NOVARTIS

Patient Safety & Pharmacovigilance

Sacubitril/valsartan

LCZ696

EU Safety Risk Management Plan

Active substances (INN or common name)	Sacubitril/valsartan
Product concerned (brand names)	Entresto® and Neparvis®
Document status:	Final
Version number:	9.0
Data lock point for this RMP	DLP for LCZ696B2014: 14-Jul-2024 & LCZ696B2015: 09-Jul-2024
Date of final sign off	15-Nov-2024

Template version *6.4, Effective from 12-Dec-2023*

Rationale for submitting an updated RMP:

This version update of the RMP (v 9.0) reflects the removal of several safety concerns as mentioned below in accordance to the GVP Module V (Rev.2) guidance, and the accumulated clinical trial and post-marketing experience with sacubitril/valsartan, including two completed post-authorisation safety studies (PASS) LCZ696B2014 and LCZ696B2015**.**

Important Identified Risks (LCZ696B2014)

- Angioedema
- Hypotension
- Hyperkalemia
- Renal impairment

Important Potential Risk (LCZ696B2014)

- Hepatotoxicity

Missing information (LCZ696B2014)

- Use in ACEI/ARB-naïve HF patients

Important Potential Risk (LCZ696B2015)

- Statin drug-drug interaction

Summary of significant changes in this RMP:

Part	Major changes of RMP v9.0 compared to RMP v8.0
Part I	No update
Part II	Table 3-1 was updated to include "Study CLCZ696B2014 results." Part II Module SIV.3: Table 5-3 was updated to remove the information regarding PASS studies completion. Module SVII.3: Updated the section 8.2 with the justification for removal of the following risks: **Important Identified Risks (LCZ696B2014)** • Angioedema • Hypotension • Hyperkalemia • Renal impairment **Important Potential Risk (LCZ696B2014)** • Hepatotoxicity **Missing information (LCZ696B2014)** • Use in ACEI/ARB-naïve HF patients **Important Potential Risk (LCZ696B2015)** Statin drug-drug interaction.

Part		Major changes of RMP v9.0 compared to RMP v8.0
		Module SVII.3: “Long -term effects on growth, bone growth and mineralisation in the pediatric population” as an important potential risk in Section 8.3.1.10 was removed.
		Module SVII.3.1 Section 8.3.1 was updated to remove the tables for risks angioedema, hypotension, hyperkalemia, renal impairment, hepatotoxicity, statin drug-drug interaction, and use in AECI/ARB naïve HF patients.
		Module SVIII: Table 9-1 was updated to remove “hypotension, renal impairment, hyperkalemia, angioedema” as important identified risks, “hepatotoxicity and statin drug-drug interaction” as important potential risks, and “use in ACEI/ARB naïve HF patients” as missing information.
Part III		Part III.1. Section 10.1.1 was updated to remove information related to AE follow-up checklists. Part III.2: Table 10-1 was deleted to update the milestones for studies LCZ696B2014 and LCZ696B2015. Part III.3: Table 10-2 Ongoing study was updated to remove Studies CLCZ696B2319E1, CLCZ696B2014, and CLCZ696B2015.
Part IV		No update.
Part V		Table 12-1 was updated to remove important identified risks “angioedema, hypotension, renal impairment, hyperkalemia” important potential risk “hepatotoxicity, statin drug-drug interaction”, and missing information “use in ACEI/ARB naïve HF patients”.
		Table 12-2 was updated to remove important identified risks “angioedema, hypotension, renal impairment, hyperkalemia” important potential risk “hepatotoxicity, statin drug-drug interaction”, and missing information “use in ACEI/ARB naïve HF patients” and CLCZ696B2014, CLCZ696B2015 as additional pharmacovigilance activity.
Part VI		Part VI: II.A: Table 13-1 was updated to remove important identified risks “angioedema, hypotension, renal impairment, hyperkalemia” important potential risk “hepatotoxicity, statin drug-drug interaction”, and missing information “use in ACEI/ARB naïve HF patients”.
		Part VI: II.B: Section 13.2.2 was updated and summary of important risks was removed for important identified risks “angioedema, hypotension, renal impairment, hyperkalemia” important potential risk “hepatotoxicity, statin drug-drug interaction”, and missing information “use in ACEI/ARB naïve HF patients”.
Part VII	Annex-1	No update.
	Annex-2	Table 14-1: Ongoing studies were updated to remove Studies CLCZ696B2319E1, CLCZ696B2014, CLCZ696B2015 as an additional pharmacovigilance activity.
		Table 14-2: Completed studies were updated with the list of Ongoing Studies CLCZ696B2319E1, CLCZ696B2014, CLCZ696B2015 information.
	Annex-3	Table 14-3 was deleted to reflect category 3 studies were completed and no ongoing studies required previously agreed protocols.
	Annex-4	Follow-up checklists for angioedema, hepatotoxicity, statin related events were removed.
	Annex-5	No update.
	Annex-6	No update
	Annex-7	No update.
	Annex-8	Updated to reflect summary of changes to the risk management plan overtime.

Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within procedure number
CCI	CCI	CCI

Details of the currently approved RMP:

Version number: 7.0
Approved with procedure number: EMEA/H/C/xxxx/WS/2535 (Entresto and Neparvis)

Date of approval (opinion date): 31-Aug-2023

QPPV name: Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization (MA) holder´s QPPV. The electronic signature is available on file.

