced bodyweight gain) but no effect on physical development or behavioural performance in F1 pups or F1 adults at 750 mg/kg/day (equivalent to 1.1 times the clinical exposure based on AUC).

A peri postnatal development study in rats with valsartan was considered in a previous application and showed adverse effects on birth weight, postnatal growth, survival and physical development of the offspring at a maternal dose level of 600 mg/kg/day, with a no-effect dose level of 200 mg/kg/day (equivalent to 3.6 and 0.9 times clinical exposure based on valsartan AUC at Day 13 in Study 0670220 with sacubitril/valsartan complex).

In the juvenile development (7-70 days post partum [pp]) study in rats with sacubitril, there was evidence of toxicity, including decreased bone length, width and mass at 400 mg/kg/day on Day 64 pp (equivalent to 0.60 times the clinical exposure based on AUC). Given the low relative exposure at the NOAEL on day 64pp (100 mg/kg/day, equivalent 0.12 times the clinical exposure), the effects on bone development should be considered clinically relevant, particularly in paediatric patients, although use of sacubitril/valsartan complex in paediatric patients is not proposed currently. A further investigative study was conducted over a shorter 4 week time frame (7-35 days pp). There were decreases in parameters related to bone growth and strength, but not bone turnover, at 400 mg/kg/day on the day of highest exposure, Day 21 pp (equivalent to 1.75 times the clinical exposure based on AUC). All the observed changes were reversed after the 16 week recovery period. The results of this study suggest the observed changes are transient and most relevant during the period of rapid bone growth. In a 4 week study (from day 28 pp) in juvenile rabbits, there was no effect on any bone parameters at the maximum dose of 150 mg/kg/day sacubitril (equivalent to 0.41 times the clinical exposure based on AUC).

Pregnancy classification

The sponsor has proposed Pregnancy Category D,² based on the clinical evidence from the use of valsartan. On this basis, Pregnancy Category D for sacubitril/valsartan complex is appropriate.

Local tolerance

Studies in rats established that sacubitril/valsartan complex caused significant inflammation at the injection site following subcutaneous administration, but no inflammation in the glandular stomach, despite high systemic exposure. In the mouse lymph node assay, sacubitril was shown to be a weak sensitiser. In studies in the rabbit, sacubitril was shown not to be a skin irritant, but was an eye irritant.

Other toxicity studies

A short term study to examine the potential for amyloid β accumulation in the CNS of monkeys as a result of neprilysin inhibition showed increased levels of newly-formed amyloid β and decreased clearance of total amyloid β in the CSF at an exposure level to sacubitrilat which was 0.3 times the clinical exposure, based on AUC. There was no increase in amyloid containing plaques or amyloid deposition in the brain of monkeys in a 39 week study (0670621) at twice the clinical exposure (based on AUC). Also, a study in healthy humans did not produce any changes to the CSF concentration of amyloid β 40 or amyloid β 42 (Study LCZ696A2126). The available data suggest that changes in amyloid β levels in the CSF are unlikely to be clinically relevant.

In a 13 week investigative study in 19 week old rats (sexually mature, but with ongoing bone deposition), no increase in bone resorption was observed. Minimal decreases in bone mineral density were observed, consistent with ongoing bone deposition at 400 mg/kg/day (approx. equivalent to the clinical exposure based on AUC). The results suggest that the observed changes to bone formation are not relevant in an adult population.

In 13 week studies in mice, pulmonary lesions observed after oral exposure to 2000 mg/kg/day sacubitril in the CD-1 strain were not observed after gavage exposure or in the B6C3F1 strain. No adverse effects at 1000 mg/mg/day (approximately equivalent to the clinical exposure).

Impurities

The proposed specifications for impurities/degradants in sacubitril/valsartan complex are below the ICH qualification thresholds.

Paediatric use

Sacubitril/valsartan complex is not currently proposed for paediatric use.

² Category D: "Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details."

Nonclinical summary and conclusions

Summary

- The data provided were adequate to analyse and assess the nonclinical pharmacological, pharmacokinetic and toxicological properties of sacubitril/valsartan complex in relation to its proposed clinical use, as well as the properties of sacubitril alone. The studies on valsartan alone have been previously considered. The data examined were in general accordance with ICH guidelines. The pivotal studies were GLP compliant and conducted with the proposed clinical formulation. The exposure ratios were low but considered adequate to address the clinical relevance of the observed toxicities.
- The primary pharmacology studies were conducted with sacubitril/valsartan complex, sacubitril and its metabolite sacubitrilat. In vitro studies identified sacubitrilat as the major inhibitor of the enzyme neprilysin (NEP) derived from both animals and humans at concentrations well below the clinical exposure. In vivo studies conducted in rats, dogs and monkey examined NEP activity, as well as measuring atrial natriuretic peptide (ANP) levels, and biological markers of increased ANP levels following sacubitril/valsartan complex treatment. Sacubitril inhibited NEP activity and increased ANP levels in vivo at a clinically relevant exposure. In suitable animal models (DSS rats, transgenic rats with hypertension, and Stroke-Prone Spontaneously Hypertensive (SHRSP) rats, and dogs of low salt diet), sacubitril/valsartan complex was able to modulate both the NP system and RAAS leading to a greater reduction in adverse effects than obtained by treatment with either sacubitril or valsartan alone.
- In in vitro secondary pharmacodynamic studies, sacubitrilat was shown to be a potent inhibitor of NEP, but was not strongly active against other enzymes. Neither sacubitril nor sacubitrilat were active against 57 receptors, transporters and ion channels. In spontaneously hypertensive rats, sacubitril did not potentiate bradykinin induced angioedema; however, the clinical relevance of this study is uncertain and the potential for clinical angioedema needs to be examined.
- Safety pharmacology studies in mice or rats examining the potential acute effects of sacubitril/valsartan complex or sacubitril alone found no evidence of potential CNS effects, cardiovascular effects (in vitro studies of hERG tail current or in vivo studies in monkeys), or respiratory effects. Studies were conducted at dose levels well in excess of the clinical exposure.
- Pharmacokinetic studies showed that sacubitril/valsartan complex was rapidly absorbed, achieved >60% bioavailability in all species; and upon absorption was rapidly converted to sacubitril and valsartan. The very high clearance in rats reflected conversion of sacubitril to sacubitrilat. Rapid metabolism to sacubitrilat was reflected in the AUC and C_{max} values for sacubitril and sacubitrilat in mice, rats and humans. The terminal half lives varied with species, with a t_{1/2} of 12 h in humans. In repeat dose studies, exposure was dose-proportional. Plasma protein binding was high in both animals and humans, with no significant uptake into red blood cells. Tissue distribution was extensive, but mainly in kidney, liver and bile, with no significant accumulation in melanin containing tissues or in brain tissues. The major metabolic step is ethyl ether hydrolysis to form sacubitrilat, which is the major circulating metabolite and excretion product. There are other minor metabolites, but none are human-specific. Neither sacubitril nor sacubitrilat was metabolised significantly by cytochrome P450 enzymes. Weak inhibition by sacubitrilat of CYP2C9 was not considered clinically relevant. Excretion was via faeces and urine in monkeys and humans, with sacubitrilat the major excretion component. The pharmacokinetic

results support the rat and monkey as appropriate models for assessment of sacubitril/valsartan complex-related toxicity in humans.

- There was no evidence of a pharmacokinetic interaction between sacubitril and valsartan. In vitro studies indicated that sacubitril may be a low affinity substrate for P-glycoprotein, but its high permeability suggests inhibition of P-gp would be unlikely to affect its absorption. Transportation of sacubitrilat by OATP1B1 and OATP1B3 was significant and co-administration of inhibitors of these transporters may increase systemic exposure to sacubitrilat.
- Single dose studies demonstrated that sacubitril/valsartan complex and sacubitril alone have low acute toxicity via both oral and IV routes. There is no potential for acute toxicity in humans.
- Treatment related toxicity observed in the repeat-dose studies with sacubitril/valsartan complex in rat and monkeys was restricted to renal effects, gastrointestinal effects, haematological changes and changes to heart weight. In the kidney, juxtaglomerular hypertrophy/hyperplasia was considered to be related to the pharmacology of AT1 receptor blockage, and has been reported in studies with valsartan in marmosets. There were no reports of this effect in rats or marmosets treated with sacubitril alone. The potential for juxtaglomerular hypertrophy/hyperplasia is clinically relevant, but unlikely to lead to changes in renal function. Gastrointestinal inflammation and erosion in the glandular stomach was reversible and likely to be attributed to local irritancy, as it was also observed following sacubitril treatment. Using a dose based approach to relative exposure, it seems unlikely to be clinically relevant. The decrease in red blood cell parameters was also observed following treatment with valsartan, but not in rats and marmosets treated with sacubitril, and should be considered clinically relevant. Heart weight changes were also observed in some studies with sacubitril and in previous studies with valsartan, and are likely due to pharmacological effects. These changes are not considered clinically relevant.
- In genotoxicity studies, neither sacubitril/valsartan complex, sacubitril alone nor sacubitrilat produced any evidence of genotoxic potential.
- Carcinogenicity studies were conducted with sacubitril and valsartan separately in order to achieve higher exposure ratios. In 2 year studies in mice and rats, sacubitril did not produce any evidence of an increase in treatment related tumours at clinically relevant exposures.
- Reproduction and developmental toxicity studies were conducted in rats and rabbits with sacubitril/valsartan complex and with sacubitril alone. Placental transfer was low in pregnant rats and rabbits, but there was ready transfer of sacubitrilat to milk. Potential breast-fed infant intake was estimated to be <1% of adult clinical exposure.
- There was no effect of sacubitril/valsartan complex or sacubitril alone on fertility in rats.
- Embryofoetal studies with sacubitril/valsartan complex showed increased embryo lethality in both rats and rabbits, and teratogenicity (low but dose dependent increase in hydrocephaly) in rabbits at maternotoxic doses (≥ 10 mg/kg). The sacubitril/valsartan complex is contraindicated during pregnancy and has Pregnancy Category D, which is appropriate and consistent with that of other drugs acting on the RAAS.
- In embryofoetal development studies with sacubitril alone, embryofoetal toxicity and delayed ossification were only observed in rabbits, and only at maternotoxic doses (relative plasma exposure to sacubitrilat ~ 5 , with NOAEL ~ 2 ; based on AUC)

- A pre/postnatal development study in rats with sacubitril showed no evidence of effects on physical development or behavioural performance, but body weight was reduced in F1 pups at clinically relevant exposures. A previous peri postnatal in rats with valsartan alone also showed adverse effects on birth weight, postnatal growth, survival and physical development of the offspring at low exposure levels.
- In juvenile development studies in rats, there was evidence of reversible effects on bone growth and strength (but not bone turnover) at a clinically relevant exposure, although the use of sacubitril/valsartan complex is not currently proposed in paediatric patients. Subsequent studies suggest the changes are transient and only relevant during the period of rapid bone growth in juveniles.
- A short term study in monkeys treated with sacubitrilat showed increased levels of newly formed amyloid β and decreased clearance of total amyloid β in the CNS, but not in the brain. These changes are unlikely to be clinically relevant as they were not seen in the long term monkey studies or in studies in healthy human volunteers.

Conclusions

- There were no major deficiencies in the nonclinical data.
- The primary pharmacology data on sacubitril/valsartan complex demonstrate its nonclinical efficacy and support its use for the proposed indication.
- The secondary pharmacodynamic studies did not identify any clinically relevant adverse effects; however, the potential for NEP inhibition related angioedema needs further examination.
- The safety pharmacology studies did not identify any clinically relevant adverse effects.
- The pharmacokinetic data support the rat and monkey as appropriate models for assessment of sacubitril/valsartan complex related toxicity in humans.
- The repeat dose toxicity studies identified renal effects (juxtaglomerular hypertrophy/hyperplasia), gastritis, and decreased red blood cell parameters as potentially clinically relevant.
- Sacubitril/valsartan complex is not considered to have any genotoxic or carcinogenic potential.
- The reproductive toxicity studies identified breast milk as a potential source of exposure for breast fed infants. Juvenile development studies identified reversible effects on bone growth and strength as clinically relevant to a juvenile population only.
- The observed embryofoetal toxicity (rats, rabbits) and teratogenicity (rabbits) with sacubitril/valsartan at low relative exposure levels warrant its contraindication during pregnancy and a Pregnancy Category D, which is appropriate and consistent with that of other drugs acting on the RAAS. Moreover, adverse effects were seen on F1 pup bodyweight (pre/postnatal development studies in rats with sacubitril alone) and on F1 postnatal growth, survival and physical development (peri/postnatal study in rats with valsartan alone) at low relative exposure levels (about 1 to 4 times based on AUC).
- Amyloid β accumulation in monkey CSF is considered unlikely to be clinically relevant.
- There are no objections to the registration of sacubitril/valsartan complex.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Entresto is a sodium salt complex which when taken orally dissociates into two components, the pro drug sacubitril, and valsartan. Sacubitril (AHU377) is metabolised to a novel NEP inhibitor (sacubitrilat), and valsartan is an ARB approved for the treatment of hypertension and HF.

The proposed indication is:

Entresto is indicated for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. Entresto has been shown to reduce the rate of cardiovascular death and heart failure hospitalisations.

Comment: Entresto is a pure and stable salt complex which dissociates into its active ingredients when taken orally. However, the TGA has ruled that the complex should be regarded as an FDC for the purposes of the clinical evaluation.

The submission proposes registration of sacubitril/valsartan sodium salt complex: 50, 100 and 200 mg film coated tablets.

Comment: The TGA has asked the evaluators for an opinion on the proposed use of single dose strengths, for example, LCZ696 200 mg although the tablet contains sacubitril 97 mg and 103 mg valsartan. While accepting the TGA's position on fixed dose combination products, the evaluator believes there is a rationale for using single dose strengths in this instance. Technically, the sponsor's proposal is justified because chemically the product is a stable salt which only dissociates after ingestion. More importantly, patients should be able to recognise and recall what medications and dose strengths they are receiving, particularly in emergency situations. Simple rounded numbers also make prescribing and dispensing errors less likely.

The target dose of Entresto is 200 mg BID taken orally with or without food. The 50 mg and 100 mg strengths are proposed starting doses with the selection dependent on other HF medications and the medical status of the patient.

Clinical rationale

HF is common and the prevalence is increasing worldwide due to increasingly ageing populations. It is associated with progressively severe symptoms, poor quality of life, frequent hospitalisations, and a high mortality rate. According to the National Heart Foundation, approximately 300,000 Australians are living with HF, and another 30,000 patients are diagnosed annually. Approximately 20-30% of patients with mild-moderate HF, and 50% with severe HF, die within one year of diagnosis. In patients with HF, approximately 80% of deaths are caused by sudden arrhythmias or progressive pump failure, and HF is the most common reason for hospital admissions

HF is associated with overstimulation of the RAAS which promotes vasoconstriction and fluid overload mediated by angiotensin II and aldosterone. ACE inhibitors block the deleterious effects of angiotensin II and, usually combined with a diuretic, they have formed the basis of treatment for many years. Additional complementary therapies include β blockers and aldosterone antagonists (MRAs). ACE inhibitors are recommended as first line treatment in the leading international treatment guidelines as they have been shown to reduce mortality by up to 20% compared with placebo in several major clinical trials. Two early, placebo controlled, landmark studies of enalapril were particularly

encouraging (CONSENSUS, 1987; SOLVD, 1991). In the CONSENSUS study, there was a 27% reduction in overall mortality, and a 50% reduction in deaths due to progressive HF in patients with severe CHF (NYHA class IV). In the SOLVD study, there was a 16% reduction in overall mortality and a 22% reduction in deaths due to progressive HF in patients with CHF and ejection fractions $\leq 35\%$. Beta blockers³ and MRAs⁴ have also been shown to reduce the risk of death when added to ACE inhibitors. ARBs are an alternative treatment used when ACE inhibitors are not tolerated, particularly in the event of angioedema. However, the evidence that ARBs reduce mortality is inconsistent. In the Val-HeFT study in patients with NYHA class II-IV, valsartan was not superior to placebo for reduction in all cause mortality or cardiovascular deaths. In addition, a meta analysis of 24 trials (conducted on behalf of the Cochrane Heart Group in 25,051 HF patients) demonstrated no reduction in mortality, disability or hospital admissions for ARBs compared with placebo.⁵

ANP is a 28 amino acid peptide stored mainly in the right atrium. It is released in response to atrial distension and it promotes diuresis and natriuresis. ANP infusions increase cardiac output with decreases in pulmonary wedge pressure, pulmonary vascular resistance, and plasma renin levels. ANP and other natriuretic peptides such as BNP and CNP are degraded by neutral endopeptidase found in many tissues. Neprilysin is a neutral endopeptidase found in many organs and tissues. It degrades ANP and other endogenous vasoactive peptides including bradykinin. In order to enhance the effects of ANP, NEP inhibitors were developed for potential use in hypertension and HF. Highly specific NEP inhibitors including candoxatril and ecadotril were shown to promote natriuresis and diuresis and reduce filling pressures as monotherapy in exploratory studies of patients with mild HF. However, they did not improve symptoms and were less effective in patients with severe HF, possibly due to decreased renal perfusion.⁶

Omapatrilat is a NEP and ACE inhibitor which reduces the breakdown of endogenous vasodilator peptides, in addition to blocking the generation of angiotensin II. However, it was no more effective than enalapril alone in OVERTURE, a large HF trial in 5,770 patients.⁷ Moreover, its use was associated with an increased risk of angioedema compared with the ACE inhibitor. The main treatment objectives in HF are to reduce symptoms, improve quality of life, reduce hospitalisations, and prolong survival. It is postulated that with the use of Entresto, the novel NEP inhibitor sacubitril will promote natriuresis and diuresis, while the compensatory stimulation of angiotensin II will be blocked by the ARB valsartan. It is hoped that the complementary effects of the FDC will lead to improved outcomes compared with ACE inhibitors alone, and that the risk of angioedema associated with ACE inhibitors will be reduced.

Guidance

A pre-submission meeting with the TGA was held on 8 August 2014. In response to TGA requests, the sponsor provided the following:

- A justification for the FDC
- A justification for an active comparator arm rather than placebo in the pivotal study PARADIGM-HF

³ Packer M, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 344: 1651-58 (2001).

⁴ Zannad F, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 364: 11-21 (2011).

⁵ Heran BS, et al. Angiotensin receptor blockers for heart failure. *Cochrane Database Syst Rev.* 4: CD003040.

⁶ Cleland JG, Swedberg K. Lack of efficacy of neutral endopeptidase inhibitor ecadotril in heart failure. The International Ecadotril Multi-centre Dose-ranging Study Investigators. *Lancet* 351: 1657-1658 (1998).

⁷ Packer M, et al. Comparison of omapatrilat in patients with chronic heart failure: the omapatrilat versus enalapril randomised trial of utility in reducing events (OVERTURE). *Circulation* 106: 920-926 (2002).

- A justification for the use of enalapril as a comparator in PARADIGM-HF
- A justification for not including a separate valsartan arm in PARADIGM-HF
- Responses to questions regarding the selection of objectives, clinical endpoints, hepatotoxicity, and age related effects in PARADIGM-HF

A summary of these discussions has been provided by the sponsor and reviewed by the evaluators.

Contents of the clinical dossier

The submission contained the following clinical information:

- 31 clinical pharmacology studies.
- One population pharmacokinetic analysis.
- One pivotal Phase III efficacy/safety study.
- Two Phase II efficacy/safety studies of direct relevance to the proposed indication.
- One dose response analysis of two biomarkers.
- An integrated summary of efficacy.
- An integrated summary of safety.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies were conducted according to the principles of ICH Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies are presented. Table 7 below shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 7. Submitted pharmacokinetic studies.

| PK topic | Subtopic | Study ID |
|---------------------------|------------------------------------|--|
| PK in healthy adults | General PK - Single dose | LCZ696A2101 |
| | mass balance | LCZ696B2105 |
| | Japanese | LCZ696A2102 LCZ696A1101 |
| | - Multi-dose | LCZ696A2102 |
| | Bioequivalence† - Single dose | LCZ696B2114 |
| | - Multi-dose | LCZ696A2103 LCZ696B2126 |
| | Food effect | LCZ696B2107 |
| PK in special populations | Target population § - Single dose | |
| | - Multi-dose | LCZ696A2222 LCZ696A2117 |
| | Hepatic impairment | LCZ696B2203 |
| | Renal impairment: mild/moderate | LCZ696A2204 |
| | Severe renal impairment multi-dose | LCZ696A2205 |
| | Elderly | LCZ696B2109 |
| Genetic/gender-related PK | Males vs. females | LCZ696B2109 |
| PK interactions | Atorvastatin (Chinese subjects) | LCZ696B2115 |
| | Metformin (Japanese subjects) | LCZ696B2122 |
| | Amlodipine | LCZ696A2119 |
| | Hydrochlorothiazide | LCZ696A2120 |
| | Digoxin | LCZ696B2111 |
| | Warfarin | LCZ696B2112 |
| | Omeprazole | LCZ696B2113 |
| | Carvedilol | LCZ696B2125 |
| | Furosemide | LCZ696B2116 |
| | Nitroglycerin | LCZ696B2128 |
| | Oral Contraceptive | LCZ696A2124 |
| Population PK analyses | Healthy subjects | CLCZ696A2204, CLCZ696A2205, CLCZ696A2117, CLCZ696B2203, CLCZ696B2314 |
| | Target population | CLCZ696B2223 |

* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

LCZ696 is a combination of sacubitril and the registered product valsartan. Sacubitril is converted in vivo by hydrolysis to an active metabolite sacubitrilat. The studies presented characterised the PK parameters for sacubitril (AHU377), the active metabolite sacubitrilat and valsartan. The PK characteristics of valsartan following administration of the combination were not different from those of valsartan given alone. In general, the PK studies presented by the sponsor were well designed and for most subject numbers were based on a priori power calculations. Some studies may have limited power as noted in the comments.