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ACEI	Angiotensin Converting Enzyme Inhibitor
ADR	Adverse Drug Reaction
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin receptor neprilysin inhibitor
CHD	Congeniality Heart Disease
CHF	Congestive Heart Failure
CM	Cardiomyopathy
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DDI	Drug-drug interaction
EEA	European Economic Area
EMEA	European Medicines Evaluation Agency
EF	Ejection Fraction
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GBD	Global burden of disease
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
HTN	Hypertension
IHD	Ischemic Heart Disease
IR	Incidence Rate
LVEF	Left Ventricular Ejection Fraction
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial Infarction
NEP	Neutral endopeptidase
NYHA	New York Heart Association
PASS	Post-authorisation safety studies
PL	Package leaflet
PSUR	Periodic Safety Update Report
PTY	Patient-Treatment Year
PY	Person-Year
RAAS	Renin-Angiotensin-Aldosterone System
RMP	Risk Management Plan
RSI	Reference safety information
SAE	Serious adverse event
SmPC	Summary of Product Characteristics

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substances (INN or common name)	Sacubitril/valsartan
Pharmacotherapeutic group (ATC Code)	C09DX04
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Entresto®, Neparvis®
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class and summary of mode of action:** Entresto (LCZ696, sacubitril/valsartan) exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657 (sacubitrilat), the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type1 (AT1) receptor via valsartan. The complementary cardiovascular benefits of LCZ696 in chronic heart failure (CHF) patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. Natriuretic peptides exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and antihypertrophic and antifibrotic effects. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling.
	Important information about its composition: Entresto is a salt complex of the anionic forms of sacubitril and valsartan, sodium cations and water molecules in the molar ratio of 1:1:3:2.5 (ratio of 6:6:18:15 in the asymmetric unit cell of the solid-state crystal). Following oral administration, Entresto dissociates into the pro-drug sacubitril (which is further metabolized to LBQ657) and valsartan. The sacubitril component is a New Molecular Entity (NME). LBQ657 (sacubitrilat) actively inhibits neprilysin. In the solid state, Entresto cannot be separated by physical means into sacubitril and valsartan.
Hyperlink to the Product Information	[Current approved SmPC] [Proposed SmPC]
Indications in the EEA	**Current:** Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Entresto is also indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

Dosage in the EEA	**Current:** **Adult:** The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. **Pediatric:** The pediatric starting dose of Entresto is a weight-based posology. Table 1 of the [SmPC] provides the recommended dose for pediatric patients. The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient. For more details, please refer to SmPC section 4.2.
Pharmaceutical forms and strengths	**Current:** **Adult:** ● Each 24 mg/26 mg film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan. ● Each 49 mg/51 mg film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan. ● Each 97 mg/103 mg film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan. **Pediatric:** ● Each 6 mg/6 mg granules in capsules for opening contains four granules equivalent to 6.1 mg sacubitril and 6.4 mg valsartan. ● Each 15 mg/16 mg granules in capsules for opening contains ten granules equivalent to 15.18 mg sacubitril and 16.07 mg valsartan.
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication and target population

2.1 Indication

Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction and in pediatric patients aged one year and older with chronic heart failure. Heart failure (HF) is a complex clinical syndrome characterized by the reduced ability of the heart to pump and/or fill with blood (Savarese and Lund 2017). Among patients with the clinical syndrome of HF, left ventricular ejection fraction (LVEF) has emerged as a clinically useful phenotypic marker indicative of unique pathophysiological mechanisms. The LVEF among patients with HF shows a bimodal distribution for both sexes, and patients can be classified as having HF with reduced EF (HFrEF) or preserved EF (HFpEF) (Dunlay et al 2017, Savarese and Lund 2017). The ejection fraction criteria for defining HFrEF have varied (Dunlay et al 2017). However, the 2021 HF guidelines of the European Society of Cardiology (ESC) (McDonagh et al 2021) as well as the 2022 AHA/ACC/HFSA HF guidelines (Heidenreich et al 2022) define HF patients as HFrEF if they have an EF ≤ 40% (Ponikowski et al 2016). The 2013 US guidelines from the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) however, define HFrEF slightly differently as EF ≤ 40% (also referred to as systolic HF).

2.2 Incidence

Adult population

The global adult HF incidence ranges from approximately 1-9 cases per 1,000 person-years (PYs) depending on the diagnostic criteria used and populations studied. The incidence has shown signs of stabilization and possible reduction in particular populations, mainly driven by the improvements in the primary prevention of cardiovascular diseases (CVD) and the treatment of ischemic heart disease (IHD) (Ziaeian and Fonarow 2016). Overall, the HF incidence increases markedly after 60 years of age, initially with a more rapid increase in men, whereas the incidence in women may exceed that of men after 85 years of age (Magnussen et al 2019). The incidence is generally higher in males than females both in HF overall and HFrEF, while it is usually similar or slightly higher in females versus males in HFpEF (Gomez-Soto et al 2011, Brouwers et al 2012, Gerber et al 2015, Dunlay et al 2017, Savarese and Lund 2017, Magnussen et al 2019, Mentzer and Hsich 2019). The below sub-sections provide information on the incidence rates of HF in the adult populations. For the adult population the incidence rates are presented as overall rates (no distinction between HFrEF and HFpEF), together with some specific HFrEF incidence estimates. The focus is mostly on (large) studies published over the last 10 years focusing on France, Germany, Italy, Spain, UK, and other European countries, North America (US and Canada), Asia, with primary focus on Japan and China, and on the rest of the world.

In general, comparisons between studies are difficult due to differences in methodology, particularly for diagnosing HF (out-/inpatient HF diagnosis, staging of HF, HF phenotype, classification of HF severity), in collecting data (e.g. prospective primary data collection versus retrospective secondary use of existing data [e.g. from healthcare databases]) or because of different incidence estimate measures (e.g. incidence rate [IR] versus cumulative incidence over varying years of follow-up [FU]; with or without age-standardization). Furthermore, results may differ because of different inclusion/exclusion criteria, especially with respect to age (e.g., studies including also pediatric and/or adolescent populations versus studies focusing on adults only), diversity in demographics of the study populations (e.g., age distribution, co-morbidities), or in the prevalence of etiologic/risk factors of HF (e.g., hypertension, diabetes, IHD, obesity, etc.). This has to be taken into account when evaluating the results presented in the following sections. In addition, the information provided below is not considered to be thoroughly comprehensive, there may be published studies with incidence estimates deviant from the ones reported below.

Pediatric population

A global pediatric HF incidence rate has not yet been estimated as when compared to the adult HF epidemiology, the pediatric one has not yet been well researched and characterized.

2.2.1 Europe

Adult population

Incidence estimates of HF overall reported from European non-interventional studies are in the range of approximately 1.0 to 8.8 per 1,000 PYs or per 1,000 population/year (Gomez-Soto et

al 2011, Brouwers et al 2013, Seferovic et al 2013, Zarrinkoub et al 2013, Ohlmeier et al 2015, Störk et al 2017, Conrad et al 2018, Lindmark et al 2019, Magnussen et al 2019).

The incidence of HFrEF was reported by Brouwers et al (2013) as 2.8% (over 11.5 years of FU) and Gomez-Soto et al (2011) as 2.1 per 1,000 PYs.

Based on a large Danish study in the entire Danish population aged ≥18 years, the HF incidence declined over the last two decades among individuals >50 years but increased in those ≤50 years. The study also showed an increase in comorbid diseases like diabetes mellitus, cardiomyopathy, adult congenital heart disease, and morbid obesity, which could all possibly have contributed to the increase in the incidence of young individuals with HF (Christiansen et al 2017).

The heterogeneity of reported incidence estimates is largely explained by the factors outlined earlier.

Pediatric Population

There are only two relevant studies with large population sizes that have estimated the incidence rates in the pediatric population in the last 5 years: a population-based retrospective cohort study from France (Bichali et al 2020) and a register-based cohort study from Sweden (Carr et al 2017).

Bichali et al 2020 conducted a population-based retrospective cohort study using hospital data in France with the aim of estimating the incidence of HF in the pediatric population (age<16 years) between 2007 and 2016. The overall incidence proportion of HF was 2.1 per 100,000 children. When the incidence proportion of HF was reported by etiology, it was 0.98 and 1.12 per 100,000 children, respectively in the CM and CHD subgroups.

In a registry-based cohort study from Sweden for a study period 1987-2013 with the use of Medical Birth register, National Patient register and the Cause of Death register, Carr et al (2017) estimated the incidence rate of HF in children and adolescents born in Sweden and registered in the medical birth register for the period 1987-2012. The incidence rate of HF was 0.84 per 100,000 person-year for children born between 1996 and 2003 and increased to 1.03 per 100,000 person-year for those born between 2004 and 2012 (Carr et al 2017).

2.2.2 North America

Adult population

For the US, the number of incident adult HF patients ≥ 55 years in 2014 was reported to be 1.0 million (males: 495,000; females: 505,000) (Benjamin et al 2019). For Canada, the annual incidence was estimated for 2006 at approximately 50,000 new HF cases (Blair et al 2013).

Gerber et al (2015) reported the age-/sex-adjusted HF annual incidence from 2000 to 2010 in Olmsted County, Minnesota. The overall HF incidence declined from 3.2 per 1,000 in 2000 to 2.2 per 1,000 in 2010, corresponding to a decline of 37.5% over the decade-long study period. Although the HF incidence declined for both HFpEF (EF ≥50%) and HFrEF (EF <50%), the declines were greater for HFrEF (-45%) than for HFpEF (-28%).

In the US Multi-Ethnic Study of Atherosclerosis (MESA), a cohort study of four ethnicities in adults aged 45-84 years, the overall HF incidence rate was reported as 3.1 per 1,000 PYs

(Bahrami et al 2008). The incidence was lowest in Chinese and highest in African Americans. IRs stratified by ethnicity are displayed in the table below.

Table 2-1 Heart failure incidence rates by ethnicity from the US Multi-Ethnic Study of Atherosclerosis (MESA)

Ethnicity	Incidence rate (per 1,000 PYs)
African Americans	4.6
Hispanic	3.5
White	2.4
Chinese	1.0
Overall	3.1

PY = person-year; US = United States
Source: Bahrami et al 2008

Although the (unadjusted) relative risk of developing HF was higher among African American compared with white participants, adding hypertension and/or diabetes mellitus to the models eliminated statistically significant ethnic differences in incident HF (Bahrami et al 2008).

Remarkably higher estimates were reported in adults aged 40-79 years from the Southern Community Cohort Study (SCCS) by (Akwo et al 2017) with age-standardized IRs of 34.8, 37.3, 34.9 and 35.6 per 1,000 PYs in white women, white men, black men and black women, respectively. In models adjusted for age and other HF risk factors, black women had a significantly lower risk of HF when compared with white women, while the risk of HF was similar among white and black men compared with white women. The higher IR estimates are explained in part by notably higher prevalence of CVD risk factors and possibly by generally low socio-economic status of participants (Akwo et al 2017).

Based on data from the Framingham Heart Study and the Cardiovascular Health Study in participants aged ≥60 years the age-/sex-standardized IRs for HF overall during the period of 2000-2009 was 18.9 per 1,000 persons per 1-year follow-up, and 6.2 per 1,000 persons per 1-year follow-up for HFrEF (Tsao et al 2018).

A recent study from eastern Ontario, Canada, showed that the HF incidence in adults aged 40-105 years declined in a stable pattern from 1994 to 2013, with higher estimates in males than females, and in a rural compared to an urban setting. Annual age-standardized IR estimates were around 4-10/1,000 population (Sun et al 2018).

Another recent Canadian study from Ontario reported age-standardized IRs of hospitalization for HF in adults aged 40-105 years as 1.9/1,000 PYs for men and 1.8/1,000 PYs for women for 'long-term residents', and markedly lower estimates for immigrants (Di Giuseppe et al 2019).