Absolute bioavailability was estimated from the mass balance study and not determined with IV administration as such a formulation could not be developed. Bioequivalence was established for clinical trial and proposed market formulations. Dose proportionality of kinetics was demonstrated across doses, which included the recommended therapeutic dose. Twice daily dosing is appropriate based on the results of the PK studies.

Generally moderate to severe renal impairment does not appear to require adjustment of the dose LCZ696, despite the fact that compounds are mostly renally excreted. This conclusion was supported by the population PK analysis. Similarly, the effects of mild and moderate hepatic impairment on the PK indicate that dose adjustment is not required. There were no studies in patients with end stage renal impairment undergoing dialysis and there were no studies in severe hepatic impairment.

There was an extensive series of studies examining potential PK drug-drug interactions. Since the two components are only minimally metabolised by hepatic enzymes there was little or no effect on PK parameters when LCZ696 was co-administered with known enzyme inducers or inhibitors. The in vitro data suggested some potential effects on transporter molecules. A relatively modest interaction was demonstrated with atorvastatin. Caution was recommended when LCZ696 is co-administered with atorvastatin or other statins that are substrates of OATP1B1 and OATP1B3. Gender, age and ethnicity/race did not appear to significantly affect the PK parameters of the analytes examined.

In patients with HF steady state PK parameters were higher than in healthy controls. An analysis of combined data suggested that PK parameters of valsartan, sacubitril and sacubitrilat were up to two fold higher than in healthy subjects. The reduced clearance and increased half life are presumably due to reduced renal blood flow in these patients. No other limitations were noted in the PK studies.

Pharmacodynamics

Studies providing pharmacodynamic data

Summaries of the pharmacodynamic studies are presented. Table 8 below shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 8. Submitted pharmacodynamic studies.

| PD Topic | Subtopic | Study ID |
|--|--------------------------------------|---|
| Primary Pharmacology | Effect on neprilysin inhibition | LCZ696A2102 |
| | | CLCZ696A2117 LCZ696B2223 |
| | | VNP489A2103 |
| Secondary Pharmacology | Other neprilysin substrates | CLCZ696B2223 |
| | | CLCZ696A2117 VNP489A2103 |
| | Amyloid- β | CLCZ696A2126 |
| | Renin Angiotensin Aldosterone System | CLCZ696A2102 CLCZ696A2117 LCZ696A2222 |
| | Natriuresis and diuresis | LCZ696B2223 LCZ696A2222 |
| | Glucose and fatty acid metabolism | CLCZ696B2207 |
| | Blood pressure | LCZ696B2223 |
| | Thorough QTc Study | CLCZ696B2123 |
| Gender other genetic and Age-Related Differences in PD Response | Effect of gender | No studies |
| | Effect of age | No studies |
| PD Interactions | Warfarin | CLCZ696B2112 |
| | Nitroglycerin | CLCZ696B2128 |
| | Frusemide | CLCZ696B2116 |
| | Sildenafil | CLCZ696B2225 |
| Population PD and PK-PD analyses | Healthy subjects | CLCZ696A2102 CLCZ696B2205 |
| | Target population | |

* Indicates the primary aim of the study.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

LCZ696 is a combination treatment of a neprilysin inhibitor (sacubitril) and an angiotensin II type-1 (AT1) receptor antagonist (valsartan). As a consequence, the mechanism-of-action of LCZ696 is described as an angiotensin receptor neprilysin inhibitor (ARNI). This results in complementary effects on the cardiovascular (CV) system that are beneficial in HF patients. The sponsor has presented a series of PD studies which

provide confirmatory evidence for the proposed mechanism of action. A series of surrogate biomarkers have been measured in healthy controls and HF patients and are consistent with simultaneous neprilysin inhibition and RAAS blockade. Neprilysin is one of multiple enzymes involved in the clearance of amyloid- β ($A\beta$) from the brain and cerebrospinal fluid (CSF). Administration of LCZ696 was associated with an increase in CSF $A\beta$ 1-38 compared to placebo; there were no changes in concentrations of CSF $A\beta$ 1-40 and 1-42. The clinical relevance of this finding is unknown. In a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1200 mg LCZ696 had no effect on cardiac repolarisation. A potential PD drug-drug interaction has been identified with LCZ696 and sildenafil with increased effects on blood pressure.

Dosage selection for the pivotal studies

No formal Phase II dose ranging clinical trial was performed in HF patients due to the ethical concerns of under or over treating vulnerable HF patients not receiving ACE inhibitors. Moreover, due to the nature of HF, efficacy and safety could not be extrapolated from clinical trial data in other patient populations such as hypertension.

Final dose selection was based on several factors including biomarker studies, historical valsartan PK data, a single ascending dose PK study of sacubitril in hypertensive subjects, a multiple ascending dose study of sacubitril in mildly hypertensive subjects, the degree of NEP inhibition demonstrated in pharmacology studies, and extrapolation from the Phase II dose ranging hypertension Study CLCZ696A2201.

By comparing AUCs, the dose of LCZ696 200 mg BID was shown to deliver similar valsartan exposure as a dose of 160 mg BID, the approved dose for HF. The dose of LCZ696 200 mg BID delivers a 97 mg dose of sacubitril which was shown to provide near maximal NEP inhibition.

The half lives of valsartan and sacubitrilat offer once daily dosing. However, the sponsor opted for a BID dosing regimen to ensure full 24 hour coverage and minimise the risk of PD breakthrough at trough (a possible factor in the failure of the OVERTURE study). The BID regimen also reduces the risk of hypotension in the elderly and patients with more severe cardiac impairment. The CLCZ696B2228 (TITRATION) study compared 3 and 6 week up-titration regimens.

Study VNP489A2102

This was a Phase I, randomised, double blind, placebo controlled, parallel group, ascending single dose study of AHU377 in mildly hypertensive patients. It was conducted at two centres in Germany between October 2004 and December 2004. The main objectives were to assess safety and tolerability, and to evaluate the PK of AHU377 and sacubitrilat after single oral doses of AHU377.

Methodology

In Part 1, single ascending doses of AHU377 10, 30, 100 and 200 mg were investigated in cohorts of 12 patients (10 active, 2 placebo). Fed/fasted arms were included in the 100 mg cohort. In Part 2, an exploratory study of the effects of AHU377 200 mg and 30 mg during infusion of nesiritide (recombinant human brain natriuretic peptide [BNP]) was conducted. A total of 68 patients were included and all completed the study (48 in Part 1, 20 in Part 2). Single doses of AHU377 were given under standard conditions to all patients. Male and female patients aged 21-65 years with untreated mild hypertension were included (msSBP between 140 and 160 mm Hg, msDBP between 87 and 95 mm Hg). In Part 1, blood samples were taken at various intervals up to 72 h post dose for measurement of plasma AHU377 and sacubitrilat (Table 9). In Part 2, samples were taken at intervals up to 12 h post dose.

Table 9. Study schematic VNP489A2102.

| Dose | 10 mg | 30 mg | 100 mg | 200 mg |
|---------|-------|-------|-------------|--------|
| Cohorts | A | | | |
| | | B | | |
| | | | C (fasting) | |
| | | | C (fed) | |
| | | | | E |

Results

After oral administration, AHU377 was rapidly absorbed and converted to sacubitrilat with systemic exposure to sacubitrilat 50-fold higher than for AHU377. AUC and C_{max} for AHU377 and sacubitrilat were dose proportional with an sacubitrilat half life of approximately 16 h. Food did not affect sacubitrilat exposure. Urinary recovery of sacubitrilat was approximately 33%.

Comment: The pro-drug AHU377 was rapidly converted to the active compound sacubitrilat in a dose proportional manner with a half-life of approximately 16 hours. Urinary recovery was approximately 33%. Food had no meaningful effect on sacubitrilat exposure.

Study VNP489A2103

This was a Phase I, randomised, double blind, placebo controlled, time lagged, parallel group, multiple ascending oral dose study of AHU377 given alone and in combination with valsartan in healthy volunteers. It was conducted at one centre in Germany between November 2006 and February 2007. The main objectives were the safety, tolerability and PK of multiple doses of AHU377, alone and in combination with valsartan 320 mg.

Methodology

The study design is shown in Table 10. Multiple oral doses of AHU377 (10, 30, 100, 200, 400, and 600 mg), given alone or in combination with valsartan 320 mg were assessed in seven cohorts of 12 healthy subjects over two treatment periods. In Period 1, Cohorts A-E underwent 14 day, multiple dose treatment periods. Cohorts F and G underwent single dose treatment periods followed by 14 day multiple dose treatment periods. In Period 2, the study was repeated with co-administration of valsartan 320 mg. Male and female healthy subjects aged 18-50 years were enrolled in 11 cohorts of 12 subjects. Blood samples for measurement of plasma and urine AHU377, sacubitrilat and valsartan were taken at intervals for 24 h post dose.

Table 10. Study schematic VNP489A2103.

| Cohorts | | Screening, Stabilization, and Baseline | Multiple Dose |
|--|--|---|---|
| | | | Period 1 (Days 1-14) |
| | | | Period 2 (Days 15-28) |
| Cohorts A-C, E | -- | -- | 10, 30, 100, and 200 mg AHU377 (8 subjects per cohort) OR Placebo (4 subjects per cohort) |
| | | 21-day Screening period, 4-day stabilization period, Baseline on Day -1 | 10, 30, 100, or 200 mg AHU377 plus 320 mg valsartan (8 subjects per cohort) OR Placebo plus 320 mg valsartan (2 subjects per cohort) OR Placebo (2 subjects per cohort) |
| Cohort D | -- | -- | 320 mg valsartan (8 subjects) OR Placebo (4 subjects) |
| | | 21-day Screening period, 4-day stabilization period, Baseline on Day -1 | 320 mg valsartan plus 100 mg AHU377 (8 subjects) OR Placebo (4 subjects) |
| Screening, Stabilization, and Baseline | | Single Dose | Stabilization and Baseline |
| | | Period O (Days 1-4) | Multiple Dose |
| | | | Period 1 (Days 1-13) |
| | | | Period 2 (Days 14-27) |
| Cohorts F and G | 21-day Screening period, 4-day stabilization period, Baseline on day prior to single dose administration | Single dose 400 or 600 mg AHU377 (8 subjects per cohort) OR Single dose Placebo (4 subjects per cohort) | 400 or 600 mg AHU377 (8 subjects per cohort) OR Placebo (4 subjects per cohort) |
| | | 2-day evaluation period, Baseline on Day -1 | 400 or 600 mg AHU377 plus 320 mg valsartan (8 subjects per cohort) OR Placebo plus 320 mg valsartan (2 subjects per cohort) OR Placebo (2 subjects per cohort) |

Results

For AHU377, AUC and C_{max} were less than dose proportional at steady state. AHU377 was rapidly cleared and no accumulation was observed over 14 days. Dose proportionality was observed following the single doses of 400 mg and 600 mg. For sacubitrilat, AUC and C_{max} were dose proportional at steady state with minor accumulation noted over 14 days. Mean AUC_τ for sacubitrilat was approximately 30 fold higher than for AHU377, while mean C_{max} was approximately 5 fold higher. The valsartan PK profile was comparable to historical data. Compared with AHU377 alone, valsartan decreased AHU377 AUC_τ and C_{max} by 17% and 14%, respectively. Compared with valsartan alone, AHU377 decreased valsartan AUC_τ and C_{max} by 7% and 6%, respectively.

Comment: After 14 days multiple doses, exposure for the active compound sacubitrilat was dose proportional with no significant accumulation at steady state. No significant drug-drug interactions were observed between AHU377 and valsartan.

Formal dose ranging studies of the efficacy and safety of LCZ696 were not considered appropriate in HF populations because of the risks of under- or over-treatment in patients not receiving ACE inhibitors. A Phase II study was not performed using surrogate and biomarker endpoints as they do not predict CV outcomes. The optimal dose of the valsartan component of LCZ696 was based on historical pharmacological, efficacy, and safety data in HF patients, incorporating the modest drug-drug interaction data with sacubitril in VNP489A2103. In mildly hypertensive volunteer subjects, single doses of sacubitril 10-200 mg were assessed in VNP489A2102, and multiple ascending doses of sacubitril 10-600 mg were assessed in VNP489A2103. The PK profile of sacubitril was defined and all doses were well tolerated. In the absence of efficacy markers, the sacubitril dose selected for the LCZ696 200 mg dose was based on effective NEP inhibition. In support, the exploratory Phase II study

CLCZ696B2214 in patients with HFpEF showed that LCZ696 was superior to valsartan alone for reduction in NT-pro-BNP and LAVI.

Given the perceived constraints, this best guess approach for dose selection was reasonable, but the dose of sacubitril was based almost entirely on effective NEP inhibition rather than clinical data (see Clinical Questions).

Efficacy

Evaluator's conclusions on efficacy

Evaluable efficacy data to support the proposed indication were obtained almost exclusively from the pivotal Phase III study CLCZ696B2314 (PARADIGM-HF). The open-label, Phase II study CLCZ696B2228 (TITRATION) compared two titration protocols to initiate LCLZ696 treatment in heart failure with reduced ejection fraction (HFrEF), but the primary endpoint was tolerability and no efficacy assessments were made. The Phase II study CLCZ696B2214 was submitted in support of the pivotal study but the patient population with heart failure with preserved ejection fraction (HFpEF) is not relevant to the proposed indication.

PARADIGM-HF was a very large and well controlled Phase III study with clearly defined and widely accepted endpoints. The study design, clinical endpoints and dose selection for the comparator were based on guidance from the US, EU and Canadian authorities. In particular, the acceptability of a single, large, pivotal study was agreed, justified on internal validity, data quality, statistical significance, internal consistency, and applicability to the target population as recommended in EU guidelines.⁸ An important FDA stipulation was that a minimum mean daily dose of 16.6 mg enalapril should be achieved to match that achieved in the SOLVD study which demonstrated a survival benefit compared with placebo (The SOLVD Investigators, 1991). This target was exceeded with an achieved mean final daily dose of 18.9 mg.

The primary endpoints of CV death and hospitalisations for worsening HF, alone and combined, are those most commonly used in HF outcome trials. To ensure uniform reporting and to reduce potential bias, a blinded adjudicating committee assessed each clinical endpoint. The choice of enalapril as the active comparator was appropriate because it is the standard of care for patients with HFrEF based on proven efficacy compared with placebo (CONSENSUS, 1987; SOLVD, 1991). NYHA class is a generally accepted prognostic indicator of adverse outcomes. In CONSENSUS, a significant efficacy benefit in favour of enalapril was demonstrated in patients with severe CHF of NYHA class IV. In SOLVD, a benefit was also demonstrated in patients with CHF predominantly in NYHA class II or III (mostly with a baseline EF \leq 35%). Although a small number of patients in PARADIGM-HF had an EF $>$ 35%, the great majority of patients were in NYHA class II or III. In general, this population matched that of the SOLVD study, justifying the use of enalapril as a comparator. A placebo control arm was not appropriate for ethical reasons, and valsartan is not as effective as enalapril in HF. In Val-HeFT, a large controlled trial in HF patients, valsartan reduced hospitalisations for HF but it did not reduce mortality compared with placebo.⁹ Based on these and similar data, valsartan is approved in Australia only for HF patients who are intolerant to ACE inhibitors. Sacubitril alone was not an appropriate study arm. It cannot be added to background ACE inhibitor therapy because of the risk of angioedema, and withdrawal of ACE inhibitor therapy to permit sacubitril monotherapy would be unethical in HF patients.

⁸ European Medicines Agency, "Points to consider on application with: 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

⁹ Carson P, et al. Effect of valsartan on hospitalisation: results from Val-HeFT. *J Card Fail.* 9: 164-71 (2003).

The duration of the trial was driven by endpoint targets rather than time and the DMC stopped the study when the primary endpoint was met after the third interim analysis. At this point, the median treatment period (including the run-in) was approximately 27 months. LCZ696 proved superior to enalapril, reducing the risk of the composite endpoint of CV death or HF hospitalisations by 20%. The primary outcome occurred in 914 patients (21.8%) in the LCZ696 group compared with 1,117 patients (26.5%) in the enalapril group (HR 0.80; 95% CI: 0.73 to 0.87, $P < 0.001$). There were 711 (17.0%) deaths from any cause in the LCZ696 group, and 835 (19.8%) deaths in the enalapril group (HR 0.84; 95% CI: 0.76, 0.93, $P < 0.001$). There were 558 (13.3%) deaths from CV causes in the LCZ696 group and 693 (16.5%) in the enalapril group (HR 0.80; 95% CI: 0.71, 0.89, $P < 0.001$).

Compared with enalapril, LCZ696 also reduced the risk of hospitalisation for HF by 21% ($p < 0.001$) and decreased the symptoms and physical limitations of HF ($p = 0.001$).

The LVEF $\leq 40\%$ inclusion criterion was changed to $\leq 35\%$ by protocol amendment following publication of the EMPHASIS-HF trial.¹⁰ In this study in patients with mild HF (NYHA class II, EF $\leq 30\%$), there was a 37% reduction in death from CV causes or hospitalisations for the MRA eplerenone compared with placebo. Increased use of eplerenone was expected to reduce the number of events and the step was taken to increase the incidence rate to complete the trial in the proposed time frame. Relatively few randomised patients had an EF $\geq 35\%$ and this amendment is unlikely to have introduced bias for or against either trial medication. In addition, the overall study population in PARADIGM-HF is comparable to the target population. The run-in periods ensured that patients were able to tolerate the 10 mg BID dose of enalapril and the LCZ696 200 mg BID dose at least in the short term, and the 36 hour washout periods minimised the risk of angioedema at cross-over points.

In summary, in patients with HFrEF, inhibition of angiotensin II and neprilysin with LCZ696 was 20% more effective than enalapril in reducing the primary composite endpoint of CV death and hospitalisation for HF, and for CV death alone. All-cause mortality was also reduced by 16%. The percentage endpoint reductions were both highly meaningful and statistically significant. LCZ696 also reduced symptoms and physical limitations associated with HF, and the benefit was observed in a patient population already receiving other effective HF medications such as β blockers and MRAs. No clinically significant differences in subgroups compared with the overall populations were observed. The overall exposure in more than 4,000 patients for approximately 27 months is sufficient to justify life long treatment, particularly in patients with reduced life expectancy.

The absolute risk reductions compared with enalapril were small (4.7% for the combined endpoint, 3.1% for CV death, and 2.8% for HF hospitalisations). Nonetheless, this novel product is a significant advance in the treatment of patients with systolic dysfunction.

Safety

Studies providing safety data

Pivotal efficacy study

- CLCZ696B2314 (PARADIGM-HF): A pivotal, Phase III, long term outcomes study in 8,442 randomised patients with a median follow-up time of 27 months.

In the pivotal efficacy study, the following safety data were collected:

¹⁰ Zannad F, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 364: 11-21 (2011).

- General adverse events (AEs) were assessed by primary SOC and PT according to severity and causality using MedDRA version 17.0.
- AEs of particular interest were identified based on the known safety profiles of valsartan, ACE inhibitors and MRAs. These were hypotension, hyperkalaemia, renal impairment, angioedema, and embryofoetal and infantile toxicity. Other events of special interest were hepatotoxicity, hypersensitivity and statin drug-drug interaction based on routine pharmacovigilance for new chemical entities.
- Routine laboratory tests for the pivotal study were processed centrally and collated by Cognizant Technology Solutions (India).

Dose response and non pivotal efficacy studies

No formal dose response study of LCZ696 in HF was conducted.

The following non pivotal efficacy studies provided evaluable safety data:

LCZ696 HF studies

- CLCZ696B2214 (PARAMOUNT): A supportive, Phase II, 12 week study in 301 randomised patients.
- CLCZ696B2228 (TITRATION): A supportive, Phase II study comparing LCZ696 3 and 6 week titration regimens in 498 patients.

Sacubitril monotherapy studies

Sacubitril monotherapy is not proposed for the treatment of HF and no studies have been performed. A sacubitril monotherapy arm of 165 hypertensive patients was included in CLCZ696A2201. These data are included in the pooled HTN analysis.

LCZ696 HTN studies (pooled)

The results of six short term hypertension studies (CLCZ696A2201, CLCZ696A2219, CLCZ696A2223, LCZ696A1306, LCZ696A2316, and LCZ696A2319) were pooled to support the pivotal LCZ696 safety data set.

LCZ696 HTN studies (non pooled)

Six LCZ696 hypertension studies were not pooled, either because they were ongoing or because of significant differences in study populations or design (CLCZ696A2219E, LCZ696A1304, LCZ696A1305, CLCZ696A2315, LCZ696A2318, and CLCZ696A2216).

Valsartan HF studies

Safety data from the large Phase III studies CVAL489B0107 (VAL-HeFT) and CVAL489B0108 (VALIANT) are considered with a pooled analysis from five other controlled HF trials (CVAL489B0106, CVAL489B0110, CVA489B0103, CVAL489B0104, and CVALB0107).

Valsartan HTN studies (pooled)

Pooled safety data have been provided for the valsartan 320 mg hypertension indication submitted to the EMA in 2005. A total of 7,228 patients were treated with valsartan of whom over 2,300 received the 320 mg dose. Summarised data are provided from five large controlled, Phase III trials (CVAL489A031, CVAL489H2301, CVAH631B0301, CVAH631C2301, and CVAA489A2201), three controlled Phase IV trials (CVAH631B2401, CVAH631B2403, and CVAH631B2405), two uncontrolled trials and one long-term extension study.

Clinical pharmacology studies

A total of 30 clinical pharmacology studies enrolled 1,117 healthy subjects, patients with HTN and HF, and special populations including the elderly and those with renal or hepatic

impairment. Safety data from studies in healthy subjects were pooled. No pooled safety analyses in patients were provided due to small sample sizes, different dose regimens and different populations.

Patient exposure

A total of 14,997 patients were exposed to LCZ696 in the development program (HF 10,106, HTN 3,874, and clinical pharmacology 1,117). A summary of patients exposed to LCZ696 200 mg BID, enalapril and valsartan is shown. In PARADIGM-HF, 4,203 patients were exposed to LCZ696 for at least one day with a total exposure of 8,636 patient years. The median duration of exposure was 27 months for the LCZ696 group, and exposure was ≥ 6 months in 92.5% of patients. A total of 149 and 497 patients received LCZ696 200 mg BID for at least one day in the HF studies CLCZ696B2214 and CLCZ696B2228, with total exposures of 89.7 and 108.9 patient years, respectively.

In the pooled HTN studies, mean study duration was 8 weeks and median duration of LCZ696 treatment ranged from 56.0 to 61.0 days. In the long term study CLCZ696A2219E1, the median duration of exposure was 358.0 days and $>90\%$ of patients were exposed for more than 300 days.

Safety issues with the potential for major regulatory impact

Liver toxicity

Significant liver function test (LFT) abnormalities were independently reviewed if they met standard pre-defined criteria (aspartate transaminase/alanine transaminase [AST/ALT] $>3x$ upper limit of normal [ULN] and total bilirubin $>2x$ ULN on the same day, or AST/ALT $>5x$ ULN at any visit). All liver related serious adverse events (SAEs) by preferred term (PT) were also reviewed. No significant treatment differences or safety signals were detected.

LFT abnormalities in CLCZ696B2314 are shown. The incidence of hepatic events was low in both treatment groups but marginally higher in the LCZ696 group compared with enalapril. In the LCZ696 group, there were 21 cases of transaminases $>5x$ ULN and four were considered drug related. There was only one case of AST/ALT $>3x$ ULN and total bilirubin $>2x$ ULN at the same visit. Shifts from normal to high transaminase values were reported more frequently in the enalapril group compared with LCZ696 (ALT 10.0% versus 8.0%, total bilirubin 10.4% versus 9.1%). Only one significant hepatic event was reported in the other LCZ696 HF studies, and no events were reported in the sacubitril arm of CLCZ696A2201. In the pooled LCZ696 HTN studies, hepatotoxicity was reported in 1.2% of the LCZ696 monotherapy group and 0.6% in the placebo group. The majority of events were related to increases in transaminases and bilirubin (0.9% versus 0.6%). In CVAL489B0107, the incidence of hepatic events was also low and comparable in the valsartan and placebo groups (hepatic function abnormal 0.12% versus 0.28%, respectively).

Comment: LFT abnormalities are to be expected in patients with HF due to hepatic ischaemia and liver congestion associated with right heart failure. However, the incidence of significant liver events was low in HF patients treated with LCZ696, sacubitril or valsartan.

Haematological toxicity

No issues were identified.

Serious skin reactions

In CLCZ696B2314, skin disorders by System Organ Class (SOC) were reported in 6.9% and 7.2% of the LCZ696 and enalapril groups, respectively. In CLCZB2214, skin AEs were

reported in 4.0% and 6.6% of patients in the LCZ696 and valsartan groups, respectively. Skin AEs identified by PT in the LCZ696 HF studies are shown. The most common events were rash, skin ulcer, eczema, and generalised pruritus. No significant treatment differences or safety signals were identified.

Cardiovascular safety

In a Thorough QTc study (LCZ696B2123), there were no significant changes in QTcF when LCZ696 was given in therapeutic (400 mg) or supra therapeutic doses (1200 mg).

Unwanted immunological events

Angioedema

In CLCZ696B2314, 147 cases of non adjudicated angioedema were reported after the start of study medication, 7.1% of the LCZ696 group and 7.4% of the enalapril group. A total of 54 cases were adjudicated, 25 cases during the run-in period, and 29 cases during the double-blind period. During the run-in period, adjudicated angioedema was reported in 10 patients (0.11%) in the LCZ696 group and in 15 patients (0.14%) in the enalapril group. There were no cases of severe angioedema with airway compromise or death. During the double-blind treatment period, adjudicated angioedema was reported in 0.45% and 0.24% of the LCZ696 and enalapril groups, respectively. Most events were mild or moderate. Only three patients (0.07%) in the LCZ696 group experienced severe events but there were no cases of airway compromise. In CLCZ696B2214, angioedema was reported in 4.0% and 6.6% of the LCZ696 and valsartan groups, respectively. Adjudicated angioedema was uncommon in all treatment groups. In CLCZB2314, it was reported more frequently in the LCZ696 group compared with enalapril (0.5% versus 0.2%). In CLCZ696B2214, there was a single event in the LCZ696 group (0.7%) compared with none in the valsartan group. In CLCZ696B2228, there were two cases of adjudicated angioedema, both cases in the conservative titration group.

In the LCZ696 HTN studies, 3/2880 (0.001%) patients experienced adjudicated angioedema. In the 30 clinical pharmacology studies, there was only one report of angioedema in a single dose study. In all studies of the LCZ696 program, approximately 14,000 patients received LCZ696. Of these, 35 patients experienced adjudicated angioedema but the majority were not severe. There were three SAEs but no patients required airway support.

Post marketing data

At time of TGA submission, LCZ696 had not been marketed in any jurisdiction.

Evaluator's conclusions on safety

Overall, the safety profile of LCZ696 was defined by its expected pharmacodynamic properties and no unexpected safety concerns were identified.

To increase the frequency of endpoints in PARADIGM-HF, patients were required to have modestly increased BNP levels and LVEF \leq 35%. However, the patient population was otherwise comparable to those of other major HF trials. At screening, nearly all patients were in NYHA class II or III, and nearly all were receiving optimal treatment for HF including ACE inhibitors or ARBs, β blockers, and MRAs. Approximately 12% of patients withdrew due to AEs in the run-in period. However, the remainder were stabilised on effective doses of LCZ696 or enalapril, permitting a meaningful comparison of the long-term safety and tolerability of each treatment.

In PARADIGM-HF, LCZ696 200 mg BID was well tolerated in more than 4,000 patients with HF treated for a mean duration of 27 months. Compared with enalapril, the LCZ696 treatment group had fewer deaths (17.3% versus 20.1%), SAEs (46.1% versus 50.7%),

and AEs leading to study drug discontinuation (10.7% versus 12.2%). AEs leading to dose adjustment or interruptions were more common in the LCZ696 group (27.7% versus 26.8%), due mainly to a higher incidence of hypotension (9.8% versus 7.0%).

Common AEs associated with RAAS inhibition in HF are hypotension, renal impairment, and hyperkalaemia. Compared with enalapril, hypotension was more commonly reported in the LCZ696 group (17.6% versus 12%) due to its greater vasodilator effects, but the number of discontinuations due to hypotension was low in both groups (0.6% versus 0.5%). Despite the higher incidence of hypotension, renal impairment was less common in the LCZ696 group (10.1% versus 11.5%). Hyperkalaemia was reported less frequently in the LCZ696 group (11.6% versus 14.0%), and severe hyperkalaemia was reported infrequently in both groups. These class adverse effects are familiar to clinicians and they can usually be managed with dose reductions or interruptions. Only rarely are they severe or life threatening.

The incidence of angioedema (including all related MedDRA categories) was similar in both treatment groups (7.1% versus 7.4%), but the incidence of adjudicated angioedema was much lower in both groups (0.5% versus 0.2%). The incidence of adjudicated angioedema was higher in the LCZ696 group, but only three (0.07%) patients in the LCZ696 group experienced severe angioedema. Although no life threatening angioedema was reported in the LCZ696 group, previous experience with omapatrilat warrants contraindication for the use of concomitant or overlapping LCZ696 with any ACE inhibitor.

In PARADIGM-HF, there was no valsartan control arm so the safety profile of the sacubitril component of LCZ696 could not be determined. However, with the exception of an increased incidence of hypotension, no safety concerns were apparent. In CLCZ696B2214, some events did occur more commonly in the LCZ696 group compared with the valsartan group; these included hypotension, hyperkalaemia, diarrhoea, and dizziness.

In controlled trials in large numbers of HTN patients, the safety profile of LCZ696 was comparable to placebo, with the exception of nasopharyngitis which occurred more commonly in the LCZ696 group. In CLCZ696A2201, the incidence of AEs was lower in 165 patients in the sacubitril monotherapy arm compared with placebo (23.1% vs 23.7%). ADRs identified in the PI include class effects and other common AEs, including headache, cough, nausea, diarrhoea, fatigue and dyspnoea. However, the incidence of AEs in the HF studies was similar or lower in the LCZ696 group compared with the enalapril group.

Predefined AEs of special interest were based on the known class effects of NEP inhibitors and ARBs, potential safety signals identified in the preclinical program, and standard regulatory indices of interest. The ADRs related to class effects were reported as expected, but there was no evidence of hepatotoxicity, haematological toxicity or QTc prolongation. No safety signals were detected in relation to other events of interest, including cognitive impairment, hypersensitivity reactions, changes in bone growth and/or bone mineral density, gastric lesions, malignancies, or stimulation of lipolysis.

In PARADIGM-HF, the incidence of adverse events in special populations was comparable to the overall population. As would be predicted, adverse events were more commonly reported in the elderly (≥ 65 years) and very elderly (≥ 75 years) but, with the exception of hypotension, the incidence was comparable or lower than in the elderly enalapril group. Most events in the elderly were mild to moderate and manageable, and no reduction in the target dose is required. There were no meaningful differences based on gender or race, although Blacks had a higher incidence of angioedema (a known racial tendency). No dosage reductions are required for patients with hepatic or renal impairment; however, patients with more severe renal impairment have a higher incidence of adverse reactions.

First round benefit-risk assessment

First round assessment of benefits

Compared with enalapril, the benefits of Entresto in the proposed usage are:

- Approximately 20% reductions in CV death and HF hospitalisations.
- A 16% reduction in all-cause mortality
- Sudden death was reduced by 20%
- Pump failure was reduced by 21%
- Modest improvements in mean symptom scores and NYHA class
- Efficacy and safety benefits applicable to all patient subgroups, including the elderly
- Well tolerated in patients with renal impairment
- Reduced risk of renal impairment
- Reduced risk of hyperkalaemia
- No dose adjustment required in patients with mild to moderate hepatic impairment
- Overall safety profile superior to enalapril
- A treatment alternative for patients who are intolerant of ACE inhibitors
- Low dosage strengths permit gradual up-titration or dose adjustments

First round assessment of risks

Compared with enalapril, the risks of Entresto in the proposed usage are:

- Increased risk of hypotension
- Increased but low risk of severe angioedema
- Risk of severe angioedema if co-prescribed with ACE inhibitors
- Few patients studied in NYHA class I or IV
- No studies have been performed in patients with severe hepatic impairment or in patients on dialysis.

First round assessment of benefit-risk balance

Following publication of the CONSENSUS study, enalapril and other ACE inhibitors have been the cornerstone treatment for chronic HF. Although HF symptoms were only modestly improved in the pivotal study, ENTRESTO was clearly superior to enalapril for the reduction of all cause mortality, CV deaths, and HF hospitalisations. The safety profile of Entresto was comparable to enalapril. While hypotension was more frequent, most events were mild or moderate and easily managed without withdrawing therapy. The benefit-risk balance of Entresto, given the proposed usage, is favourable. It is a superior alternative for patients who are already receiving ACE inhibitors, and it is particularly valuable for patients who are ACE inhibitor intolerant.

First round recommendation regarding authorisation

Subject to satisfactory responses to the clinical questions, authorisation is recommended for the proposed indication:

Entresto is indicated for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. Entresto has been shown to reduce the rate of cardiovascular death and heart failure hospitalisations.

Clinical questions

Pharmacokinetics

No questions.

Pharmacodynamics

No questions.

Efficacy

Question 1

At various points in the submission, the sponsor posits the futility of comparing LCZ696 with valsartan or sacubitril alone. This approach is acceptable from the clinical perspective because valsartan is not recommended for first line HF treatment, and sacubitril will not be marketed as monotherapy. The absence of dose ranging and Phase II studies in vulnerable patients with HFrEF is also justified on ethical grounds. However, the sponsor should be asked to demonstrate at least some clinical evidence that sacubitril has additive haemodynamic effects when combined with valsartan in HFrEF patients (as was demonstrated in HTN and HFpEF patients). Phase II studies, including a dose ranging study of sacubitril versus placebo, could have been conducted in ACE inhibitor intolerant HF patients treated with valsartan alone. Please provide a rationale for not adopting this approach.

Question 2

In the Phase II study CLCZ696B2214, echocardiography was performed at Weeks 0, 12 and 36 in patients with HFpEF, nearly all with hypertension. This was conducted to support CLCZ696D2301 (PARAGON-HF), an ongoing major Phase III study of CLCZ696 in patients with diastolic dysfunction. No such Phase II study was performed in patients with HFrEF, and echocardiographic changes were not assessed in the pivotal study CLCZ696B2314. As such, there appears to be no information relating to acute or chronic haemodynamic or structural changes in HFrEF patients treated with LCZ696. Arguably, it would be useful to understand how LCZ696 affects haemodynamics and cardiac structure compared with valsartan alone, even if the effects of valsartan alone are well described (for example, VAL489B0102, CLCZ696B0103, and VAL489B0104). In retrospect, it required confidence to embark on a Phase III mega trial without this basic information. Please explain the rationale for not performing such assessments as part of the HFrEF development program.

Question 3

In relation to the first two questions, there appears to be no clinical evidence that LCZ696 is superior to valsartan alone in patients with HFrEF. As, justifiably, a valsartan monotherapy arm was not included in PARADIGM-HF, the evidence that LCZ696 is superior to valsartan alone depends entirely on comparisons with historical valsartan HF studies. Please comment.

Question 4

At the final visit in CLCZ696B2314, approximately 25% of patients were not receiving the target dose of LCZ696 200 mg BID. However, a dose response analysis was not performed.

What evidence is there to support continued treatment in patients who cannot attain or maintain the target dose?

Safety

Question 5

The incidence of sudden death and pump failure is shown in Table 12-12 of the CLCZ696B2314 Clinical Safety Report (CSR). However, with reference to sudden death and pump failure, the evaluators' are unable to locate the tables referred to on page 6 of the proposed annotated PI (Module 2.7.3 SCE: Appendix 1: Tables 14.2-1.5 and 14.2-1.4). Nor can they locate these tables in the CLCZ696B2314 CSR, and they are not included in the summary of efficacy. Please provide both sources.

Second round evaluation

Question 1

At various points in the submission, the sponsor posits the futility of comparing LCZ696 with valsartan or sacubitril alone. This approach is acceptable from the clinical perspective because valsartan is not recommended for first line HF treatment, and sacubitril will not be marketed as monotherapy. The absence of dose ranging and Phase II studies in vulnerable patients with HFrEF is also justified on ethical grounds. However, the sponsor should be asked to demonstrate at least some clinical evidence that sacubitril has additive haemodynamic effects when combined with valsartan in HFrEF patients (as was demonstrated in HTN and HFpEF patients). Phase II studies, including a dose ranging study of sacubitril versus placebo, could have been conducted in ACE inhibitor intolerant HF patients treated with valsartan alone. Please provide a rationale for not adopting this approach.

Sponsor's response to Question 1

In summary, the sponsor suggests that Phase II studies were not relevant based on the following arguments:

- Haemodynamic improvements do not predict outcomes so any changes observed in a Phase II study would not have influenced the design of the Phase III study.
- Cardiac inotropes have been shown to increase mortality in previous studies.
- Compared with an ACE inhibitor or an ARB such as valsartan, LCZ696 was not expected to produce marked and immediate haemodynamic effects.

Evaluators' response

The sponsor has not provided a reason for not performing a Phase II comparison of sacubitril versus placebo in HF patients who are ACE inhibitor intolerant. In the absence of such a study, there is no direct clinical evidence that the safety and efficacy of LCZ696 is superior to valsartan alone. The argument that haemodynamic changes are irrelevant as they do not predict survival is in general acceptable. However, while haemodynamic changes might not have influenced the primary outcome, LCZ696 is a novel therapy. If nothing else, haemodynamic changes would have increased our understanding of neurohumoral responses in HF.

While not fully accepting the sponsor's arguments, the overall response is satisfactory.

Question 2

In the Phase II study CLCZ696B2214, echocardiography was performed at Weeks 0, 12 and 36 in patients with HFpEF, nearly all with hypertension. This was conducted to

support CLCZ696D2301 (PARAGON-HF), an ongoing major Phase III study of LCZ696 in patients with diastolic dysfunction. No such Phase II study was performed in patients with HFrEF, and echocardiographic changes were not assessed in the pivotal study CLCZ696B2314. As such, there appears to be no information relating to acute or chronic haemodynamic or structural changes in HFrEF patients treated with LCZ696. Arguably, it would be useful to understand how LCZ696 affects haemodynamics and cardiac structure compared with valsartan alone, even if the effects of valsartan alone are well described (for example, VAL489B0102, CLCZ696B0103, and VAL489B0104). In retrospect, it required confidence to embark on a Phase III mega trial without this basic information. Please explain the rationale for not performing such assessments as part of the HFrEF development program.

Sponsor's response to Question 2

In summary, the sponsor repeats and expands on the arguments for not performing haemodynamic studies outlined in their response to Question 1. Given the poor predictive value of Phase II haemodynamic studies, the decision was made to proceed directly with a Phase III study.

Evaluators' response

In the sponsor's view, the potential effects of LCZ696 on haemodynamics are largely irrelevant and outdated. Instead they view LCZ696 as "a neuromodulator with the potential to affect natriuresis/diuresis, cardiac hypertrophy and fibrosis, aldosterone levels and sympathetic tone over a longer period of time". However, the pivotal study was not designed to assess these variables or to explore their relationships. Compared with enalapril, the absolute risk reduction for CV deaths or HF hospitalisation was 4.69%. Despite the clinically significant benefit achieved with enhanced neurohumoral modulation, the prognosis for HF remains poor and the underlying haemodynamics should not be ignored.

Despite the lack of haemodynamic data, the decision to proceed directly to Phase III was not unreasonable based on the pragmatic arguments proposed by the sponsor. The benefits observed in the pivotal study justify the decision and post marketing studies will no doubt fill the knowledge gap.

While not fully accepting the sponsor's arguments, the overall response is satisfactory.

Question 3

In relation to the first two questions, there appears to be no clinical evidence that LCZ696 is superior to valsartan alone in patients with HFrEF. As, justifiably, a valsartan monotherapy arm was not included in PARADIGM-HF, the evidence that LCZ696 is superior to valsartan alone depends entirely on comparisons with historical valsartan HF studies. Please comment.

Sponsor's response to Question 3

In summary, the sponsor's principal argument is that valsartan alone is not approved for HF except in patients who are ACE inhibitor intolerant. There would be no rationale to compare LCZ696 with valsartan alone as the latter is not a treatment option in the great majority of HF patients.

Evaluators' response

Given the positive outcome of the pivotal study, the sponsor's response is satisfactory.

Question 4

At the final visit in CLCZ696B2314, approximately 25% of patients were not receiving the target dose of LCZ696 200 mg BID. However, a dose response analysis was not performed. What evidence is there to support continued treatment in patients who cannot attain or maintain the target dose?

Sponsor's response to Question 4

In summary, the sponsor has provided a detailed response after making the following points:

- The pivotal study was designed to compare the overall LCZ696 and enalapril treatment regimens rather than specific doses of either medication.
- The target dose of LCZ696 (equivalent to valsartan 160 mg BID based on PK data) was appropriate as it is the valsartan dose recommended in international HF guidelines.
- Every attempt was made to attain or maintain the target dose throughout the pivotal study.
- The majority of patients achieved the target dose.

At the end of the treatment period in the pivotal study, 69.64% of the LCZ696 group were receiving the target dose of 200 mg BID; 6.71% were receiving 100 mg BID; 1.97% were receiving 50 mg BID; and 21.67% were receiving no study medication. Patients taking $\leq 50\%$ of the target dose tended to be older, to be in NYHA class III rather than class II, to have higher mean NT-proBNP values, and to have lower mean eGFR values. Similar trends were observed in the enalapril group.