Pediatric Population

No studies from the US describing the incidence of HF patients in the pediatric population were identified.

2.2.3 Asia

Adult population

There is very limited information on the HF incidence in Asia (Sakata and Shimokawa 2013).

China: Approximately 500,000 new HF cases are diagnosed annually (Sakata and Shimokawa 2013). A study from Hong-Kong estimated HF incidence of 0.7 per 1,000 population/year. In the age group 85+ years, the incidence in women was 20 per 1,000 population, and 14 per 1,000 population in men (Hung et al 2000).

Japan: It was estimated that >0.3 million Japanese developed incident HF among the population aged ≥65 years in 2013 (Shimokawa et al 2015). In a population-based cohort study in adults 20+ years hospitalized for HF in a rural setting in Japan, (Ogawa et al 2007) reported a crude overall IR of 0.9 per 1,000 PYs.

India: In India, the annual number of incident HF cases is estimated at 0.5-1.8 million people (Bloom et al 2017).

Pediatric Population

No studies from Asia describing the incidence of HF patients in the pediatric population were identified.

2.2.4 Rest of the World

Adult population

A recent systematic review (Ciapponi et al 2016) identified three studies from South America (two from Argentina, one from Brazil) reporting IR estimates from 1.4-5.6/1,000 PYs.

Pediatric population

No studies from other countries describing the incidence of HF patients in the pediatric population were identified.

2.3 Prevalence

Adult population:

Population statistics have consistently demonstrated an increasing HF prevalence over recent decades, despite stable or even decreasing incidence trends. However, with the ageing of the world's population, a higher proportion of individuals are at risk of developing HF (such as individuals with obesity, diabetes mellitus and hypertension) (Bloom et al 2017). The Global Burden of Disease (GBD) study (with data for 204 countries) estimated that worldwide approximately 56.2 million individuals had HF in 2019 (GBD 2019 Diseases and Injury Incidence and Prevalence Collaborators 2020). Among the countries represented by the ESC, there are an estimated 15 million patients with HF (Ambrosy et al 2014). In the US, an estimated 6.2 million adults ≥20 years of age had HF between 2013 and 2016 (3.2 million females, 3.0 million males) (Benjamin et al 2019).

The table below provides GBD estimates for 2019 of the number of prevalent HF patients together with an age-standardized annual prevalence rate estimate (across all age groups [not only adults]) for region Europe, France, Germany, Italy, Spain, UK, and other European countries, US, Canada, China and Japan.

Table 2-2 Number of HF patients and age-standardized HF prevalence rate by region/country

Country/region	Estimated number of HF patients (in millions)	Prevalence* (%)
Region Europe	10.16	0.6
France	0.71	0.5
Germany	1.31	0.6
Italy	1.45	0.9
Spain	0.47	0.5
UK	0.54	0.4
US	6.69	1.2
Canada	0.53	0.8
China	18.51	1.0
Japan	1.80	0.5

* Estimated for an age-standardized global general population across all age groups
Source: Global Burden of Disease Collaborative Network 2019

The most often reported prevalence estimate for the adult population at large is 2% (1-3%). Based on a systematic review, the median HF prevalence in the older population aged ≥60 years at large was estimated at 11.8% (range 4.7-13.3%) while HF is rather uncommon below 60 years (van Riet et al 2016).

HF prevalence estimates in European countries – based on a study by Seferovic et al (2013) – ranged most frequently between 1% and 3%, with the highest prevalence reported for Russia (7%).

In the US, the prevalence was estimated at 2.2% in adults ≥20 years of age between 2013 and 2016 (females 2.1%, males 2.4%) (Benjamin et al 2019).

There are a limited number of studies on the prevalence of HF in Asia, ranging from, 1.3% to 6.7% (Sakata and Shimokawa 2013).

The heterogeneity of reported prevalence estimates is largely explained by factors already outlined earlier for incidence estimates, but mainly driven by the age range of the studied population.

Pediatric population:

In the last five years there has only been one population based retrospective study identified to report prevalence rates in the pediatric population (Mejia et al 2018). This US study evaluated the prevalence of HF related visits in 2010 using the nationwide emergency department sample, the healthcare cost and utilization project, and the agency for healthcare research and quality.

Among 28.6 million national pediatric visits, 5,971 visits were HF related. The reported prevalence of HF related visit was estimated at 20.9 per 100,000 children (Mejia et al 2018).

Based on the data coming from the GBD published by the Institute for Health Metrics and Evaluation (IHME) for the period of 2017-2019 the following prevalence rates for the pediatric population were obtained:

- Among newborns (age< 1 year), the prevalence of HF ranged from 13.5 to 13.7 per 100,000 children. When stratifying by gender, the prevalence of HF ranged from 13.2 to 13.4 per 100,000 children in girls and from 13.8 to 13.9 per 100,000 children in boys.
- In the age group 1- 4 years, the overall prevalence of HF ranged from 36.0 to 36.2 per 100,000 children. When stratifying by gender, the prevalence of HF ranged from 35.0 to 35.2 per 100,000 children in girls and from 36.9 to 37.2 per 100,000 children in boys.
- In children (age 5 - 9 years), the overall prevalence of HF ranged from 28.2 to 28.3 per 100,000 children. The sex-specific prevalence of HF ranged from 27.6 to 27.7 per 100,000 children in girls and from 28.7 to 28.8 per 100,000 children in boys.
- In adolescents (age 10-14 years), the overall prevalence of HF ranged from 19.4 to 19.5 per 100,000 children. The sex-specific prevalence of HF ranged from 19.3 to 19.4 per 100,000 children in girls and from 19.4 to 19.6 per 100,000 children in boys.
- In adolescents (age 15-19 years), the overall prevalence of HF decreased from 20.1 to 19.7 per 100,000 children over the years. The sex-specific prevalence of HF ranged from 19.7 to 20.5 per 100,000 children in girls and from 19.4 to 20.0 per 100,000 children in boys.