Kaplan-Meier plots of first confirmed primary endpoint (CV death or HF hospitalisation) by treatment group in the $\leq 50\%$ and $>50\text{-}75\%$ mean actual dose subgroups are shown below. The hazard ratios in favour of LCZ696 were 0.442 (95% CI: 0.222, 0.883) and 0.544 (95% CI: 0.371, 0.789), respectively. Although the patient numbers in each group were small, the results were comparable to the overall population.

Figure 2. Confirmed primary endpoint in patients taking $\leq 50\%$ target dose (B2314).

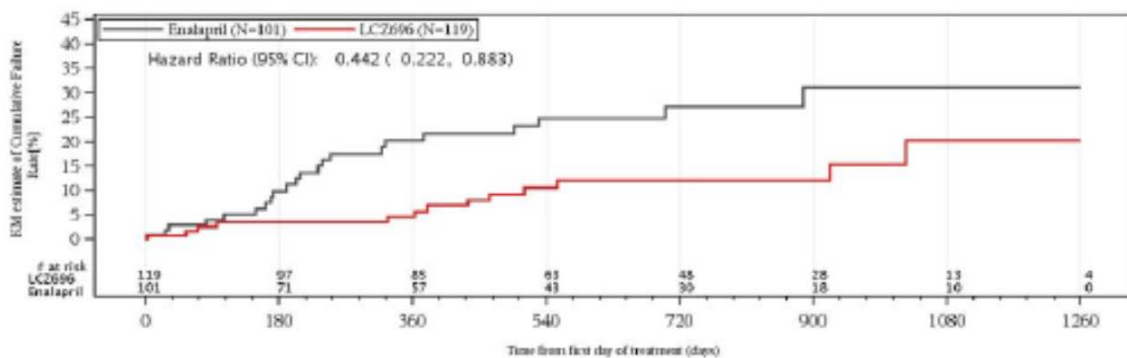
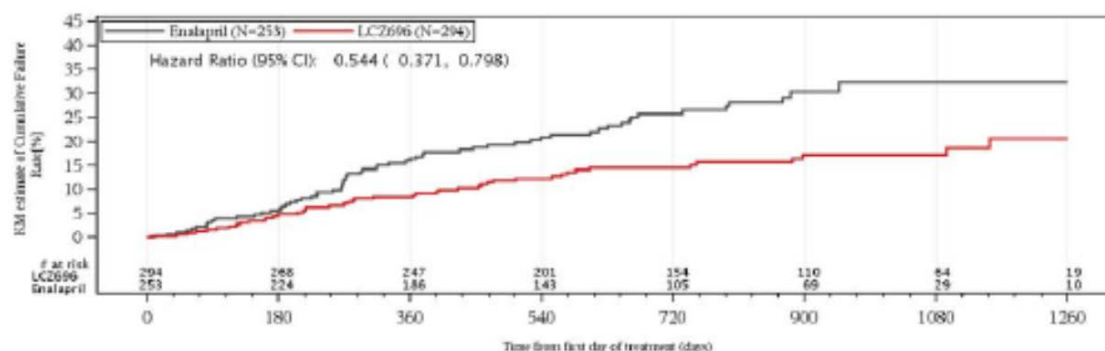


Figure 3. Confirmed primary endpoint in patients taking >50-75% target dose (B2314).



Evaluators' response

The sponsor's response is satisfactory.

Question 5

The incidence of sudden death and pump failure is shown in Table 12-12 of the CLCZ696B2314 CSR. However, with reference to sudden death and pump failure, the evaluators are unable to locate the tables referred to on page 6 of the proposed annotated PI (Module 2.7.3 SCE: Appendix 1: Tables 14.2-1.5 and 14.2-1.4). Nor can they locate these tables in the CLCZ696B2314 CSR, and they are not included in the summary of efficacy. Please provide both sources.

Sponsor's response to Question 5

The requested tables and their sources have been provided.

Evaluators' response

The sponsor's response is satisfactory.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Entresto in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Entresto in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of Entresto, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Authorisation is not recommended for the proposed indication:

Entresto is indicated for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. Entresto has been shown to reduce the rate of cardiovascular death and heart failure hospitalisations.

However, authorisation is recommended for the following indication:

Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Comment: The proposed indication for Australia is rejected in favour of the indication approved by the CHMP. The latter is essentially synonymous with the first sentence of the former. However, the second sentence of the proposed Australian version constitutes a claim rather than an indication. On balance, it would be more appropriate to delete it.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP) Version 1.0 (dated 5 December 2014, DLP 5 August 2014) and Australian Specific Annex (ASA) Version 1.0 (dated 2 March 2015); Updated EU-RMP version 1.4 (dated 30 September 2015, DLP 5 August 2014) and ASA version 2.0 (dated 23 October 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 11.

Table 11. Ongoing safety concerns.

| | |
|----------------------------|--|
| Important identified risks | Hypotension Renal impairment Hyperkalemia Angiodema Embryofoetal and infantile toxicity |
| Important potential risks | Hypersensitivity (other than angioedema) Hepatotoxicity Stain DDI |
| Missing information | Cognitive impairment Paediatric patients Patients with severe renal impairment Patients with severe hepatic impairment Long term data on LCZ696 use in HF patients |

RMP reviewer comment

Notwithstanding to the evaluation of the nonclinical and clinical aspects of the Safety Specification, the summary of safety concerns is considered incomplete. Additional or more specific concerns are identified in the Precautions section of the PI; the sponsor should include, or provide evidence to justify the omission of, the following in the Summary of Safety Concerns:

- There are clear warnings in the PI to avoid co-administration of ACE inhibitors, direct renin inhibitors, and ARBs. This is further reinforced by Contraindications on use of LCZ696 concomitantly with ACE inhibitors or aliskiren (aliskiren in patients with Type

2 diabetes). 'Co-administration with ACE inhibitors, direct renin inhibitors and ARBs' should therefore be added to the Summary of Safety Concerns as an Important Identified Risk.

- There is a precaution in the PI relating to patients with renal artery stenosis, advising that Entresto may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. 'Use in patients with renal artery stenosis' should be added to the Summary of Safety Concerns as an Important Potential Risk.

The inclusion of these into the Summary of Safety Concerns of the RMP will ensure that continued monitoring and periodic updates may assist in assessing risk mitigation measures.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance for the identified/potential risks and missing information presented in the Summary of Safety Concerns (above).

Routine adverse event follow-up using a targeted checklist is also proposed for the safety concerns of angioedema, hepatotoxicity and cognitive impairment.

Investigation of the potential effect of LCZ696 on cognitive function is also indicated as an objective of the PARAGON HF study (Study LCZ696D2301, scheduled for submission of the final report in March 2020).

It is noted that the RMP document indicates no plans for post-authorisation efficacy studies.

RMP reviewer's comments

The submitted RMP documentation indicates that no further studies were ongoing or planned for LCZ696 beyond the PARAGON-HF study (with focus on the cognitive endpoint). A search online¹¹ has identified that several trials with LCZ696 are currently 'recruiting':

- A randomized, double-blind, active-controlled, parallel group, 52-week study to evaluate the effect of LCZ696 compared to olmesartan on regional aortic stiffness in subjects with essential hypertension (NCT01870739), last verified online April 2014.
- A multicentre, randomized, double-blind, parallel groups, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in Japanese patients with chronic HF and reduced ejection fraction (NCT02468232), last verified online June 2015.
- A multicentre study to evaluate safety and tolerability in patients with chronic HF and reduced ejection fraction from PARADIGM-HF receiving open-label LCZ696 (NCT02226120), last verified online October 2014.
- Multiple patient program to ensure access to LCZ696 treatment to patients diagnosed with HF with reduced ejection fraction (HF-rEF) (NCT02389933), last verified online February 2015.

These studies are additional to the PARAGON-HF study:

- A multicentre, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and

¹¹ www.clinicaltrials.gov

mortality in HF patients (NYHA Class II-IV) with preserved ejection fraction (NCT01920711)

last verified online July 2014. The PARAGON-HF study includes Australian patients.

The sponsor should provide more detail about the additional studies, including justification as to why the studies have not been considered part of the pharmacovigilance plan.

It is noted in the ASA that there is no planned submission of the final report of the CFA substudy of PARAGON HF (cognitive endpoints) to the TGA unless requested. It is therefore recommended that final report be provided to the TGA.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor is only proposing routine risk minimisation activities (that is, PI labelling) for all identified/potential safety concerns and missing information.

RMP reviewer comment

The sponsor's conclusions with regards to proposed risk minimisation activities are considered acceptable in the context of this submission, with the exception of providing advice on switching from valsartan alone to LCZ696. This is discussed further below.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

No safety related questions were raised by the clinical or nonclinical evaluator during their assessment of the submitted dossier.

Evaluator's comment

The sponsor's response is satisfactory.

Recommendation #2 in RMP evaluation report

It was advised in the submission that a decision on approval in the EU was expected September 2015. The sponsor should provide an update, if any, on the status of the EU application and an updated EU-RMP, if available.

Sponsor response

Novartis received a positive opinion from the CHMP on the Entresto application on 25-Sep-2015, including a positive opinion on an updated version of the EU RMP. Novartis is expecting the final European Committee approval before the end of the year (around 67 days after the positive opinion). The positive opinion was obtained after implementing

various updates to the initially provided draft EU RMP (which was identical to the version submitted to TGA). The current EU RMP, Version 1.4 therefore includes a number of changes, of which the key ones are highlighted below.

The key changes included in the current EU RMP, Version 1.4 are the following:

- Neonatal/infantile toxicity through exposure from breast milk added as Important potential risk
- Cognitive impairment upgraded to Important potential risk
- Thrombocytopenia, Neutropenia, and Statin drug-drug interaction (DDI) added as Important potential risk
- Paediatric patients, Patients with severe renal impairment, Long term data on LCZ696 use in HF patients, and Use in angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACE inhibitor/ARB) naïve HF patients added as Missing information
- Updated Targeted Follow Up Questionnaires for Hepatotoxicity events, Dementia-related events, and Angioedema-related events
- Commitment to send out the revised Hepatotoxicity Targeted Follow Up Questionnaire also for Statin-related events, to further characterise the Important identified interaction between atorvastatin and LCZ696.
- Several Post Approval Safety Studies (PASS) added in the Pharmacovigilance Plan

The revised EU RMP therefore now includes the following safety concerns: (RMP evaluator comment: tables not included)

Evaluator's comment

The sponsor's response is satisfactory.

Recommendation #3 in RMP evaluation report

The ASA should provide a table comparing the differences, if any, between advice in the EU SmPC and the Australian PI. Updates to the ASA should be in the format outlined in the TGA guidance.

Sponsor response

The table comparing differences between advice in the EU Summary of Product Characteristics (SmPC) and the Australian PI is included in updated ASA version 2.0 dated 23-Oct-2015 enclosed with this response.

Evaluator's comment

The sponsor's response is satisfactory.

Recommendation #4 in RMP evaluation report

There are warnings in the PI to avoid co-administration of ACE inhibitors, direct renin inhibitors, and ARBs. This is reinforced by Contraindications on use of LCZ696 concomitantly with ACE inhibitors or aliskiren (aliskiren in patients with Type 2 diabetes). 'Co-administration with ACE inhibitors, direct renin inhibitors and ARBs' should therefore be added to the Summary of Safety Concerns as an Important Identified Risk.

Sponsor response

Co-administration of Entresto with other agents, including ACE inhibitor, direct renin inhibitors and ARBs may cause a number of clinically significant AEs to occur. Mainly, angioedema with ACE inhibitors, hypotension with concomitant antihypertensives and worsening of renal impairment and hyperkalemia with concomitant administration of drugs that act on the RAAS. In order to focus on the clinical relevance of the events of

possible concern with Entresto, AEs anticipated with the co-administration of these medications are classified as separate Important Identified risks, rather than under one broader risk, such as 'Co-administration with ACE inhibitors, direct renin inhibitors and ARBs'. Each Important identified risk includes discussion in the relevant section of the EU RMP safety specification of risk factors, including concomitant administration with other agents and preventability (see EU RMP Part II Module SVII.3). The EU RMP also includes a discussion of identified and potential interactions under Part II Module SVII.4. Routine risk minimisation (that is, PI labelling) and routine pharmacovigilance activities are proposed for angioedema, hypotension, worsening in renal impairment and hyperkalemia. Routine pharmacovigilance activities for angioedema also include a targeted follow-up checklist to investigate prior use of ACE inhibitors and ARBs. In addition, PASS study 1 will help evaluate the risks of angioedema, hypotension, hyperkalemia, renal impairment and hepatotoxicity.

Evaluator's comment

The evaluator has noted that the EU-RMP SVII.4 addresses the 'important identified interaction – concomitant use with ACE inhibitors and ARBs', and 'concomitant use with aliskiren'. The sponsor's proposal to mitigate the risks through routine risk minimisation is acceptable. However, the risk of angioedema, hypotension, effect in renal function and hyperkalaemia are all pharmacological class effects. The focus of pharmacovigilance and risk minimisation activities is to manage these adverse events related to the use of Entresto, not the effects of concomitant use with other medications. Further, the EU-RMP outlines the objective of the PASS 1 study as 'to estimate risks of specific safety outcomes (angioedema, hypotension, hyperkalemia, hepatotoxicity and renal impairment) in HF patients **regardless of prior use of ACE inhibitors or ARBs**' (EU-RMP). This does not appear to address the issues of drug-drug interaction and should not be considered pharmacovigilance for the risk.

Recommendation #5 in RMP evaluation report

There is a precaution in the PI relating to patients with renal artery stenosis, advising that Entresto may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. 'Use in patients with renal artery stenosis' should be added to the Summary of Safety Concerns as an Important Potential Risk.

Sponsor response

Renal impairment occurs in approximately one third of HF patients. Consistent with drugs that act on the RAAS, use of Entresto can be associated with decreased renal function, and consequently increased blood urea and blood creatinine. Patients at greatest risk for renal impairment are those with pre-existing conditions known to decrease renal function, such as bilateral renal artery stenosis. Renal impairment, with bilateral renal artery stenosis included as a risk group/factor (see EU RMP v1.4 Table 8-4), is already included in the EU RMP as an Important identified risk.

Evaluator's comment

The evaluator has noted the precaution provided in the PI, which is an acceptable risk minimisation activity to mitigate the risk of 'use in patients with renal artery stenosis'.

Recommendation #6 in RMP evaluation report

Clinical studies with LCZ696 have been identified¹² to include NCT01870739, NCT02468232, NCT0222612, and NCT02389933. The sponsor should provide more detail about these studies, including justification as to why the studies have not been considered part of the pharmacovigilance plan.

¹² www.clinicaltrials.gov

Sponsor response

Studies CLCZ696A2216, CLCZ696B1301, CLCZ696B2317, and CLCZ696B2318M were not designed to specifically address any safety issues related to the use of LCZ696 in HF patients; therefore, none have been considered to be a significant part of the pharmacovigilance plan. Each of the studies will contribute to the denominator of patients treated with LCZ696, and SAEs will be reported to the Novartis Argus Pharmacovigilance database. However, all of the studies are smaller than PARADIGM-HF and will not add a meaningful amount of controlled data that will further elucidate use of LCZ696 in patients with HFrEF. Each of the studies is described briefly below.

- NCT01870739, Study CLCZ696A2216, “A randomized, double-blind, active-controlled, multicenter, 52-week study to evaluate the safety and efficacy of an LCZ696 regimen on arterial stiffness through assessment of central blood pressure in elderly patients with essential hypertension” is a study that was planned to include 432 patients randomized to LCZ696 or olmesartan. The data base was recently locked and preliminary data reported at the European Society of Cardiology meeting in August. The patient population included in this trial is elderly hypertensives who would not be expected to have the same AE profile as HF patients. The CSR for this study is under preparation and not yet available.
- NCT02468232, Study CLCZ696B1301, “A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in Japanese patients with chronic HF and reduced ejection fraction” is planned to randomize approximately 220 patients, 110 in each group to LCZ696 or enalapril. This study was requested by the Japanese Health Authority but only recently enrolled the first patient, will require at least 3 years to complete and will reflect the efficacy and safety in a specific demographic.
- NCT02226120, Study CLCZ696B2317, “A multicenter study to evaluate safety and tolerability in patients with chronic HF and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696” will evaluate safety and tolerability of LCZ696 in patients previously treated in PARADIGM-HF. It is estimated that about 5000 patients from the trial would be eligible. However, these patients have previously contributed to the database for PARADIGM-HF and are not unique patients. The SAEs from this uncontrolled open label extension study will be evaluated for any new or changing safety signal, however, as this study is not designed to answer a specific safety question, they are not considered to meet criteria to be in the pharmacovigilance plan.
- NCT02389933, Study CLCZ696B2318M, “Multiple Patient Program to ensure access to LCZ696 treatment to patients diagnosed with HFrEF”, is designed as a compassionate use program to ensure access to LCZ696 treatment for patients similar to those treated in PARADIGM-HF when the drug would not otherwise be available to patients in need. This is an uncontrolled study without a specific safety question as part of the objectives and therefore will contribute to safety evaluation with the review of SAEs reported.

When available, the CSRs for the trials can be submitted to TGA, if requested.

Evaluator’s comment

The evaluator has noted the sponsor’s response. It is also noted that four clinical studies, including three post authorisation safety studies, have been added to the updated EU-RMP. The sponsor should note that results from all clinical studies, including findings from interim and final study reports, should be analysed in the Periodic Safety Update Reports (PSURs) and submitted to the TGA. Significant safety findings should be communicated to the TGA as soon as they have been identified.

Recommendation #7 in RMP evaluation report

It is noted in the ASA that there is no planned submission of the final report of the CFA sub-study of PARAGON HF (cognitive endpoints) to the TGA unless requested. It is therefore recommended that final report be provided to the TGA.

Sponsor response

Novartis commits to submitting the final CSR for PARAGON HF (CLCZ696D2301) when available to the TGA (expected in 2020). The CSR will be submitted alongside the PSUR, allowing the findings to be placed in the correct context of the Benefit Risk evaluation of LCZ696 in patients with HF.

Evaluator's comment

The sponsor's response is satisfactory.

Recommendation #8 in RMP evaluation report

The sponsor advises that switching from valsartan to LCZ696 carries a potential risk for medication error (see RMP). In the Section 31 response the sponsor should clarify what particular risks are potentially related to switching from valsartan to LCZ696. In addition, the sponsor should consider mitigation of any risk by including appropriate statements in the PI/CMI.

Sponsor response

Valsartan within LCZ696 is more bioavailable than the valsartan in other marketed tablet formulations. Therefore, the risk of switching from a certain dose of valsartan to a similar dose of LCZ696 may result in an overdose of LCZ696.

There are very few cases (n = 5) of overdose within the LCZ696 development program. In most cases, no AEs were reported after overdose. However, it is likely that commonly reported AEs like hypotension, hyperkalemia, and renal impairment could occur more frequently in cases where the patient was inappropriately switched from valsartan to LCZ696.

It is noted in the RMP that "Potential risks include medication error (especially if switching from valsartan) and/or accidental ingestion of medication by children". The section goes on to state that this risk is actually very unlikely. The doses of LCZ696 – 50 mg, 100 mg, and 200 mg or when described as the combination (sacubitril/valsartan) - 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg are very different from the doses of valsartan – 80 mg, 160 mg and 320 mg. The concern that was intended to be highlighted is that the valsartan in LCZ696 is more bioavailable than that in the commercially available formulation of valsartan in a ratio of approximately 1.6 to 1, such that the 200 mg tablet of LCZ696 containing approximately 103 mg of valsartan provides an exposure to valsartan that is similar to the 160 mg tablet. Novartis believes that the possible risk of inappropriately switching is minimized by clear language in the updated PI, Pharmacology, Pharmacokinetics section (please see updated PI provided with Novartis Response to TGA Consolidated Section 31 Request for Information) which states:

The valsartan contained within [trade name] is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in Entresto is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.

Evaluator's comment

The sponsor's response is acceptable. The advice provided in the PI on bioavailability is important for prescribers to decide a suitable starting dose for patients who have been on valsartan. Therefore, it is recommended to the Delegate that the following information is repeated under 'Dosage and administration' of the PI:

The valsartan contained within [trade name] is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in Entresto is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.

Recommendation #9 in RMP evaluation report

The sponsor advises that a Paediatric Investigation Plan (PIP) is being developed; however, no further details of this Plan appear in the remainder of the pharmacovigilance plan. As the sponsor has indicated that off-label paediatric use of LCZ696 cannot be ruled out, further details of the PIP should be submitted for consideration by the TGA.

Sponsor response

The LCZ696 Paediatric Investigation Plan (PIP) application in the condition of HF received a positive EMA Decision (P/0096/2012) on 30 May 2012 (with references EMA/273210/2012 and EMA/PDCO/249277/2012).

A deferral on paediatric studies was agreed with the Paediatric Committee of the EMA (PDCO) in light of need for completion of juvenile nonclinical studies and adult HF program (LCZ696B2314 study), prior to initiating any trials in children at that time. Data from nonclinical juvenile studies are required to guide a further decision on the need for a waiver, and for the cut off for the age range.

No paediatric studies have been performed to date.

Evaluator's comment

The sponsor's response is acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 request has adequately addressed most issues identified in the RMP evaluation report (see Outstanding issues, below).

Outstanding issues

Issues in relation to the RMP

Recommendation 8: The sponsor's response is acceptable. The advice provided in the PI on bioavailability is important for prescribers to decide a suitable starting dose for patients who have been on valsartan. Without this knowledge, prescribers might provide additional valsartan which could lead to over dosage. Therefore, it is recommended to the Delegate that the following information is repeated under 'Dosage and administration' of the PI:

The valsartan contained within [trade name] is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in Entresto is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM papers, including the question sheet for the ACSOM, and a copy of the ratified advice, will be provided in a separate document when they become available.

Comments on the safety specification of the RMP

Clinical evaluation report

First round comments on clinical aspects of the safety specification in the draft RMP:

The Safety Specification in the draft Risk Management Plan is satisfactory... The safety specifications identified by the sponsor in the RMP are consistent with the safety profile identified in the clinical trial program. The evaluators' agree that routine pharmacovigilance and risk minimisation measures are appropriate for Australia.

Second round comments on clinical aspects of the safety specification in the draft RMP:

The sponsor did not provide new clinical information after the first round and has not changed the Safety Specification in the draft RMP. There are no changes to the comments on the Safety Specification made in Section 11.3.

Nonclinical evaluation report

The following comments have been provided in the non-clinical evaluation report:

Results and conclusions drawn from the nonclinical program for sacubitril/valsartan detailed in the sponsor's draft Risk Management Plan (Section 1.13.1) are in general concordance with those of the Nonclinical Evaluator.

Key changes to the updated RMP

- EU-RMP Version 1.0 (dated 5 December 2014, DLP 5 August 2014) and ASA Version 1.0 (dated 2 March 2015)

have been superseded by:

- EU-RMP version 1.4 (dated 30 September 2015, DLP 5 August 2014) and ASA version 2.0 (dated 23 October 2015)

A summary of the risk management activities proposed in the updated EU-RMP is provided below.

Table 12. Summary of safety concerns.

| | |
|----------------------------|---|
| Important identified risks | Hypotension Renal impairment Hyperkalemia Angiodema Embryofoetal and infantile toxicity |
| Important potential risks | Neonatal/infantile toxicity through exposure from breast milk Hepatotoxicity Cognitive impairment Stain DDI Thrombocytopenia Neutropenia |
| Missing information | Paediatric patients Patients with severe renal impairment Long term data on LCZ696 use in HF patients Use in ACEI/ARB naïve HF patients |

Table 13. Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan.

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final Reports (planned or actual) |
|---|--|---|--|--|
| PASS 1: Non-interventional post-authorization European database safety study (Category 3;PASS) | To further characterize specific safety outcomes (angioedema, hypotension, hyperkalemia, renal impairment, hepatotoxicity) in HF patients newly starting treatment with LCZ696 (regardless of prior use of ACEIs or ARBs) | Angioedema Use in ACEI/ARB naïve patients Hypotension Hyperkalemia Renal impairment Hepatotoxicity | Planned | Yearly progress reports (1st report planned to be submitted Q4 2017, or with PBRER in 2018). Final report submission within 12 months after end of data collection (i.e., after reaching the necessary number of cases) – latest in Q2 2020 |
| PASS 2: Multicenter, randomized, double-blind, active-controlled study (CLCZ696B2320) (Category 3;PASS) | To evaluate the effects of LCZ696 compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and brain amyloid plaque deposition as assessed by PET imaging in patients with chronic heart failure with preserved ejection fraction (HFpEF) | Cognitive impairment | Planned | Planned March 2022 (Final report submission) |
| PASS 3: Non-interventional post-authorization European database safety study (Category 3;PASS) | To assess the risk of statin-related events associated with concomitant exposure to LCZ696 and statins compared to statin exposure alone in HF patients | Statin DDI | Planned | - planned Q2 2020 (Final report submission) |
| Cognitive function assessment in study CLCZ696D2301 (PARAGON HF study) (Category 3; Non-PASS) | To evaluate cognitive function in patients with chronic HFpEF | Cognitive impairment | Started | Planned March 2020 (final report) |
| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final Reports (planned or actual) |
| Observational US database study | To assess the risk of serious angioedema in | Angioedema in US Blacks | Planned | Planned Q3 2019 (final report) |
| (Category 3; Non-PASS) | association with sacubitril/valsartan (Entresto) use in Black HF patients in the United States | | | |

Routine risk minimisation is proposed for all the safety concerns except 'thrombocytopenia', 'neutropenia', and 'long-term data on LCZ696 use in HF patients'.

RMP Evaluator's comments:

The evaluator has no objection to the above changes. It is noted that the important potential risk of 'hypersensitivity' has been removed from the summary of safety concerns in the EU-RMP. As 'hypersensitivity' is a listed contraindication and appears to be a common risk for most medicines rather than specific risk for the product. The risk is adequately mitigated from the RMP perspective.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

Wording regarding the RMP condition of registration cannot be provided at this stage as the ACSOM may provide additional recommendations, which may require further updates to the RMP documents.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The Quality evaluator has recommended approval with respect to chemistry, quality control and manufacturing. LCZ696 exists as a crystalline salt hydrate complex with a molar ratio of 1 sacubitril anion: 1 valsartan anion: 3 sodium cations: 2.5 water molecules. The complex cannot be separated by physical means into its molecular moieties, but dissociates at the right pH and chemical conditions, e.g. after oral ingestion and absorption. The tablets are not scored. The tablets will be available in 24.3/25.7 mg, 48.6/51.4 mg, and 97.2/102.8 mg strengths of sacubitril/valsartan. The stability data provided supports a shelf life of 18 months when stored below 30°C. Bioequivalence was demonstrated between the 50mg formulation used in the clinical trials and the proposed marketed formulation. Food intake demonstrated a reduction in C_{max} for all analytes and a delay in t_{max}. AUC was decreased by 34% for valsartan but there was no significant change for the active sacubitril metabolite. The clinical evaluator did not consider this effect of food to be clinically significant and the pivotal Phase III study was undertaken without regard to meals. The application was not considered by the Pharmaceutical Subcommittee of ACPM.

Nonclinical

The nonclinical evaluator has no objections to the registration of LCZ696. The nonclinical data were adequate and no major deficiencies were identified. The data were in general accordance with ICH guidelines and the pivotal studies were GLP compliant and conducted with the proposed clinical formulation. The exposure ratios were low but considered adequate. Sacubitril's active metabolite, sacubitrilat, is the major inhibitor of the enzyme neprilysin. LCZ696 was able to modulate both the natriuretic peptide system and the RAAS. Safety pharmacology studies did not identify any clinically relevant adverse effects. Tissue distribution was extensive, but mainly in kidney, liver and bile, with no significant accumulation in melanin containing tissues or in brain tissues. The major metabolic step is ethyl ether hydrolysis to form sacubitrilat. Neither sacubitril nor sacubitrilat were metabolised significantly by cytochrome P450 enzymes. There was no evidence of a pharmacokinetic interaction between sacubitril and valsartan. Transportation of sacubitrilat by OATP1B1 and OATP1B3 was significant and co-administration of inhibitors of these transporters may increase systemic exposure to sacubitrilat. Single dose studies demonstrated that LCZ696 and sacubitril alone have low acute toxicity via both oral and IV routes. The repeat dose toxicity studies identified renal effects (juxtaglomerular hypertrophy/hyperplasia), gastritis, and decreased red blood cell parameters as

potentially clinically relevant. Heart weight changes were also observed in some studies with sacubitril and in previous studies with valsartan, but were not considered clinically relevant. There is potential for NEP inhibition related angioedema. There was no evidence of genotoxicity, carcinogenicity or effects on fertility. sacubitrilat was transferred to milk with potential breast Fed infant intake estimated to be <1% of adult clinical exposure. Embryofoetal toxicity in rats and rabbits and teratogenicity in rabbits was observed at maternotoxic doses, therefore LCZ696 is contraindicated in pregnancy with pregnancy Category D. Adverse effects on bodyweight and growth, survival and physical development were seen at low relative exposure levels. Studies in monkeys showed increased levels of newly formed amyloid β and decreased clearance of total amyloid β in the CNS, but not in the brain. The evaluator considered these changes unlikely to be clinically relevant as they were not seen in the long term monkey studies.

Clinical

The clinical evaluator has recommended approval for a modified indication of:

Entresto is indicated in adult patients for treatment of symptomatic chronic HF with reduced ejection fraction.

The evaluator commented that the indication proposed by the CHMP in Europe was preferred and that the second sentence of the proposed Australian version constitutes a claim rather than an indication, therefore the evaluator thought on balance it would be more appropriate to delete it.

The clinical dossier included the following data:

- 30 clinical pharmacology studies.
- One population pharmacokinetic analysis.
- One pivotal Phase III efficacy/safety study.
- Two Phase II efficacy/safety studies.
- One dose response analysis of two biomarkers.
- An integrated summary of efficacy.
- An integrated summary of safety

Pharmacology

Pharmacokinetics

The submitted pharmacokinetic studies noted the following findings:

- Absolute bioavailability of sacubitril is $\geq 60\%$, valsartan is 23%, exposure to sacubitril increased proportionally to dose and valsartan almost did (1.69 fold), T_{max} was 0.5 h for sacubitril and 1.5hr for valsartan. After repeated doses of 200 mg BD, the respective mean volume of distribution, V_z/F (L), were: 180.83, 19.15 and 70.47 for sacubitril, sacubitrilat and valsartan, respectively, indicating extensive distribution to the tissues.
- Plasma protein binding for both sacubitril (97%) and sacubitrilat (97%) was high and the amount of sacubitril excreted in urine was $\sim 60\%$ and in faeces $\sim 40\%$. Most of the dose appeared as sacubitrilat. Plasma clearance (Cl/F) was 76.8 L/h for sacubitril, 2.3 L/h for sacubitrilat and 8.2 L/h for valsartan. Terminal half life was 1.43 h, 11.48 h, and 9.9 h respectively, for sacubitril, sacubitrilat, and valsartan in healthy subjects after single oral doses, supporting BD dosing.

- Inter subject variability (CV%) of PK parameters after multiple dose administration was estimated to be 20-56% for sacubitril, 11-26% for sacubitrilat, and 17-58% for valsartan.
- Food has no significant impact on the systemic exposures of sacubitril and sacubitrilat, while valsartan exposure decreased by about 40%. The evaluator did not consider this clinically relevant and hence no dosage adjustment is required when administered with food because food was not shown to impact on the blood pressure lowering ability of valsartan.
- The average exposure of valsartan was higher by about 60% when LCZ696 is administered compared to valsartan monotherapy.
- Sacubitril, sacubitrilat and valsartan are not significantly metabolised by CYP450 enzymes and do not inhibit or induce many of the CYP450 enzymes to any significant level. Therefore, co-administration with drugs that inhibit or induce CYP450 enzymes is not likely to influence the pharmacokinetics of LCZ696 analytes.
- No clinically relevant PK interactions were demonstrated with digoxin, warfarin, hydrochlorothiazide, amlodipine, metformin, frusemide, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol except: metformin had a 23% reduction in AUC and frusemide showed a 26% reduction in AUC, frusemide caused a 15% increase in valsartan, amlodipine caused a 21% increase in valsartan and sildenafil caused a 29% decrease in valsartan.
- Co-administration of LCZ696 increased the C_{max} of atorvastatin and its metabolites by up to 2 fold and AUC by <1.3 fold. These effects may potentially be due to the OATP1B1 and OATP1B3 inhibitory effects of sacubitril and OAT3 by sacubitril, sacubitrilat, and valsartan.
- Sacubitril is a substrate of P-gp, but there is a low likelihood for a drug interaction of LCZ696 when co-administered with a P-gp inhibitor.
- In HF, steady state exposure of sacubitril, sacubitrilat, and valsartan are higher by 55%, 110%, and 132%, respectively, compared to healthy subjects.
- In mild, moderate and severe renal impairment, exposure of sacubitril and valsartan are not affected but the exposure of the sacubitril metabolite, sacubitrilat, is increased by 2.1 fold, 2.2 fold and 2.7 fold, respectively. No studies have been performed in patients undergoing dialysis.
- In mild and moderate hepatic impairment (Child-Pugh classes A and B, respectively), the exposures of sacubitril increased by 1.5 and 3.4 fold, sacubitrilat increased by 1.5 and 1.9 fold, and valsartan increased by 1.2 and 2.1 fold, respectively, compared to matching healthy subjects. No studies have been conducted in patients with severe hepatic impairment.
- Ethnicity, gender, and body weight have no significant PK effects on LCZ696.
- In elderly subjects (>65 years), the exposure of sacubitrilat and valsartan was higher by 42% and 30%, respectively, compared to younger subjects, with no significant change in their terminal elimination half life values.
- The pharmacokinetics of valsartan was similar to when administered alone.

Pharmacodynamics

The submitted pharmacodynamic studies noted the following findings:

- LCZ696 effects are likely to result from enhancement of protective endogenous systems such as the natriuretic peptide system and other vasoactive neprilysin

substrates, and the simultaneous inhibition of organ injury driven by activation of the RAAS.

- Twice daily dosing is required for sustained neprilysin inhibition.
- LCZ696 provides AT1 receptor blockade comparable to valsartan and a reduction of aldosterone in multiple populations and results in a transient increase in natriuresis and diuresis in patients with HF and hypertension.
- LCZ696 resulted in a slight increase in local adipose tissue lipolysis.
- Single doses of LCZ696 400 mg (therapeutic dose) and 1200 mg (supratherapeutic dose) did not affect cardiac conduction or repolarization as evidenced by a lack of effect on the PR interval, QRS duration, QTc interval, and electrocardiogram (ECG) morphology.
- Co-administration of LCZ696 with sildenafil resulted in a more than additive BP reduction in patients with hypertension. No clinically relevant PD interactions were identified upon co-administration of LCZ696 and warfarin, frusemide (reduced sodium excretion) or nitroglycerin.
- Increased CSF amyloid- β 1-38 was seen but no changes in CSF amyloid- β 1-40 and 1-42 concentrations in healthy subjects.

Efficacy

Dose selection

No specific Phase II dose ranging studies were performed in HF patients. Dose selection was based on several factors including biomarker studies, valsartan and sacubitril PK, sacubitril dosing in hypertensive subjects, NEP inhibition and a Phase II dose ranging hypertension study. The dose of LCZ696 200 mg BD was shown to deliver similar valsartan exposure as a dose of 160 mg BD, the approved dose for HF. The dose of LCZ696 200 mg BD delivers a 97 mg dose of sacubitril which was shown to provide near maximal NEP inhibition. The half lives of valsartan and sacubitrilat offer once daily dosing, however the sponsor opted for BD dosing to ensure full 24 h coverage, minimise the risk of PD breakthrough at trough and reduce the risk of hypotension in the elderly.

Note that in the following clinical trial description:

- 50 mg = 24mg sacubitril / 26 mg valsartan
- 100 mg = 49mg sacubitril / 51 mg valsartan
- 200 mg = 97mg sacubitril / 103 mg valsartan

Study CLCZ696B2314 (PARADIGM-HF)

This was a Phase III, multi centre, multi national, randomised, double blind, parallel group, active controlled study to compare the efficacy and safety of LCZ696 200mg BD with enalapril 10 mg BD in 8399 patients with chronic HF (mean baseline BNP was 120.6 pmol/L and mean NT-proBNP was 341.4 pmol/L, White (66.1%), male (78.1%), mean age 64 years (19% \geq 75 years), NYHA class II (70.3%) or class III (24.1%) or class IV (0.71%), mean baseline eGFR was 67.7 mL/min) and reduced ejection fraction (LVEF \leq 40%, changed to \leq 35% after 1,285 patients had been recruited, mean baseline LVEF was 29.5%). Study treatments were to be taken BD in addition to the patients' usual optimal HF therapy; however, additional ACE inhibitors and ARBs were prohibited. A total of 18,071 patients were screened of whom 7,534 (41.7%) were ineligible, most commonly due to low BNP/NT-pro BNP levels. The median treatment period was 2.26 years (max. follow up of 51 months) in this event driven study (preceded by a single blind run in period of 5-10 weeks, during which patients received enalapril 10 mg BD for 2 weeks,

followed by LCZ696 100 mg BD for 1-2 weeks, and then 200 mg BD for 2-4 weeks). The majority of patients had achieved the target doses at the last visit (LCZ696 75.7%, enalapril 74.6%) and 1,603 (19.0%) discontinued. To minimise the potential risk of angioedema, there were two 36 hour washout periods, one after completing the enalapril run-in and one after completing the LCZ696 run-in. The study was discontinued early due to convincing efficacy based on pre specified statistical criteria, including significance $p < 0.001$ in favour of LCZ696 versus enalapril.

Some of the main cardiac related exclusion criteria were: history of angioedema; requirement for treatment with both ACE inhibitors and ARBs; current acute decompensated HF; symptomatic hypotension, eGFR < 30 mL/min, serum potassium > 5.2 mmol/L at screening; acute coronary syndrome, stroke or TIA within 3 months of screening; cardiac, carotid or other major CV surgery or investigation within 3 months of screening, heart transplant or intent to transplant; history of severe pulmonary disease, documented untreated ventricular arrhythmia with syncopal episodes within 3 months of screening; symptomatic bradycardia or second or third degree heart block without a pacemaker; hemodynamically significant mitral or aortic valve disease; hemodynamically significant ventricular or aortic outflow obstruction.

The study had 97% power to detect a 15% reduction in the primary endpoint based on an annual event rate of 14.5% in the enalapril group. Multiple testing procedures were used to control for multiplicity for the secondary endpoints. Baseline demographics and disease characteristics were similar in each group: 62.8% previous hospitalisations for HF, 43.2% previous myocardial infarction, 54.6% coronary heart disease and 25.2% permanent atrial fibrillation. Prior to enrolment, 77.7% and 22.6% of patients were receiving ACE inhibitors and ARBs, respectively.

The primary efficacy endpoint, which was a composite of adjudicated cardiovascular death or HF hospitalisation, was statistically significantly in favour of LCZ696 with 21.8% of patients meeting the primary composite endpoint compared with 26.5% in the enalapril group (4.69% ARR, 20% RRR, HR 0.80; 95% CI: 0.73, 0.87, $p < 0.0001$). The benefit occurred soon after starting treatment and was sustained throughout the study.

Table 14. Primary efficacy analysis of CEC confirmed first primary endpoint (CV death, HF hospitalisation) and its components for double blind period (FAS).

| Response variable | LCZ696 vs Enalapril | | | | | |
|------------------------|---------------------|----------------------|--|---|---------------------|-------------|
| | LCZ696 n/N (%) | Enalapril n/N (%) | LCZ696 n/T (EAIR)(1) (95% CI) | Enalapril n/T (EAIR)(1) (95% CI) | HR (95% CI) | p-value |
| Primary Composite | 914/4187 (21.83) | 1117/4212 (26.52) | 914/87.22 (10.48) (9.81,11.18) | 1117/84.93 (13.15) (12.39,13.95) | 0.80 (0.73,0.87) | $< .0001^*$ |
| CV death | 558/4187 (13.33) | 693/4212 (16.45) | 558/93.08 (5.99) (5.51,6.51) | 693/92.35 (7.50) (6.96,8.08) | 0.80 (0.71,0.89) | $< .0001^*$ |
| 1st HF Hospitalization | 537/4187 (12.83) | 658/4212 (15.62) | 537/87.22 (6.16) (5.65,6.70) | 658/84.93 (7.75) (7.17,8.36) | 0.79 (0.71,0.89) | $< .0001^*$ |

Source: Table 14.2-1.1

The analysis is performed using a Cox-regression model with treatment and region as fixed factors. p-value is from a 1-sided test.

n: Total number of events included in the analysis; N: Total number of patients included in the analysis.

(1) EAIR (Exposure-adjusted incidence rate per 100 patient years) = n/T : T(100 years): total up-to-event/censoring duration-time summarized over patients in the respective treatment group.

* Indicates statistical significance (1-sided) with an alpha level of 0.001, used for the 3rd IA. Events which occurred in the double-blind period up to 31 Mar 2014 are included in the analysis.

For the primary endpoint, no significant interactions were identified in subgroups including age, gender, and race, but the benefit in favour of LCZ696 was significantly less in NYHA class III/IV patients compared with NYHA class I/II ($p = 0.034$) however the interaction was not significant when adjusted for multiplicity. There was a treatment

benefit in favour of LCZ696 in the small number of patients with baseline EF >35%, and in the larger group with baseline EF ≤35%.

Secondary efficacy endpoints demonstrated the following:

- Deaths due to CV causes were reported in 13.3% on LCZ696 compared with 16.5% on enalapril (HR 0.80; 95% CI: 0.71, 0.89).
- Adjudicated hospital admissions for HF were reported in 12.8% on LCZ696 compared with 15.6% on enalapril (HR 0.79; 95% CI: 0.71, 0.89).
- All-cause mortality was 17% on LCZ696 compared with 19.8% on enalapril (HR 0.84; 95% CI: 0.76, 0.93).
- Minor improvements in the KCCQ (physical function, symptoms, quality of life) were seen but these were not significant when adjusted.
- There were no significant differences between the groups for the composite renal endpoint (HR 0.86; 95% CI: 0.65, 1.13, p = 0.28), or for new onset AF (HR 0.97; 95% CI: 0.72, 1.31, p = 0.84).
- A post hoc analysis of NYHA classes from baseline to Month 8 showed a statistically significant improvement in functional class in the LCZ696 group (15.8% vs 14.0%, p = 0.03) but this was not significant when adjusted for multiple comparisons.