2.4 Demographics of the population in the heart failure indication – age, gender, racial and/or ethnic and risk factors for the disease

2.4.1 Demographics

Adult population:

Differences in demographic characteristics across different populations of HF patients from different studies can largely be explained by the types of populations (e.g., incident versus prevalent HF populations; HF out- versus inpatients), duration of HF, HF stage/severity (e.g., as per New York Heart Association [NYHA] or ACC/AHA classification), proportion of HF patients with HFrEF versus HFpEF, as well as potential geographic differences, etc.

The demographic and clinical characteristics of HF have been widely described in Europe and the US and have been shown to differ considerably between HFpEF and HFrEF, with further variation according to the populations enrolled and the definitions of HFpEF and HFrEF adopted. In particular, it has emerged that HFpEF patients are more likely to be women and older, obese, with a higher NYHA class and cardiovascular co-morbidities (such as hypertension, diabetes, atrial fibrillation, valvular disease) and non-cardiovascular co-morbidities (such as a anemia, chronic kidney disease, chronic pulmonary disease, hypothyroidism, cancer, peptic ulcer and psychiatric disorders), whereas IHD is the main determinant of HFrEF (Savarese and Lund 2017). However, among individuals of similar age with similar prevalence of other HF risk factors, women are not at an intrinsically higher risk of HFpEF than men, but are at a lower risk of HFrEF. The prevalence of HFpEF increases later and more sharply with age (Dunlay et al 2017).

In a US study based on data from the Cardiovascular Research Network (CVRN) including almost 12,000 newly diagnosed HF patients aged ≥21 years, the mean age in the overall HF cohort was 72.4 years, 69.1 years in those with HFrEF (LVEF ≤40%). The proportion of patients ≥65 years was 72.7% and 63.1% for HF overall and HFrEF, respectively. The proportion of female patients was 46.2% in HF overall and 32.6% in HFrEF (Gurwitz et al 2013).

For racial/ethnic information see also data from Bahrami et al (2008) and Akwo et al (2017) provided above in the 'Incidence' section for North America.

Pediatric population:

In the identified studies, the proportion of males varied between 48.7% (Mejia et al 2018) and 60% (Dipchand et al 2018). Depending on the study, newborns/infants (age ≤ 1year), children (1-12 years) and adolescents represented 29.2-82.9%, 12.1-25.9% and 5-26.9%, respectively, of all pediatric HF cases (Dipchand et al 2018, Mejia et al 2018, Bichali et al 2020, Morales-Demori et al 2021). HF cases in the pediatric population were predominantly white (37.5%) followed by Hispanics (20.4%) and African American subjects (11.0%) (Morales-Demori et al 2021).

2.4.2 Risk factors

Adult population:

IHD notably increases the risk of developing HF: 7-8 years after a myocardial infarction (MI), up to 36% of patients will experience HF, especially those with left ventricular systolic dysfunction. Although the HF risk associated with hypertension is smaller than that associated with MI, hypertension contributes considerably to the population HF burden, as it occurs more frequently than MI. Obesity (BMI >30 kg/m^2) doubles the HF risk after adjustment for associated risk factors. Valvular abnormalities, factors indicative of heart disease (left ventricular hypertrophy, left ventricular dilatation), a parental HF history, conventional risk factors (such as smoking, diabetes), as well as extra-cardiac conditions (renal dysfunction, obstructive pulmonary disease, etc.) all may increase the HF risk (Mosterd and Hoes 2007).

Risk factors for HFrEF from pooled data from three prospective, observational, community-based cohort studies are provided in the table below (Ho et al 2016).

Table 2-3 Risk factors for incident HFrEF

	HR* (95% CI)
Risk factor	**HFrEF (n=584)**
Age (per 10 years)	1.88 (1.75-2.01)
Male sex	2.00 (1.69-2.37)
Systolic blood pressure (per 20 mmHg)	1.27 (1.18-1.37)
Diastolic blood pressure (per 10 mmHg)	1.12 (1.04-1.21)
Body mass index (per 4kg/m^2)	1.26 (1.18-1.35)
Diabetes mellitus	2.34 (1.90-2.89)
Current smoker	1.28 (1.04-1.58)

Risk factor	HR* (95% CI) HFrEF (n=584)
Previous myocardial infarction	2.95 (2.37-3.68)
Previous stroke	1.77 (1.27-2.48)
ECG LV hypertrophy	2.60 (1.92-3.52)
Left bundle branch block	3.68 (2.51-5.40)

CI = confidence interval; ECG =electrocardiogram; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; LV = left ventricular
* HR is for the presence versus absence of dichotomous predictors, and per increase in continuous predictors as specified in the table with all covariates shown in the model simultaneously with individual factors adjusted for age and sex
Source: Ho et al 2016

In addition to the above risk factors, socio-economic status is another important independent predictor of HF development and adverse outcomes, based on a systematic review (Hawkins et al 2012). For instance, in a large UK database study, socio-economically deprived individuals were 60% more likely to develop HF than were affluent individuals (Conrad et al 2018).

Pediatric population:

To date only one study assessed risk factors associated with HF in the pediatric population and young adults (Carr et al 2017).
In a registry-based cohort study from Sweden with the use of Medical Birth Register, National Patient Register and the Cause of Death Register, aimed to determine the association between preterm birth and risk of incident HF in children and young adults. The authors observed that incidence rates of HF were inversely related to gestational age at birth. Preterm birth was associated with an increased risk of HF across all 3 categories of prematurity, and risks increased with decreasing gestational age. After exclusion of individuals with major congenital malformation and adjusting for various confounders in different models, there was a positive association between risk of HF and extremely preterm or very preterm status. There was moderate significant increase in risk of HF for subjects born moderately preterm in the adjusted models. In addition, without controlling for any confounders, the authors found that there was also a positive association between the risk of HF and malformations at birth (incidence relative risk [IRR]: 34.50; 95% confidence interval [CI]: 28.80–41.20), patent ductus arteriosus (IRR: 33.20; 95%CI: 24.40–45.10) and maternal HF or ischemic heart disease (IRR: 3.28; 95%CI: 1.99–5.40), respectively (Carr et al 2017).