At the end of the treatment period, 69.64% of the LCZ696 group were receiving the target dose of 200 mg BD; 6.71% were receiving 100mg BD; 1.97% were receiving 50 mg BD; and 21.67% were receiving no study medication. Patients taking ≤50% of the target dose tended to be older, to be in NYHA class III rather than class II, to have higher mean NT pro BNP values, and to have lower mean eGFR values. Similar trends were observed in the enalapril group. Kaplan-Meier plots of first confirmed primary endpoint (CV death or HF hospitalisation) by treatment group in the ≤50% and >50-75% mean actual dose subgroups showed hazard ratios in favour of LCZ696 of 0.442 (95% CI: 0.222, 0.883) and 0.544 (95% CI: 0.371, 0.789), respectively. The results were comparable to the overall population.

Study CLCZ696B2228 (TITRATION)

This was a 12 week, multicentre, randomised, double blind, parallel group, Phase II study comparing two titration regimens (3 and 6 week) for initiating LCZ696 to a target dose of 200mg BD in 498 HF patients (NYHA Class II-IV) with LVEF ≤35%. The primary endpoint showed a comparable incidence of hypotension (9.7% versus 8.4%) and renal dysfunction (7.3% versus 7.6%) in the 3 and 6 week titration groups, however hyperkalaemia was more common in the 3 week titration group compared with the 6 week titration group (7.7% versus 4.4%). The starting dose of 50 mg BD was well tolerated. More patients achieved the target dose of 200 mg BD with no down titration or dose interruptions with the 6 week regimen than the 3 week regimen (85.2% versus 81.1%). The evaluator considered both titration regimens as acceptable alternatives to the 100 mg BD starting dose recommended in the proposed PI.

Study CLCZ696B2214 (PARAMOUNT)

This was a 12 week plus 24 week extension, randomised, double blind, multi centre, parallel group, active controlled, Phase II study to compare the efficacy and safety of 200 mg BD LCZ696 and 160 mg BD valsartan in 308 patients with chronic HF and **preserved** left-ventricular ejection fraction (LVEF ≥45%). The primary endpoint showed a reduction in NT pro BNP from baseline to Week 12 which was 23% greater in the LCZ696 group than in the valsartan group (p = 0.0050). At Week 36, there was a 15% difference in favour of LCZ696 but the difference was no longer statistically significant (p = 0.20). Subgroups were consistent with the overall population.

Other studies

The clinical evaluation report describes other studies that cover the use of LCZ696 in patients with hypertension, and for valsartan in patients with HF or hypertension and also in combination with other medicines. Of note, the Val-HeFT study which assessed valsartan compared to placebo in 5,010 patients with stable, chronic congestive HF (NYHA Class II-IV) showed valsartan was not superior to placebo for reduction in all cause mortality or cardiovascular deaths; however, it did reduce the time to first HF hospitalisation by 27.5%. Also of note was the VALIANT study which compared valsartan with captopril and their combination in 14,703 high risk patients after myocardial infarction which showed all-cause mortality rates were nearly identical in the three treatment groups (valsartan 19.9%, captopril 19.5%, valsartan + captopril 19.3%) with hazard ratios close to 1.0.

Safety

A total of 14,997 patients were exposed to LCZ696 in the development program (HF = 10,106).

In the pivotal study, 4203 were exposed to LCZ696 with 3606 for ≥ 1 year and 2153 for ≥ 2 years. In the run in period, adverse events were slightly higher on LCZ696 than enalapril (28.7% versus 22.5%) but similar overall in the double blind period (81.4% versus 82.8%). The most common events were hypotension (17.6% versus 12.0%), cardiac failure (17.4% versus 19.7%), hyperkalaemia (11.6% versus 14.0%), renal impairment (10.1% versus 11.5%), cough (8.8% versus 12.6%), and dizziness (6.3% versus 4.9%). Hypotension and dizziness occurred more commonly on LCZ696. During the LCZ696 run-in period, 7.3% of patients reported adverse drug reactions (ADRs), most commonly hypotension (2.3%), hyperkalaemia (1.3%) and renal impairment (1.1%). The most common ADRs in the double blind period (LCZ696 versus enalapril) were: hypotension (10.2% versus 6.9%), hyperkalaemia (4.6% versus 5.6%), renal impairment (2.8% versus 4.2%) and cough (1.5% versus 3.8%). Deaths during the double-blind treatment period occurred in 729 (17.3%) and 848 (20.1%) on LCZ696 and enalapril respectively, with most being cardiovascular causes (78.4% versus 82.9%), most commonly sudden death (35.2% versus 37.2%) and pump failure (20.6% versus 22.1%). There were no clinically relevant differences in the frequency of non cardiovascular deaths between the groups. There were fewer serious adverse events on LCZ696 (46.1%) than on enalapril (50.7%) with cardiac failure the most common (14.0% versus 15.4%). Discontinuations due to AEs were slightly higher on enalapril in the run in period (5.5% versus 6.1%) and during the double blind period (10.7% versus 12.2%) and were most commonly cardiac failure (1.50% versus 1.54%), cardiac death (0.67% versus 0.76%), hypotension (0.62% versus 0.54%), sudden cardiac death (0.59% versus 0.52%) and renal impairment (0.43% versus 0.78%). LFT abnormalities were comparable in each treatment group and clinically significant abnormalities were uncommon. Hepatic events were low in both groups and similar (ALT or AST $> 3 \times$ ULN: 1.26% versus 0.99%). There was one case of AST/ALT $> 3 \times$ ULN and total bilirubin $> 2 \times$ ULN compared with four on enalapril. Reductions in eGFR and increases in serum creatinine from baseline were experienced less frequently on LCZ696 compared with enalapril. Reductions in eGFR $> 50\%$ were reported in 5.5% and 6.4% of the respective groups. Hyperkalaemia with potassium > 5.5 mmol/L at any visit was reported in 15.5% and 16.5% on LCZ696 and enalapril respectively. Haematological changes were minor and comparable. There were no clinically meaningful changes from baseline in any ECG time interval or heart rate in either treatment group. Multiple cardiac arrhythmias were reported in both groups but most were numerically fewer in the LCZ696 group compared with enalapril. Low systolic and diastolic blood pressure (SBP and DBP) were experienced more frequently on LCZ696 compared with enalapril (SBP

4.8% versus 2.7%, DBP 3.1% versus 1.6%). Changes in heart rate were comparable in each treatment group. High body weight was more common on LCZ696 (27% versus 22%).

In the TITRATION study, AEs were less frequent in the slower titration method than the quicker method (42.2% versus 51.6%). The most common AEs (quicker versus slower titration groups) were: hypotension (9.8% versus 8.4%), hyperkalaemia (6.5% versus 4.4%), dizziness (3.7% versus 2.4%), renal impairment (4.1% versus 1.6%) and cardiac failure (3.7% versus 1.2%). During the post randomisation period, there were two (0.8%) deaths in the LCZ696 quicker titration group compared with one (0.4%) in the LCZ696 slower titration group. None of the deaths were considered drug related. SAEs were reported in 8.5% and 5.6% respectively. Discontinuations due to AEs were reported in 8.1% and 5.6% respectively, most commonly due to hypotension (2.0% versus 1.2%) and hyperkalaemia (1.2% versus 0.4%). Increases in serum creatinine occurred more commonly in the quicker titration group. Potassium > 5.5 mmol/L at any visit was reported in 7.7% and 6.0% respectively.

In the PARAMOUNT study, the most common events for LCZ696 versus valsartan were: hypotension (14.1% versus 9.9%), hyperkalaemia (8.1% versus 5.9%), diarrhoea (6.7% versus 2.6%), dizziness (6.7% versus 4.6%) and dyspnoea (4.0% versus 9.2%). During the double-blind period, there was one (0.7%) death on LCZ696 compared with two (1.3%) on valsartan, none of which were considered drug related. SAEs were reported in 14.8% and 19.7% respectively. During the double blind period, withdrawal rates were similar. Reductions in eGFR >50% from baseline were reported in 3.4% and 2.8%, respectively. Potassium > 5.5 mmol/L at any visit was reported in 16.2% and 11.2%, respectively. More patients on LCZ696 reported a fall ≥ 30 mm Hg in msSBP compared with the valsartan group (25.0% versus 15.2%) however falls in msDBP were comparable.

Multiple pooled analyses are discussed in the clinical evaluation report but in the HF studies, the most common AEs across the individual studies were hypotension, cardiac failure, hyperkalaemia, renal impairment, cough, and dizziness. Hypotension was more frequently observed on LCZ696 than on the comparator.

A sacubitril monotherapy arm in a hypertension study showed a similar AE profile to placebo. LCZ696 was also well tolerated in 30 clinical pharmacology studies with no deaths, six SAEs and 23 discontinuations due to AEs.

Hypotension-related AEs (hypotension, orthostatic hypotension, dizziness and syncope) were more frequent on LCZ696 compared with enalapril (24.4% versus 18.6%). Most hypotension related AEs were mild or moderate and most occurred during the early phase of treatment. Symptomatic hypotension was reported in 13.2% and 8.2% on LCZ696 and enalapril respectively [RR 1.7 (95% CI: 1.5, 1.9)]. Severe events were reported in 1.9% on LCZ696 compared with 2.1% on enalapril. The incidence of all renal impairment AEs was 16.2% on LCZ696 and 17.6% on enalapril [RR 0.9 (95% CI: 0.8, 1.0)]. Renal failure and renal impairment was less frequent on LCZ696 compared with enalapril. Hyperkalaemia AEs occurred less commonly on LCZ696 compared with enalapril (11.9% vs 14.3%). Serious skin reactions were comparable and there were no significant changes in QTcF. In the elderly, hypotension, renal impairment and hyperkalaemia were more common in both treatment groups compared with those aged <65 years.

Angioedema (non-adjudicated) was reported in 7.1% on LCZ696 and 7.4% on enalapril. Adjudicated angioedema in the double blind period in the pivotal study was reported in 0.45% and 0.24% on LCZ696 and enalapril, respectively. Only three patients (0.07%) on LCZ696 experienced severe events but there were no cases of airway compromise. Angioedema was more common in Black patients on LCZ696 than other groups (2.3% versus 0.5%). In the titration study, there were two events in the slower group. Compared with the overall population, no notable differences were observed in other subgroups for

hepatotoxicity, cognitive impairment, hypersensitivity reactions, bone growth/bone mineral density, gastric lesions, malignancies, or lipolysis.

Risk management plan

The Pharmacovigilance & Special Access Branch (PSAB) has provisionally accepted the EU RMP for Entresto (sacubitril/valsartan), version 1.4, dated 30 September 2015 (data lock point 5 August 2014), with the ASA, version 2.0, dated 23 October 2015, pending further updates to the EU-RMP and consequently the ASA and any advice provided by ACSOM at their meeting. One outstanding matter was a recommendation that the advice provided in the PI on valsartan bioavailability is repeated under 'Dosage and administration' of the PI, which the delegate agrees.

Routine pharmacovigilance and risk minimisation is proposed for Entresto which the clinical evaluator and RMP evaluator have both accepted. The submission will be referred to ACSOM for advice and this will be provided to ACPM. The sponsor has ongoing and planned additional pharmacovigilance studies examining safety outcomes, for example, angioedema, renal impairment, hepatic impairment, cognitive function and statin interaction which will be reported as part of the RMP.

Risk-benefit analysis

Delegate's considerations

Efficacy

The efficacy of LCZ696 was demonstrated in the Phase III study PARADIGM-HF with support for two titration methods from the Phase II study TITRATION. PARADIGM-HF used clearly defined and widely accepted clinical endpoints that were adjudicated by a blinded committee. This large study, in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction, demonstrated that LCZ696 97/103 mg BD was statistically and clinically superior to enalapril 10 mg BD, reducing the risk of the composite endpoint of CV death or HF hospitalisations by 20% (absolute risk reduction of 4.7%). All cause mortality was also reduced by 16% compared to enalapril which was driven by a reduction in cardiovascular mortality. The results of the primary endpoint were consistent across the subgroups, including age and gender. Minor improvements in the KCCQ were not significant and there were no significant differences in the composite renal endpoint or new onset atrial fibrillation. A non significant improvement in NYHA class was seen. The primary endpoint result appeared similar in subgroups who had $\leq 50\%$ and $>50-75\%$ of the target dose.

The acceptability of a single, large, pivotal study was agreed and justified as recommended in EU guidelines.¹³ The comparator, enalapril, was considered appropriate since it is approved for patients with HF based on established efficacy compared with placebo. The dose of enalapril used was based on the SOLVD study and met the FDA criteria for minimum dosing however titration to a higher dose of 20mg BD could have been investigated. A placebo control arm was not appropriate for ethical reasons and a valsartan control arm was not considered appropriate since it is second line to ACE inhibitors in HF. Sacubitril alone was not an appropriate study arm as it cannot be added to background ACE inhibitor therapy because of the risk of angioedema. Although the study was terminated early, which raises some doubt about long term outcomes, the data were significant at that median time point of 27 months (including run-in) and therefore

¹³ European Medicines Agency, "Points to consider on application with: 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

sufficient to support treatment in this population. Initial screening of patients led to 41.7% being ineligible, most commonly due to low BNP/NT pro BNP levels. The run in design, in which about 10% discontinued on enalapril and then another 10% discontinued on Entresto, would have led to a reduced adverse event rate in the double blind phase.

A supportive Phase II study in patients with preserved ejection fraction indicated a greater reduction in NT pro BNP for LCZ696 than valsartan and another supportive study in the indicated population showed support for 3 week and 6 week (slightly better) titration regimens. Sacubitril, sacubitrilat and valsartan are not significantly metabolised by CYP450 enzymes and do not inhibit or induce many of the CYP450 enzymes to any significant level.

Safety and RMP

The safety profile of LCZ696 was acceptable with no unexpected safety findings given its pharmacology. Patients with HF were exposed for an acceptable period. The ADRs related to class effects were reported as expected and there did not appear to be a signal for hepatotoxicity, haematological toxicity, QTc prolongation or cognitive effects. Compared with enalapril, the LCZ696 treatment group had fewer deaths, SAEs and AEs leading to study drug discontinuation. AEs leading to dose adjustment or interruptions were mainly due to a higher incidence of hypotension on LCZ696. AEs commonly associated with RAAS inhibition in HF are hypotension, renal impairment, and hyperkalaemia. Hypotension was more commonly reported on LCZ696 (17.6% versus 12%) but the number of discontinuations due to hypotension was low in both groups (0.6% versus 0.5%) and most events were mild or moderate. Dizziness and orthostatic hypotension were also slightly higher on LCZ696. Despite the higher incidence of hypotension, renal impairment was slightly less common. Hyperkalaemia was also slightly less frequent on LCZ696. Angioedema frequency was similar in both groups but more common in Black patients. Adjudicated angioedema was slightly higher on LCZ696 and a contraindication is proposed for concomitant use with ACE inhibitors within 36 h. AEs were more commonly reported in the elderly (≥ 65 years) and very elderly (≥ 75 years) but similar to enalapril except for hypotension. Patients with more severe renal impairment have a higher incidence of adverse reactions and a lower starting dose is recommended in the PI. The RMP proposed is mostly acceptable; however, finalisation will depend on any further advice from ACSOM.

Indication

The sponsor responded to the clinical evaluator's recommendation for the indication and proposed revising the wording to be consistent with the EU but also include the endpoint claims of "to reduce the rate of cardiovascular death and HF hospitalisations" as per their original request. The inclusion of adults and reference to reduced ejection fraction is acceptable as this is the study population that were included in the pivotal trial. The reference to symptomatic patients has been included in the EU but the US refers to NYHA Class II-IV patients which is also how patients are described in the pivotal trial and is also how the Australian approved indication for valsartan monotherapy is worded. Therefore, for consistency, NYHA Class is preferred.

There were few patients with NYHA class I status but this group is not being requested by the sponsor. Patients with NYHA Class IV comprised only 0.71% of the pivotal study population however the sponsor is requesting they be included in the indication. Canada has excluded patients with Class IV status but the US has included them. Despite the few patients in class IV in the dossier, this may be best left to clinical judgement on whether continuing treatment in this group is appropriate given that patients would be worsening if they reached class IV. ACPM's advice is requested on this matter.

The clinical evaluator has recommended that the indication not include the endpoint claims of a reduction in the rate of cardiovascular death and HF hospitalisations since

these are claims and not an indication. The EU approved indication also does not include these endpoint claims however the US wording does include them. The sponsor states that these should be included because it provides the reason to treat and the efficacy of the endpoint is supported by the pivotal study. They also state that other products approved in Australia include endpoint claims, for example, perindopril for coronary artery disease and valsartan for patients post myocardial infarction with left ventricular failure/dysfunction. Although these examples include the use of endpoints, the comparator drug used in the pivotal study, enalapril, has an indication for HF but it does not include endpoint claims. Although the endpoint claims are based on the primary composite endpoint and therefore are supported by the efficacy data, on balance, the delegate considers endpoint claims are more appropriate in the clinical trials section of the PI as they are essentially results of the studies and do not define the population as such that is indicated for treatment. Therefore, it is recommended that, consistent with the EU approved indication, endpoint claims be removed from the indication.

The pivotal study included patients who were taking their usual HF medication as background therapy and the US, Canadian and Swiss indications include wording that Entresto is administered in combination with other HF therapies. The EU has not included this statement. The clinical evaluator did not consider this was needed in the indications since it is covered elsewhere in the PI and that the data did not suggest that Entresto could not be used as monotherapy if appropriate in selected HF patients. Given the study and the statement are not specific to a particular co-administered HF treatment then a statement in the Dosage and Administration section may be acceptable. The sponsor has been asked to comment on any data in relation to monotherapy use. The statement does also mention about use in place of an ACE inhibitor or ARB, however this is covered in the Contraindications, Precautions and Dosage and Administration sections of the PI. Considering the above, the delegate's proposed wording at this stage is below. ACPM's advice is requested on this matter.

Expression of strengths

Using the example of the middle strength product, the proposed expression of strengths for Entresto in Australia is:

- Entresto 49/51 (48.6 mg sacubitril/51.4 mg valsartan)

This is similar to the EU/US labelling. Internationally there is variation in how the product is expressed in labelling and associated PI documents with some expressing both components, others the whole unit and some using one decimal place:

- US: Entresto 49/51 mg (sacubitril 49 mg and valsartan 51 mg)
- EU: Entresto 49 mg/51mg (48.6 mg sacubitril and 51.4 mg valsartan)
- Switzerland: Entresto 100 mg (48.6 mg sacubitril and 51.4 mg valsartan)
- Canada: Entresto 48.6 mg sacubitril/51.4 mg valsartan.

The clinical evaluator recommended using the single dose strength, that is, 100 mg, because chemically the product is a stable salt which only dissociates after ingestion. Patients would be able to recognise and recall what medications and dose strengths they are receiving, particularly in emergency situations. Simple rounded numbers also make prescribing and dispensing errors less likely. However, as the TGA and most other regulators consider this product to be a FDC, then the expression of both components is consistent with the TGA policy of expressing both units for a fixed dose combination. For ease of prescribing and reducing errors, it was recommended that both whole numbers be used in the name instead of expressing each component to one decimal place as in Canada but to describe to one decimal place underneath as part of the active ingredient description, as per the EU.

The valsartan in Entresto is more bioavailable than the valsartan taken in other preparations available such as the monotherapy Diovan. Valsartan is also available in other combinations and there are multiple generics. Diovan has an approved indication for the treatment of HF and therefore patients may be on this product prior to taking Entresto. The 51mg of valsartan in Entresto is equivalent to 80 mg of valsartan when taken in other preparations such as Diovan. A similar difference also exists for the other strengths. Since many patients may be taking valsartan for HF and may transfer to Entresto then this could also add to the confusion since it may be perceived that a patient is getting less valsartan when taking Entresto. Entresto should not be administered with an ARB such as valsartan as stated in the PI. The sponsor and TGA are concerned about potential confusion in dosing with the expression of the product varying internationally and also how published literature and ongoing clinical trials may express dosing. To address these concerns, the PI will include a statement on the equivalent amounts of valsartan from Entresto and other preparations and also include a statement in the Clinical Trials section that 49/51 mg may also be referred to as 100 mg as used in the clinical trials. A copy of the proposed statements are included below and it is recommended that a statement on the bioavailability issue compared with valsartan is also included in the Dosage section of the PI and the sponsor should ensure that prescribers are informed of this issue for transitioning patients. ACPM's advice is requested on this matter.

- Pharmacokinetics: The valsartan contained within [trade name] is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in Entresto is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.
- Clinical Trials: Dosing in clinical trials was based on the total amount of both components of Entresto, that is, 24/26 mg, 49/51 mg and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.