2.5 The main existing treatment options

Adult population

The goals of treatment in patients with HF are to improve their clinical status, functional capacity and quality of life, prevent hospital admission and reduce mortality. Neuro-hormonal antagonists (ACEIs, mineralocorticoid receptor antagonists [MRAs] and beta-blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (LCZ696) that combines the moieties of an ARB (valsartan) and a neprilysin (NEP) inhibitor (sacubitril) has been shown to be superior to

an ACEI (enalapril) in reducing the risk of death and of hospitalization for HF. Sacubitril/valsartan is therefore recommended to be used instead of ACEIs in all symptomatic HFrEF patients. ARBs have not been consistently proven to reduce mortality in patients with HFrEF and their use should be restricted to patients intolerant to an ARNI and ACEI. Ivabradine reduces the elevated heart rate often seen in HFrEF and has also been shown to improve outcomes and should be considered when appropriate. The above medications should be used in conjunction with diuretics in patients with symptoms and/or signs of congestion. The use of diuretics should be modulated according to the patient's clinical status (McDonagh et al 2021).

Pediatric population:

Given the progressive nature of pediatric HF, key objectives of HF management are to prevent the onset of symptoms related to the reduced LVEF, to stabilize or improve symptomatic patients, and to increase survival. In contrast to HF in adults, to date, few clinical trials have been conducted in pediatric patients with HF, and no trial has demonstrated a clear benefit of any pharmacotherapy. Consequently, treatment of HF in children is based on information and results provided by adult studies (Kantor and Mertens 2010) and includes ACEI, ARBs, β-blockers, diuretics, aldosterone-blocking agents, digoxin and anticoagulants. Enalapril, an ACEI, although not approved for the treatment of pediatric patients with HF, is the most commonly used ACEI in HF (The Report on the Expert Group Meeting of Pediatric Heart Failure, London, 29◦November◦2010 (EMA/112144/2011)) and is recommended by International Society of Heart and Lung Transplantation (ISHLT) for the treatment of symptomatic left ventricular dysfunction (Class I recommendation, Level of Evidence B; Kirk et al 2014). Enalapril is considered the standard of care in the majority of geographical regions and is classified by the WHO as an essential medicine for children with HF.

2.6 Natural history of the indicated condition in the population, including mortality and morbidity

2.6.1 Natural history

Adult population

LVEF can worsen over time because of progressive cardiac disease or ventricular remodeling, or it can improve in response to HF therapy or reversal of the underlying pathogenesis (Clarke et al 2013). The course of HF is characterized by clinical exacerbations (increase in dyspnea, orthopnea, lower limb swelling, elevated jugular venous pressure, pulmonary congestion) often requiring hospitalizations for acute, decompensated HF.

The NYHA classification provides a simple way of classifying the clinical severity of HF. It classifies patients in one of four categories based on their limitations during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain.

- Class I – No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
- Class II – Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

- Class III – Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
- Class IV – Severe limitations. Experiences symptoms even while at rest. Mostly bed-bound patients.

Pediatric population:

Most pediatric patients presenting to a tertiary center with HF are young; require hospital admission, often prolonged; and many require life support. The majority recover to be discharged with medical management (Dipchand et al 2018).

The proportion of intensive care unit (ICU) admissions in all HF pediatric patients ranged from 68% (Dipchand et al 2018) to 78.6% (Bichali et al 2020). When the analysis was conducted by etiology, the proportion of ICU admission was 86% in HF pediatric patients with CM, 91% in those with CHD and 94% in those with coexisting CM and CHD (Morales-Demori et al 2021). From 2004 through 2018, pediatric HF admissions in patients with CHD doubled, representing 87% of all HF patients' admissions (Morales-Demori et al 2021).

Hospital admissions for initial HF ranged from 59.8% to 84% (Dipchand et al 2018) in pediatric patients. 28% of HF pediatric patients with CM and 44% of those with coexisting CM and CHD required multiple hospitalizations with the number of CM admissions increasing from 7% (2004) to 8% (2018) of all HF patient hospitalizations (Morales-Demori et al 2021).

Irrespective of the etiologies, the median length of stay (LOS) for HF pediatric patients ranged from 13.5 (Dipchand et al 2018) to 35 days (Morales-Demori et al 2021) in hospital and from 5 to 15 days in ICU (Morales-Demori et al 2021). Among all HF pediatric patients, the proportion of hospitalization due to infection was 4% (Dipchand et al 2018). Morales-Demori et al (2021) reported that the proportion of infection was lower in HF pediatric patients with CHD (44%) and higher in those with coexisting CHD and CM (67%). The proportion of surgical complication was lower in HF pediatric patients with CM (58%) and higher in those with coexisting CHD and CM (89%) (Morales-Demori et al 2021). 65% of HF pediatric patients were discharged from hospital with medical management (Dipchand et al 2018).

2.6.2 Mortality

Adult population

Approximately 25% of adult patients who are hospitalized for HF are readmitted within 30 days, with 6-month readmission rates of almost 50%. In addition, 25-30% of patients die within 1 year of discharge. Despite improvements in HF survival since the late 1990s, absolute outcomes remain poor in both HF subtypes, with survival estimates of ~50% after 5 years and 10% after 10 years (Bloom et al 2017).

Pediatric population:

Five observational studies provided data on mortality rate in HF pediatric patients (Carr et al 2017, Dipchand et al 2018, Mejia et al 2018, Bichali et al 2020, Morales-Demori et al 2021).

Among any HF pediatric patients, the overall mortality rate ranged from 5.9% in a study from the US (Mejia et al 2018) to 17.3% in the study from France (Bichali et al 2020). During the first hospitalization, 12.8% of HF pediatric patients died (Bichali et al 2020).

In subgroups by HF etiology, the mortality rate decreased from 2004 to 2018 in HF pediatric patients with CHD (from 5.8% to 4.8%) and in those with CM (from 11% to 6%) while among those with coexisting CM and CHD, the mortality rate was 6.7% in 2004, peaked in 2006 at 15.1%, then, down trended to 9.0% by 2018 (Morales-Demori et al 2021).

One study from Sweden reported a mortality rate as low as 0.6% in 501 HF pediatric patients (children and young adults). In this study, only deaths caused by HF were reported with the exclusion of any other deaths in HF patients based on the study design (Carr et al 2017).

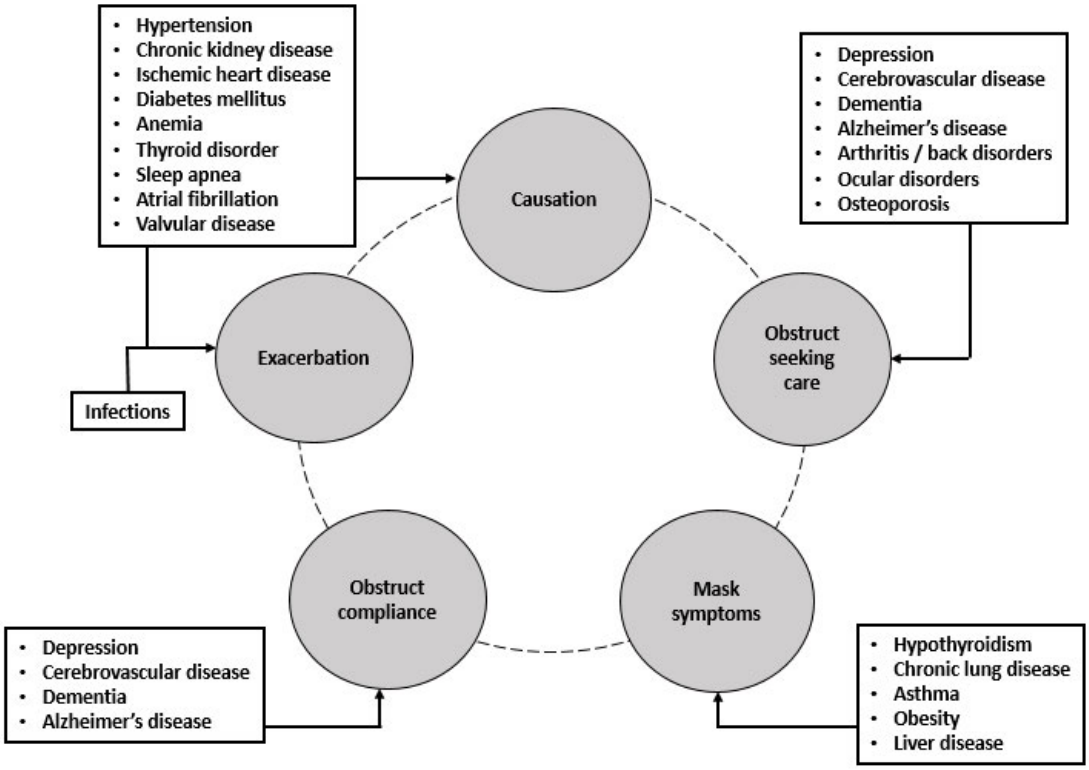
2.6.3 Important co-morbidities

Adult population

Several co-existing cardiovascular and non-cardiovascular diseases and/or conditions are present in adult HF patients, with diverse clinical relevance. Some co-morbidities may not only be a cause, but also be a consequence of HF (e.g., anemia, atrial fibrillation, diabetes mellitus, depression, chronic kidney disease). The complex inter-relationship of co-morbidities and their impact on the cardiovascular system contribute to the features of HFrEF (Triposkiadis et al 2016).

Co-morbidities often prevalent in HF can be inciting events for HF development, can complicate the HF diagnosis and management, can exacerbate symptoms, worsen HF severity or obstruct a patient from seeking care or complying with their treatments (Bloom et al 2017) – see Figure 2-1.

Figure 2-1 Co-morbidities and heart failure



Source: adapted from Bloom et al 2017

Table 2-4 shows co-morbidities commonly prevalent in HF patients and their relevant therapeutic drug options. The prevalence of individual co-morbidities may largely differ across different studies (e.g., due to prospective versus retrospective data collection, incident versus prevalent HF, in- versus outpatients, age of the studied population, regional differences etc.), but also based on HF phenotype (e.g. Brouwers et al 2012, Goldberg et al 2013, Ho et al 2016, Chioncel et al 2017, Löfman et al 2017, Shah et al 2017, Tsao et al 2018, Lindmark et al 2019).