Amyloid

Sacubitril is a neprilysin inhibitor via its active metabolite sacubitrilat. Neprilysin is one of multiple enzymes involved in the clearance of amyloid- β ($A\beta$) from the brain and cerebrospinal fluid (CSF). Administration of LCZ696 was associated with an increase in CSF $A\beta$ 1-38 compared to placebo; there were no changes in concentrations of CSF $A\beta$ 1-40 and 1-42. The clinical relevance of this finding is unknown. In cynomolgus monkeys, Entresto affected CSF $A\beta$ clearance, increasing CSF $A\beta$ 1-40, 1-42, and 1-38 levels in CSF with no corresponding increase in $A\beta$ levels in the brain. In a toxicology study in cynomolgus monkeys treated with Entresto at 146 mg sacubitril/154 mg valsartan/kg/day for 39 weeks, there was no amyloid- β accumulation in the brain. The sponsor has included a statement on this in the Pharmacodynamics section and a new heading under Precautions, "Other preclinical safety findings". Longer term data is needed to address this issue and any potential effects on cognitive function since the pivotal study was terminated early. ACPM's advice is requested on this matter.

Data deficiencies

The sponsor has not conducted a Phase II study to assess sacubitril compared to placebo in HF patients who are intolerant of ACE inhibitors. It is unknown if sacubitril has additive haemodynamic effects compared to valsartan alone. There is no direct evidence that LCZ696 is superior to valsartan alone in HF. There is no or limited data regarding improvements in haemodynamics, symptoms, quality of life or exercise capacity. No studies have been performed in patients with severe hepatic impairment or in patients with severe renal impairment (CKD Stage IV and V). Few patients with NYHA Class I or IV have been studied.

Conditions of Registration

The following are proposed as conditions of registration and the sponsor is invited to comment in the pre ACPM response:

- The implementation in Australia of the EU RMP for Entresto (sacubitril/valsartan), version 1.4, dated 30 September 2015 (data lock point 5 August 2014), with the ASA, version 2.0, dated 23 October 2015 (pending further updates to the EU-RMP and consequently the ASA and any advice provided by ACSOM), and any subsequent revisions, as agreed with the TGA.
- The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ASA, as soon as possible after completion, for evaluation as Category 1 submission(s):
 - Study CLCZ696B2317: A multicentre study to evaluate safety and tolerability in patients with chronic HF and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696.

Questions for the sponsor

The sponsor is requested to address the following issues in the pre ACPM response:

- Please provide copies of the approved Entresto labels from USA, EU, Switzerland and Canada that display how the strengths are expressed.
- What is the efficacy and safety of LCZ696 in patients with HF when taken as monotherapy compared to co-administration with other HF treatments?
- Please summarise any differences in efficacy or safety for patients in Paradigm-HF with LVEF $\leq 40\%$ compared to LVEF $\leq 35\%$.
- What are the sponsor's plans to further investigate the potential effects and risks of LCZ696 on the clearance of amyloid and cognitive function?

Summary of issues

The primary issues with this submission are as follows with further information in the Discussion section:

- Whether the use of enalapril at a dose of 10 mg BD was appropriate as a comparator in the pivotal study.
- Whether the indication should remove reference to endpoint claims of a reduction in the rate of cardiovascular death and HF hospitalisations, refer to patients with NYHA Class instead of symptomatic and include patients with NYHA Class IV who comprised only 0.71% of the pivotal study population.
- Whether the indication requires a statement regarding use with other HF treatments, as per the US PI, or not, as per the EU SmPC, or would this be more appropriate in the Dosage section of the PI.
- Whether the description of the product in the PI/CMI and labels should be as the two component medicines of sacubitril and valsartan, for example, 49/51 mg, or whether it should be described as the whole unit, for example, 100 mg.
- The bioavailability of valsartan in LCZ696 is not the same as from valsartan monotherapy and whether the proposed statement in the PI is adequate in this regard.
- Whether the changes in amyloid are of clinical significance.
- The increased risk of hypotension related events.

Proposed action

The Delegate has no reason to say, at this time, that the application for Entresto should not be approved for registration.

The Delegate's proposed wording for the indication is:

Entresto is indicated in adult patients for the treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

- Was the use of enalapril at a dose of 10 mg BD appropriate as the comparator in the pivotal study?
- Should the indication be amended to remove endpoint claims, refer to patients with NYHA class and include patients with NYHA Class IV status?
- Should a statement on use with other HF treatments be included in the Indications or in the Dosage section of the PI?
- Is the description of the product's strengths acceptable for the PI/CMI and labels or should it be expressed differently?
- Has the sponsor adequately addressed in the PI the differences in the bioavailability of valsartan in LCZ696 compared to valsartan from other preparations?
- Are the changes in amyloid of clinical significance and are the statements in the PI in relation to amyloid appropriate?
- Has the increased risk of hypotension related events been adequately addressed by the sponsor in the PI/CMI?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Presented here is the Novartis pre ACPM response to the Delegate's overview (DO) pertaining to our application to register Entresto/Novartis sacubitril/valsartan film-coated tablets (referred to as LCZ696 from this point onwards). Where appropriate, our comments have been cross-referenced to the DO, the clinical evaluation report (CER), the risk management plan evaluation report (RER) or to our original submission for marketing authorisation (MA). Please note that in our response below the Delegate's comments have been italicised for ease of reference.

Novartis welcomes the Delegates preliminary assessment to approve this application. Here, we respond to the Delegate's "Questions for the Sponsor". We also, respectively, take the opportunity to provide our comments on some of the specific advice sought by the Delegate from the Committee, which is also referred to as the "Summary of Issues" in the DO. Novartis brings to the attention of the Committee that an alternative wording of the indication was proposed with the response to the RER and CER to the TGA on 25 October 2015, as shown below and discussed below:

Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction to reduce the rate of cardiovascular death and heart failure hospitalisations.

Response to the Delegate's questions for the sponsor

- Please provide copies of the approved Entresto labels from USA, EU, Switzerland and Canada that display how the strengths are expressed.

Copies of LCZ696 labels are provided for the approved US Package Insert, the proposed EU Summary of Product Characteristics (SmPC), the approved Canadian Monograph, and the approved Swiss label. Please note Novartis is expecting the EU final approval by the end of the year. Hence, the most current draft is provided.

- What is the efficacy and safety of LCZ696 in patients with HF when taken as monotherapy compared to co-administration with other HF treatments?

Novartis acknowledges that LCZ696 has not been studied as monotherapy. HF is a chronic condition that has been studied in patients still at risk for morbidity and mortality by adding new therapies to existing therapies as they are proven. Initial therapies such as diuretics were primarily for relief of symptoms and additional therapies were added as the evidence in controlled clinical trials demonstrated efficacy. HF guidelines throughout the world support this approach to multimodal therapy, for example, the European Society of Cardiology HF guideline (in line with the Australian National Heart Foundation Guidelines) states:

three neurohumoral antagonists—an ACE inhibitor [or angiotensin receptor blocker (ARB)], a beta-blocker, and a mineralocorticoid receptor antagonist (MRA)—are fundamentally important in modifying the course of systolic HF and should at least be considered in every patient.

Thus, ethically it was not considered possible to study LCZ696 in the absence of other therapies with a proven survival benefit. In fact, all recently approved HF drugs (that is, β blocker, MRA) that showed survival benefits were studied on top of the background therapies (for example, including ivabradine).

Evidence of the effect of LCZ696 monotherapy included in our MA, comes from several short term pharmacodynamic studies as well as biomarkers in the longer term studies. Study A2117 demonstrated a sustained increase in urinary atrial natriuretic peptide and cyclic guanosine monophosphate (cGMP) in patients with HF for at least 21 days. Study B2223 demonstrated that the effect on cGMP is much greater (about 2 fold) than that seen with valsartan alone. This sustained effect on urinary cGMP was confirmed in PARAMOUNT study (B2214) at 12 and 36 weeks compared to valsartan alone and in PARADIGM-HF study (B2314) compared to enalapril, and was highly significant in all cases. This suggests that neprilysin inhibition can be demonstrated early during treatment with LCZ696 and persists during the period of administration. LCZ696 monotherapy was well tolerated and no differences in the AE profile noted when compared to LCZ696 administered in conjunction with standard of care (SOC). As is clear from the design of PARADIGM-HF, the beneficial effects of LCZ696 over enalapril with regard to outcomes of survival and hospitalisation are seen on top of beta blockers and MRAs in both treatment arms. Although it is likely that LCZ696 would have substantial benefit for outcomes if given as monotherapy compared to placebo, it is not possible to confirm that hypothesis given the standards of medical practice for the treatment of HF.

- Please summarise any differences in efficacy or safety for patients in PARADIGM-HF with LVEF $\leq 40\%$ compared to LVEF $\leq 35\%$.

The PARADIGM-HF study protocol was amended one year after trial start to modify the left ventricular ejection fraction (LVEF) entry criterion from $\leq 40\%$ to $\leq 35\%$ to ensure an adequate event rate in the study population. There were 963 patients randomised with a baseline LVEF $>35\%$ and $\leq 40\%$ representing 11.4% of the total study population. Several efficacy analyses were conducted that demonstrated a consistent benefit of LCZ696 over enalapril in HF with HFrEF patients across baseline LVEF levels. Although there were no

specific analyses conducted comparing the safety of LCZ696 versus enalapril across LVEF subgroups, the results of PARADIGM-HF indicate that LCZ696 is safe and well tolerated in patients with HF.

The subgroup analysis on the composite primary endpoint comparing LCZ696 against enalapril based on LVEF at screening ($\leq 35\%$ vs. $> 35\%$) showed hazard ratios of 0.78 and 0.89, respectively. Hazard ratios for the $\leq 35\%$ vs. $> 35\%$ subgroups were 0.78 and 0.92 for CV death and 0.79 and 0.80 for hospitalisation for HF, respectively (see PARADIGM-HF). Interaction p-values ranged from 0.3559 to 0.9679 for the three endpoints.

Additional left ventricular ejection fraction (LVEF) subgroup analyses were performed by tertiles ($< 28\%$, $\geq 28\%$ to 32% , $\geq 33\%$), which increased the number of events and sample size of the highest LVEF subgroup to more than 3 times that of the $>35\%$ subgroup, and additional analyses of the composite primary endpoint, CV death and hospitalisation for HF were also performed using 5-percent increments for subcategories of LVEF ($\leq 15\%$, 16% to $\leq 20\%$, 21% to $\leq 25\%$, 26% to $\leq 30\%$, 31% to $\leq 35\%$, and $> 35\%$). There was a consistent treatment benefit in favour of LCZ696 over enalapril for the composite primary endpoint, CV death and hospitalisation for HF regardless of the screening LVEF values (see PARADIGM-HF).

In summary, the efficacy of LCZ696 compared to enalapril to reduce CV death and HF hospitalisation has been consistently demonstrated across all LVEF subgroups, including the subset of patients with LVEF $> 35\%$ and $\leq 40\%$ representing 11.4% of the total PARADIGM-HF study population.

- What are the sponsor's plans to further investigate the potential effects and risks of LCZ696 on the clearance of amyloid- β ($A\beta$) and cognitive function?

A theoretical risk associated with neprilysin inhibition relates to the accumulation of the neprilysin substrate amyloid- β ($A\beta$) in the brain. Therefore, Novartis has conducted pre-clinical and clinical studies to assess the effects of LCZ696 on $A\beta$ clearance. In a 2-week study in young cynomolgus monkeys, LCZ696 treatment (50 mg/kg/day, equivalent to 400 mg once daily in man) resulted in an increase in total cerebrospinal fluid (CSF) $A\beta_{42}$, $A\beta_{40}$, and $A\beta_{38}$ on Day 15 (Study 1270586). However, brain tissue concentrations of $A\beta$ were not affected by LCZ696 compared to vehicle. Administration of LCZ696 400 mg once daily in healthy subjects for 14 days did not result in changes in the aggregable $A\beta$ subtypes $A\beta_{1-42}$ and $1-40$ in the CSF, although there was an increase in CSF $A\beta_{38}$ (Study A2126). The clinical relevance of the increase in CSF $A\beta_{38}$ observed in this study is unknown; however, there is no evidence that an isolated increase in $A\beta_{1-38}$ concentration facilitates $A\beta$ plaque formation. These observations suggest that enzymes and disposition pathways other than neprilysin may be important in the clearance of CSF $A\beta$ in humans. Furthermore, in the PARADIGM-HF trial where patients with HF were treated with LCZ696 for up to 4.5 years,¹⁴ there was no increased incidence of Alzheimer's disease or dementia related AEs in LCZ696 treated patients compared to patients treated with current SOC.¹⁵

As described in the proposed RMP, Novartis is committed to conducting a robust clinical assessment to further investigate the potential effect of neprilysin inhibition by LCZ696 on $A\beta$ and cognitive function in patients with HF. To this effect, Novartis will evaluate cognitive function in two separate clinical trials (ongoing PARAGON-HF and B2320) in patients with HF with preserved ejection fraction (HFpEF). These studies will provide a comprehensive scientific data set to evaluate the theoretical concern related to the effect of LCZ696 on $A\beta$ and any associated changes in cognition. Please see Comments on PI -

¹⁴ McMurray JJ, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 371: 993-1004 (2014).

¹⁵ Cannon JA, et al. 'Hearts and minds': association, causation and implication of cognitive impairment in heart failure. *Alzheimers Res Ther.* 7: 22 (2015).

Amyloid- β Risk Minimisation Activity for further details on Novartis planned studies and comments on clinical significance of A β findings. Until such evidence is available, Novartis believes that the current statements in the proposed PI ('Other preclinical safety findings' and 'Pharmacodynamics' sections) are appropriate.

Additionally, in order to further characterise the risk of cognitive impairment, targeted follow-up with the use of a cognitive impairment checklist is planned for all serious spontaneous cases to obtain detailed information from Healthcare Professionals in patients who have experienced selected cognitive impairment events. This additional pharmacovigilance activity is proposed to closely monitor, evaluate and further characterise symptoms of this potential risk and to identify and/or characterise clinical characteristics of the events, types of patients at risk (demographic factors), risk factors, and characteristics of exposure (dose, duration, co-medications). The potential risk of cognitive impairment will be monitored and reported in LCZ696 PSURs.

In summary, Novartis commits to conducting a robust set of clinical assessments to further evaluate the effect, if any, of LCZ696 on cognitive function and on A β deposition in the brain in patients with HF. These assessments include the use of cognitive function assessment (CFAs) in the PARAGON-HF study, CFAs and PET imaging in the B2320 study, as well as performing targeted follow-up for all serious spontaneous dementia-related cases identified by pharmacovigilance.

Novartis comments on the "Advice sought from the Committee"

- Whether the use of enalapril at a dose of 10mg BD was appropriate as a comparator in the pivotal study.

The enalapril 10 mg bid dose was chosen as the target dose because this is the evidence-based dose shown to reduce mortality compared with placebo in the SOLVD-Treatment study in patients with NYHA Class II-IV HF. In addition, this dose has been utilised in multiple HF clinical trials including SOLVD-Prevention, V-HeFT II,¹⁶ OVERTURE,¹⁷ CARMEN¹⁸ and CIBIS-III.¹⁹ While enalapril 20 mg bid was the target dose in the CONSENSUS trial, only 22% of patients were able to tolerate it, resulting in a mean daily dose of 18.4 mg at end of trial.²⁰ By contrast, enalapril 10 mg bid was the target dose in the SOLVD trial, achieved by 49% of patients, resulting in a mean daily dose of 16.6 mg at the end of the trial.

Recent data from the European Society of Cardiology HF long-term registry in ambulatory chronic HF patients indicates that the median dose of enalapril was 10 mg daily with 46% of patients at the target dose of 20 mg daily.²¹ Enalapril 20 mg was considered the target dose by the investigators, and enalapril and ramipril were the most widely used ACE inhibitors in this survey.

¹⁶ Cohn JN, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med.* 325: 303-10 (1991).

¹⁷ Packer M, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 106: 920-6 (2002).

¹⁸ Remme WJ, et al. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor remodelling mild heart failure evaluation trial (CARMEN). *Cardiovasc Drugs Ther.* 18: 57-66 (2004).

¹⁹ Willenheimer R, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation* 112: 2426-35 (2005).

²⁰ Maggioni AP, et al. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 12: 1076-84 (2010).

²¹ Giacobini E, Gold G. Alzheimer disease therapy--moving from amyloid- β to tau. *Nat Rev Neurol.* 9: 677-86 (2013).

Further, the choice of comparator and dose for study PARADIGM-HF was agreed with EMA and FDA, with the stipulation by the FDA that at least a mean daily dose of 16.6 mg enalapril should be achieved to provide an appropriate comparison. The mean daily dose of enalapril at trial end in PARADIGM-HF was 18.9 mg, which is higher than that achieved in SOLVD-Treatment (16.6 mg daily) and also slightly higher than that achieved in CONSENSUS (18.4 mg daily). Therefore, Novartis believes that the use of enalapril at a dose of 10 mg bid was appropriate as a comparator in the PARADIGM-HF pivotal study.

- Whether the indication should remove reference to endpoint claims of a reduction in the rate of cardiovascular death and HF hospitalisations, refer to patients with NYHA Class instead of symptomatic and include patients with NYHA Class IV who comprised only 0.71% of the pivotal study population.

Novartis believes that references to clinical outcomes should be included in the indication. Additionally, based on the PARADIGM data, there is no evidence suggesting that NYHA Class IV patients would benefit less from LCZ696 treatment. Please refer to Comments on PI - Wording of the indication for the Novartis response on inclusion of this group of patients for treatment with Entresto. We, therefore, respectfully ask the Committee to consider the alternative wording proposed by Novartis stated above.

- Whether the indication requires a statement regarding use with other HF treatments, as per the US PI, or not, as per the EU SPC, or would this be more appropriate in the Dosage section of the PI.

Novartis considers that language similar to the approved US PI is most useful for prescribing physicians for the reasons described in the Annotated PI.

- Whether the description of the product in the PI/CMI and labels should be as the two component medicines of sacubitril and valsartan, for example, 49/51 mg or whether it should be described as the whole unit, for example, 100 mg.

Currently ratios (24/26, 49/51, 97/103) are used to describe the dose strength in the proposed PI, which makes the information difficult to read and assimilate particularly the Pharmacology and Clinical Trials sections (see PI). Even if technically accurate, ratios are not intuitive, especially because the bioavailability of valsartan in LCZ696 is different than that in valsartan containing products, that is, the valsartan in LCZ696 is more bioavailable than the valsartan in other marketed tablet formulations. Hence, Novartis still believes that the 'single dose' strength expression (50 mg, 100 mg, 200 mg) would significantly reduce confusion and medication errors, as the proposed products are not equivalent on a mg to mg basis with other valsartan containing products (see Comments on PI – Dose description). Novartis, however, defers to the Committee for advice and will accept the TGA decision on this matter.

- Whether the changes in amyloid are of clinical significance.

Nepriylsin is one of multiple pathways involved in the clearance of amyloid- β ($A\beta$) from the brain and CSF. Therefore, theoretically, nepriylsin inhibition from a peripherally dosed therapy such as LCZ696 could reduce the clearance of $A\beta$ from the CNS. Alzheimer's disease is associated with the presence of $A\beta$ plaques in the brain. However, the relationship between CSF $A\beta$ concentrations and $A\beta$ plaque formation is not well understood.²² Similarly, there is limited understanding of the relationship between formation of plaques and cognitive decline.

As described above, Novartis completed a preclinical monkey study and a two week study in healthy subjects to investigate the effect of LCZ696 treatment on brain and CSF levels of $A\beta$, because of the hypothetical potential of a nepriylsin inhibitor such as LCZ696 to

²² Giacobini E, Gold G. Alzheimer disease therapy--moving from amyloid- β to tau. *Nat Rev Neurol*. 9: 677-86 (2013).

influence A β metabolism. Additional assessments were also performed on brain tissue from a chronic 39 week toxicology study of LCZ696 in monkeys.

Results from the two week cynomolgus monkey CSF study indicated that short term LCZ696 treatment had a pharmacodynamic effect on CSF A β clearance in this primate model, resulting in significant increases in CSF A β . These changes in CSF A β were not associated with a concomitant increase in brain tissue A β levels in this study. In addition, a thorough evaluation of brain tissue from the 39 week cynomolgus monkey toxicology study did not reveal evidence of plaque formation or immunohistochemical staining for A β (1-38, 1-40, 1-42). These data are consistent with LCZ696 treatment altering the CNS levels of A β , but having no effect on A β brain deposition.

Finally, the results of a study conducted in healthy subjects (A2126) showed that in contrast to the cynomolgus monkey study, administration of LCZ696 400 mg once daily for 14 days did not result in meaningful changes in CSF A β 1-40 and 1-42 concentrations in healthy subjects, despite having measurable concentrations of sacubitrilat (active metabolite of sacubitril, a neprilysin inhibitor) in the CSF sufficient to inhibit neprilysin.

This finding suggests that degradation and transport mechanisms other than neprilysin, including enzymes such as ACE, endothelin converting enzyme and insulin degrading enzyme, are more important in the clearance of CSF A β fragments in humans. Taken together, these data indicate that LCZ696 treatment in humans does not result in clinically meaningful increases in CSF A β levels.

Although Novartis believes that the data above demonstrates that LCZ696 treatment does not result in clinically meaningful increases in CSF A β , in order to further address the potential for theoretical safety concerns such as dementia related diseases from amyloid accumulation, Novartis conducted an analysis for AEs based on the Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query (SMQ) Dementia in the PARADIGM-HF study which was conducted in patients (n = 8,442) with HFREF exposed to LCZ696 for a median follow-up of 27 months and a maximum follow up of 51 months (MA).

Based on a cumulative search for the SMQ Dementia (broad and narrow) in the clinical database of the PARADIGM-HF trial, the incidence of dementia related events was comparable in LCZ696 treated patients and enalapril treated patients for the broad and narrow SMQ Dementia and for the specific dementia related preferred terms (MA).

In summary, the results from nonclinical and clinical studies conducted with LCZ696 suggest that LCZ696 does not result in clinically meaningful changes in cerebrospinal fluid A β levels or increased reporting of cognition or dementia related AEs. Novartis is committed to conducting a robust clinical assessment to further evaluate the potential effect of neprilysin inhibition via LCZ696 on A β and cognitive function in patients with HF. Please see Novartis response above on the ongoing actions for evaluation of the potential effects of LCZ696 on cognitive function.

- The increased risk of hypotension related events

Consistent with its mechanism of action, LCZ696 has a greater BP lowering effect compared with other active comparators including, enalapril or valsartan. Thus, it is not surprising that the overall incidence of hypotension was higher with LCZ696 compared to enalapril. However, hypotension events did not result in more SAEs in the PARADIGM-HF study. In fact, for hypotension events of greater severity, such as syncope, pre-syncope, or loss of consciousness, event rates were lower for LCZ696 than for enalapril. Further, few patients with hypotension had to be discontinued from the study, and the incidence of permanent study drug discontinuations due to hypotension was comparable between LCZ696 and enalapril treatment in the PARADIGM-HF study, which suggests that hypotension was manageable with dose reduction or temporary interruption.

Subgroup analyses for hypotension events were performed for age group (<65, ≥65 years), gender, race, baseline estimated glomerular filtration rate (renal impairment category), NYHA Class I/II and III/IV at baseline, aldosterone antagonist therapy at baseline and renal disease at screening. A similar pattern as for the overall safety population was observed for all subgroup categories, that is, incidence rates and annualised event rate for hypotension events were higher with LCZ696 treatment. Hypotension events were more frequently reported in patients ≥ 65 years with the same risk ratio (RR) LCZ696 versus enalapril (RR = 1.4) for both age categories. Similarly, incidence of hypotension events was higher in patients with renal impairment in both treatment groups.

Patients were also grouped by SBP category at randomisation, and the incidences of hypotension AEs, SAEs, and AEs that led to discontinuation during the double blind period were compared. In both the LCZ696 and enalapril treatment groups, the risk of experiencing hypotension AEs was higher in patients with lower baseline SBP (100 to <110 mmHg) than in those with higher SBP. However, the risks of experiencing hypotension SAEs (33/693, 4.76% versus 36/751, 4.79%) or hypotension AEs leading to study drug discontinuation (10/693, 1.44% versus 7/751, 0.93%) were low and similar between the two treatment arms in this lower SBP subgroup.

When the profile of hypotension-related AEs queried by a broader search was further examined by the baseline SBP tertiles at randomisation, it was also noted that no clinically meaningful difference was observed in the incidence of potentially more serious hypotension related AEs (dizziness, syncope, and orthostatic hypotension) among these three tertiles. This data again suggests that the majority of hypotension related AEs in LCZ696 treated patients are mild in severity regardless of baseline BP, and that these events can be managed without the need of permanent discontinuation of LCZ696 therapy.

In summary, hypotension related AEs were reported more frequently with LCZ696 than with enalapril treatment in the PARADIGM-HF study, particularly, in patients with low baseline SBP. However, the majority of these events were not severe, and few patients with hypotension related events had to be discontinued from the study drug during the trial. Therefore, it is believed that hypotension in patients treated with LCZ696 can often be managed through dose adjustment or temporary dose interruption as reflected in labelling. For patients with low baseline SBP (<112 mm Hg), when initiating therapy or during dose titration with LCZ696, it is recommended to monitor BP at an appropriate interval. The recommendation has been added to the labelling to minimise the risk of hypotension

Concluding remarks

Novartis welcomes the Delegate's recommendation to approve LCZ696, a novel HF therapy with a unique mechanism of action proven to reduce rates of death and hospitalisation in a large well controlled Phase III clinical trial with clearly defined and widely accepted endpoints studied in patients comparable to the intended to treat population (PARADIGM-HF). Moreover, LCZ696 is the first HF treatment in years to provide a significant mortality benefit versus the SOC (enalapril) and therefore addressing a remaining unmet medical need and its associated public health burden. Novartis believes the proposed indication reflects LCZ696's intended usage in clinical practice to reduce death and hospitalisation in those patients with symptomatic HF. LCZ696 has also demonstrated a reduction in symptoms and improved physical function together with a well established safety profile.

ACPM considerations

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Entresto film coated tablets containing

24/26 mg, 49/51 mg and 97/103 mg of sacubitril + valsartan salt complex to have an overall positive benefit-risk profile for the delegate's amended indication;

Entresto is indicated in adult patients for the treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction.

In making this recommendation, the ACPM:

- Advised that the indication should not include endpoint claims.
- Was of the view that inclusion of NYHA Class IV was appropriate.

Proposed conditions of registration

The ACPM agreed with the delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Highlight in the PI that Class IV patients made up a very small proportion (<1%) of the study population.
- In the DOSAGE section, advise that Entresto can be used with other HF treatments as per the US PI as follows:

Entresto is administered in conjunction with other HF therapies, in place of an ACE inhibitor or other ARB.

- Under "PRECAUTIONS- Other preclinical safety findings including amyloid – β findings" include the following suggested wording:

The long term effects of Entresto on cognitive function are unknown and are the subject of further clinical trials.

- In the CMI, include under "WHEN YOU MUST NOT TAKE IT - This medicine is not advised if you have very low blood pressure (SBP <100 mmHg)".

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

- Was the use of enalapril at a dose of 10 mg BD appropriate as the comparator in the pivotal study?

The ACPM noted that it would be unlikely that enalapril would be used in the Australian setting as most physicians would prefer a once daily angiotension converting ACE inhibitor. However, PARADIGM-HF had a large population and demonstrated efficacy of Entresto, with average doses of enalapril of approximately 18 mg. The ACPM therefore advised that enalapril, taken at a dose of 10 mg twice daily, is an appropriate comparator.

- Should the indication be amended to remove endpoint claims, refer to patients with NYHA class and include patients with NYHA Class IV status?

The ACPM advised that endpoint claims should not be included in the indication. The ACPM also advised that reference to NYHA class is appropriate and that Class IV should be included in the indication. It was the view of the ACPM that treatment of patients with Class IV HF should be at the discretion of the treating physician and noted that the patients' functional status can fluctuate over time. The ACPM advised that the PI should highlight that Class IV patients made up a very small proportion (<1%) of the study population.

- Should a statement on use with other HF treatments be included in the Indications or in the Dosage section of the PI?

The ACPM noted that the pivotal study used Entresto in adult patients with symptomatic chronic HF with a reduced ejection fraction in combination with other HF therapies. The ACPM therefore advised that inclusion of a statement regarding use with other HF treatments is more appropriate in the Dosage section of the PI and not in the Indication.

- Is the description of the product's strengths acceptable for the PI/CMI and labels or should it be expressed differently?

The ACPM considered that it might be preferable to express the strength as both the whole unit as well as the individual component, that is, Entresto 100mg (sacubitril 49mg/valsartan 51mg) for ease of prescribing.

- Has the sponsor adequately addressed in the PI the differences in the bioavailability of valsartan in LCZ696 compared to valsartan from other preparations?

The ACPM advised that the information regarding the differences in the bioavailability of valsartan in LCZ696 was adequate. However, to highlight this information, a tabular format might be more effective.

- Are the changes in amyloid of clinical significance and are the statements in the PI in relation to amyloid appropriate?

The ACPM considered that the changes in amyloid were potentially clinically significant but the significance will remain unknown until completion of ongoing studies. The ACPM advised that the PI needs to highlight this and make reference to the ongoing studies with the following suggested wording:

The long term effects of Entresto on cognitive function are unknown and are the subject of further clinical trials.

- Has the increased risk of hypotension related events been adequately addressed by the sponsor in the PI/CMI?

The ACPM advised that the increased risk of hypotension had been adequately addressed in the PI under PRECAUTIONS. However, the ACPM was of the view that the CMI should state under "WHEN YOU MUST NOT TAKE IT - *This medicine is not advised if you have very low blood pressure (SBP <100 mmHg)*".

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

ACSOM considerations

On 12 January 2016, issues raised by the Advisory Committee on the Safety of Medicines (ACSOM) relating to the safe use of Entresto were directed to the sponsor. At this time, ACSOM sought comment and/or clarification on these issues in the context of the RMP, identified safety concerns/missing information, and proposed pharmacovigilance.

1. Can the committee comment on the adequacy of the proposed safety concern list?

The committee noted emerging literature that includes that neprilysin may protect against Alzheimer's disease and that neprilysin overexpression has been associated with improved disease free survival among women with breast cancer.²³ It is reasonable that a reduction in the protective role of neprilysin should be reflected in the proposed list of

²³ Galli A, Lombardi F. Neprilysin inhibition for heart failure. *N Engl J Med.* 371: 2335 (2014); McMurray JJ, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 371: 993-1004 (2014).

safety concerns and in the pharmacovigilance plan (Question 2). Therefore, the committee advised that the 'missing information' in the proposed list of safety concerns should be amended to include malignancy and to amend 'cognitive impairment' to 'dementia or Alzheimer's disease'.

2. *Can the committee comment on the adequacy of the pharmacovigilance plan to monitor all the safety concerns?*

The committee advised that the pharmacovigilance plan should be amended to address risks that may emerge only with extended use, particularly malignancy and dementia.

It was noted that the pharmacovigilance plan does not include testing for prostate-specific antigen or breast cancer screening to monitor for malignancy.

It is unclear that routine pharmacovigilance for the missing information 'cognitive impairment' (a term that lacks clarity) and the use of a targeted checklist for adverse event follow-up will be sufficient to capture information on this risk. Assessment of cognitive impairment (including dementia and Alzheimer's disease) requires specialised clinical skills.

One-third of patients in PARADIGM-HF had diabetes. Patients being treated with DPP-4 inhibitors (gliptins) for diabetes may be at increased risk of angioedema. A possible drug-drug interaction with DPP-4 inhibitors could be considered.

3. *Can the committee comment on the adequacy of the risk minimisation plan to mitigate all the safety concerns?*

The committee noted that concomitant use of sacubitril/valsartan with ACE inhibitors is contraindicated, and the medicine must not be administered until 36 h after discontinuing ACE inhibitor therapy.

The committee advised that the routine risk minimisation plan appears sufficient to address all safety concerns. The committee noted that the wording in the CMI is very precise, that is, there is a detailed list of generic and trade name of ACE inhibitors that should not be taken with this medicine.

Sponsor response

Investigation of the potential effect of LCZ696 on cognitive function

Novartis acknowledges the Committee's comments and would like to clarify that cognitive impairment is now included as an important potential risk in the EU RMP (version 1.4, see Novartis Response to TGA RMP Report Round 1). In addition, routine and additional pharmacovigilance activities are planned in order to conduct a robust clinical assessment to further evaluate the potential effect of neprilysin inhibition via LCZ696 on A β and cognitive function, as detailed below.

Indeed, the theoretical risk associated with neprilysin inhibition relates to the accumulation of the neprilysin substrate amyloid- β (A β) in the brain. Although further studies are planned, as detailed below, to fully characterise this theoretical risk, studies in man suggest that clearance pathways other than neprilysin degradation play an important role in A β clearance. Specifically, two week treatment of LCZ696 in healthy volunteers did not increase the levels of the aggregable A β subtypes A β 1-42 and 1-40 in cerebrospinal fluid (CSF), while an isolated increase in A β 1-38 was observed. Importantly, there is no evidence in that an isolated increase in A β 1-38 concentration facilitates A β plaque formation. It is important to consider that ACE is also implicated in the degradation of amyloid β .²⁴ In vitro studies have shown ACE inhibitors increasing amyloid β subsets but a

²⁴ Hemming ML, Selkoe DJ. Amyloid β -Protein Is Degraded by Cellular Angiotensin converting Enzyme (ACE) and Elevated by an ACE Inhibitor. *J Biol. Chem.* 280: 37644-37650 (2005).

signal of cognitive impairment or Alzheimer disease (AD) with ACE inhibitors has not been raised.²⁵

In addition, in the PARADIGM-HF study, there was no indication of an increased incidence of cognitive disorders or of symptoms associated with dementia, despite the enrolment of elderly patients. PARADIGM-HF examined more than 5,000 elderly (≥ 65 years old) and more than 2,000 very elderly (≥ 75 years old) HFrEF patients. More importantly, the potential effect of LCZ696 on cognitive function, the clinical outcome of relevance, will be extensively evaluated (see Table 15). The approach consists of:

- The implementation of cognitive function assessment (CFA) in eligible patients in the ongoing PARAGON-HF study CLCZ696D2301. The report of PARAGON-HF is planned by March 2020.
- In addition, Novartis will conduct the stand alone Study CLCZ696B2320, to evaluate the effects of LCZ696 compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and brain amyloid plaque deposition as assessed by PET imaging in patients with chronic HFpEF. The study will utilise specialist research centres that have the necessary expertise in conducting cognitive studies and performing imaging. The final study report is planned by March 2022.
- In addition to these two studies, Novartis will perform targeted follow-up via use of a targeted questionnaire for all serious spontaneous dementia related cases in order to obtain relevant information from post marketing surveillance. The questionnaire (see RMP version 1.4) has been revised to include a question asking for specific symptoms, and to gather information on temporality, confounding factors and any effects of dechallenge or rechallenge, before moving onto whether a formal dementia diagnosis has been made.

²⁵ Shah K, et al. Does Use of Antihypertensive Drugs Affect the Incidence or Progression of Dementia? A Systematic Review. *Am J Geriatr Pharmacother.* 7: 250-261 (2009).

Table 15. Table of ongoing and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan.

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final Reports (planned or actual) |
|---|--|---|---------------------------------|--|
| PASS 1: Non-interventional post-authorization European database safety study (Category 3;PASS) | To further characterize specific safety outcomes (angioedema, hypotension, hyperkalemia, renal impairment, hepatotoxicity) in HF patients newly starting treatment with LCZ696 (regardless of prior use of ACEIs or ARBs) | Angioedema Use in ACEI/ARB naïve patients Hypotension Hyperkalemia Renal impairment Hepatotoxicity | Planned | Yearly progress reports (1st report planned to be submitted Q4 2017, or with PBRER in 2018). Final report submission within 12 months after end of data collection (i.e., after reaching the necessary number of cases) – latest in Q2 2020 |
| PASS 2: Multicenter, randomized, double-blind, active-controlled study (CLCZ696B2320) (Category 3;PASS) | To evaluate the effects of LCZ696 compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and brain amyloid plaque deposition as assessed by PET imaging in patients with chronic heart failure with preserved ejection fraction (HFpEF) | Cognitive impairment | Planned | Planned March 2022 (Final report submission) |
| PASS 3: Non-interventional post-authorization European database safety study (Category 3;PASS) | To assess the risk of statin-related events associated with concomitant exposure to LCZ696 and statins compared to statin exposure alone in HF patients | Statin DDI | Planned | - planned Q2 2020 (Final report submission) |
| Cognitive function assessment in study CLCZ696D2301 (PARAGON HF study) (Category 3; Non-PASS) | To evaluate cognitive function in patients with chronic HFpEF | Cognitive impairment | Started | Planned March 2020 (final report) |
| Observational US database study (Category 3; Non-PASS) | To assess the risk of serious angioedema in association with sacubitril/valsartan (Entresto) use in Black HF patients in the United States | Angioedema in US Blacks | Planned | Planned Q3 2019 (final report) |

Finally, “Cognitive Impairment” was chosen instead of dementia or AD since it is the clinical outcome of relevance which will be assessed in the proposed studies. It covers multiple aspects of cognitive functional changes, such as Alzheimer’s disease and various types of dementia. The EU-RMP version 1.4 describes the inclusion of MedDRA preferred terms ‘Dementia’ and ‘Dementia Alzheimer’s type’ under the potential risk ‘Cognitive impairment’ in the RMP. It’s also important to note that there is no absolute or clear demarcation between cognitive domains affected in Alzheimer’s disease or other forms of cognitive decline.

Therefore, Novartis considers that the inclusion of cognitive impairment, the clinical outcome of relevance, as an important potential risk in the RMP, and the robust clinical assessment proposed in the pharmacovigilance plan as detailed above, are the most relevant measures to provide clinically meaningful information.

This approach was also endorsed by key health authorities (including the EMA, FDA and Swissmedic).

No increased risk of cancer with LCZ696 treatment

There was no indication of an increased incidence of cancer in the PARADIGM-HF study, despite the enrolment of more than 8,000 patients with treatment duration up to 4.3 years, including more than 5,000 elderly and more than 2,000 very elderly patients.

In addition, there was no evidence of carcinogenicity in 2 year carcinogenicity studies involving rodents. Finally, an *in silico* evaluation of genetic variation in the gene encoding NEP, performed to explore the potential for a correlation with tumour progression based on metallo-endopeptidase (MME; also identified as NEP) gene mutation spectra in different cancer types, do not support a theoretical risk of NEP inhibition contributing to neoplastic progression.

Novartis believes that preclinical data from 2 year carcinogenicity studies conducted with both AHU377 and valsartan in rodents, as well as the genetic variation analysis, in combination the large Phase III PARADIGM-HF study in 8,442 patients are sufficient to exclude a possible role for neprilysin in tumour development and/or progression and therefore does not agree with making this risk important missing information in the RMP.

However, Novartis commits to continue to monitor for cancer analysis as a part of upcoming PSUR analysis in the relevant section of the PSUR.

2.1.3 Concomitant treatment with DPP-4 inhibitors

In the PARADIGM clinical trial experience (Table 16), there were no cases of angioedema in patients receiving DPP-4 inhibitors. This includes not only the patients receiving DPP-4 inhibitors at baseline shown below but also the 200 patients who received them at any time during the trial.

Table 16. (a) Patients in PARADIGM-HF using DDP4i at baseline. (b) Number of adjudicated cases of angioedema in patients using DDP4i during the PARADIGM-HF trial.

| PARADIGM (Safety set) | LCZ696 N = 4203 N (%) | Enalapril N = 4229 N (%) |
|---|-----------------------------|--------------------------------|
| A. Number of patients using DPP4i at baseline | 45 (1.07%) | 62 (1.47%) |
| PARADIGM (Safety set) | LCZ696 N = 4203 N (%) | Enalapril N = 4229 N (%) |
| B. Number of patients with confirmed angioedema | 0 (0.00%) | 0 (0.00%) |

The absolute incidence rate of angioedema when ACE inhibitors and DPP-4 inhibitors are used concomitantly is low (~0.5). The postulated mechanism through increased substance P when ACE is inhibited may be much less important when neutral endopeptidase (NEP) is inhibited. Sacubitril does not inhibit ACE which is the primary enzyme responsible for the inactivation of substance P.²⁶

²⁶ Brown NJ, et al. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. *Hypertension* 54: 516-23 (2009).

Given that the incidence rate for the combination of ACE inhibitors and DPP-4 inhibitors is similar to that seen in PARADIGM for the overall population, as the proposed mechanism for the interaction may not apply to NEP inhibition, and as this risk is not outlined in current ACE inhibitor labels in Australia, Novartis does not believe that there is a clinically meaningful interaction between LCZ696 and DPP-4 inhibitors. This is further supported by the absence of any cases in the clinical trial data base.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of:

- *Entresto 97/103 sacubitril/valsartan (combined as a sodium salt hydrate complex) 97.2/102.8 mg film coated tablet blister pack*
- *Entresto 24/26 sacubitril/valsartan (combined as a sodium salt hydrate complex) 24.3/25.7 mg film coated tablet blister pack*
- *Novartis Sacubitril/Valsartan 97/103 sacubitril/valsartan (combined as a sodium salt hydrate complex) 97.2/102.8 mg film coated tablet blister pack*
- *Novartis Sacubitril/Valsartan 24/26 sacubitril/valsartan (combined as a sodium salt hydrate complex) 24.3/25.7 mg film coated tablet blister pack*
- *Entresto 49/51 sacubitril/valsartan (combined as a sodium salt hydrate complex) 48.6/51.4 mg film coated tablet blister pack*
- *Novartis Sacubitril/Valsartan 49/51 sacubitril/valsartan (combined as a sodium salt hydrate complex) 48.6/51.4 mg film coated tablet blister pack*

indicated:

in adult patients for the treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction.

Specific conditions of registration applying to these goods

- The sacubitril/valsartan EU-RMP version 1.4, dated 30 September 2015 (data lock point 5 August 2014), with the ASA version 2.0, dated 23 October 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ASA, as soon as possible after completion, for evaluation:
 - Study CLCZ696B2317: A multicentre study to evaluate safety and tolerability in patients with chronic HF and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696.

Attachment 1. Product Information

The PI approved for Entresto at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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