Table 2-4 Co-morbidities and their associated drug therapies in patients with heart failure

Co-morbidity	Drug therapy
Hypertension	Antihypertensives (including ACEIs, ARBs, diuretics, beta-blockers, calcium channel blockers, etc.)
Dyslipidemia	Statins, fibrates, ezetimibe
Ischemic heart disease (angina, prior MI, prior PCI, prior CABG)	Aspirin, antiplatelets, nitrates, beta-blockers, calcium channel blockers, statins
Obesity	--
Chronic kidney disease	ACEIs, ARBs, diuretics, statins
Sleep-disordered breathing (obstructive sleep apnoea, central sleep apnoea)	--
Diabetes mellitus	Insulin and non-insulin antidiabetic drugs (metformin, sulfonylureas, DPP-4 inhibitors, glucagon-like peptide 1 receptor agonists, SGLT2 inhibitors, etc.)
COPD	Oral/inhaled corticosteroids, bronchodilators

Co-morbidity	Drug therapy
Atrial arrhythmia (fibrillation/flutter)	Anticoagulants
Anemia	Iron, folic acid, vitamin B12
Depression	Antidepressants (TCAs, SSRIs etc.)
Stroke or TIA	Aspirin, antiplatelets
Dementia	Cholinesterase inhibitors, glutamate inhibitors
Cancer	--
Osteoporosis	Calcium, vitamin D, bisphosphonates
Osteoarthritis	Acetaminophen, NSAIDs

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; DPP-4 = dipeptidyl peptidase 4; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; SSRI = selective serotonin re-uptake inhibitor; TCA = tricyclic antidepressants; TIA = transient ischemic attack

Pediatric population:

The most prevalent comorbidities in any HF pediatric patients were CHD (17-87%), any CM (3-48.7%), pneumonia (14.8%), arrhythmia (14.3%), respiratory failure (12.9%), pulmonary hypertension (11.7%) and myocarditis (2.1-10%) (Dipchand et al 2018, Mejia et al 2018, Bichali et al 2020, Morales-Demori et al 2021).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single Dose Toxicity Studies	
● No single dose toxicity studies have been performed with LCZ696. Single oral doses of LCZ696 up to 600 mg/kg were tolerated in safety pharmacology studies in rats. ● Valsartan was well tolerated in single dose oral toxicity studies in rats (up to 2000 mg/kg) and marmosets (up to 1000 mg/kg). ● Sacubitril was well tolerated in single dose toxicity studies following oral administration (doses up to 2000 mg/kg) and intra-peritoneal (i.p.) administration (doses up to 500 mg/kg) in mice and rats. Following i.p. administration there were adverse clinical signs but no mortality. Gross necropsy findings in rats were most likely related to the intra-peritoneal method of administration of sacubitril.	There is no preclinical evidence of an increased potential for harm from a single overdose.
Repeat dose toxicity studies	
In repeat dose oral toxicity studies with LCZ696 up to 26-weeks in duration in rats, and 39- weeks in duration in primates, the NOAEL was 30 mg/kg in both species. Target organs were identified as the gastrointestinal tract and kidney with secondary effects on erythropoiesis and heart.	None
Gastrointestinal changes in LCZ696 treated animals were characterized by reversible microscopic changes of focal erosion and inflammation in the glandular stomach of rats at doses ≥ 50 mg/kg. Emesis and diarrhea in primates at doses ≥30 mg/kg occurred in the absence of any microscopic correlates. Gastritis was attributed primarily to local irritant effects of sacubitril, which produced similar changes in the marmoset (emesis, diarrhea and microscopic stomach changes) and rodents (gastritis in rats and mice) following oral but not subcutaneous administration. The contribution of valsartan to exacerbation of gastritis cannot be excluded.	In study LCZ696B2314, gastritis was reported in 1.48% of LCZ696 treated patients. The observations were not deemed of clinical relevance to human use.
Renal effects (juxtaglomerular hypertrophy) observed in monkeys treated with LCZ696 at oral doses ≥100 mg/kg and rats at doses ≥ 200 mg/kg are attributable to the pharmacology of angiotensin receptor blockade. Similar renal changes have been reported in preclinical studies with valsartan. Higher doses in the primate (600 mg/kg), but not the rat, were associated with renal tubular changes (tubular basophilia, cytoplasmic vacuolation and single cell necrosis) and attributed to decreased renal perfusion and renal ischemia following the prolonged hypotensive effects. Similar renal changes have been reported in preclinical studies with valsartan. Valsartan exposure in the primate at an LCZ696 dose	Based on preclinical evidence, adaptive renal juxtaglomerular (JG) cell changes cannot be excluded in humans. These changes are pharmacological in nature and are not associated with a decline in renal function. JG cell changes have been observed in preclinical studies with other compounds which interact with renin-angiotensin-aldosterone system **(**RAAS). The clinical relevance of juxtaglomerular hypertrophy in LCZ696 treated patients is unclear, however, renal impairment should be considered a safety concern. In the PARADIGM-HF study, events related to renal impairment (SMQ acute renal failure) were reported very commonly (10.1% in the LCZ696 group), although less frequently as compared to

Key Safety findings (from non-clinical studies)	Relevance to human usage
(600 mg/kg) associated with renal tubular changes is 3.5X the valsartan exposure (AUC0-24hr) associated with a 200 mg bid clinical dose.	enalapril treatment (11.52%). This is consistent with the observation that serious events of renal failure were reported less frequently in the LCZ696 group (1.02%) as compared to the enalapril group (1.28%). The renal tubular changes observed with high doses in primates are attributable to valsartan. Given the wide clinical experience with valsartan, and the apparent absence of renal tubular effects, these changes are of doubtful clinical significance.
Erythropoiesis: Reversible decreases in red blood cell parameters (RBC count, hemoglobin concentrations and/or hematocrit) in monkeys (doses ≥300 mg/kg) and rats (doses ≥200 mg/kg) and reticulocyte counts (decreased in rats; increased in primates) were observed. These were attributed to valsartan and the effect of the blockade of the renin angiotensin system causing a reduced production of erythropoietin by the kidney.	Based on preclinical evidence there may be a risk of decreased hemoglobin in humans. These effects on RBC parameters have been observed with other RAAS inhibitors in animals. Decreases in hematocrit and Hb have been observed in patients treated with other compounds which interact with the RAAS, however these were found to be clinically non-significant in patients with normal values at baseline (Le Meur et al 2001). In PARADIGM-HF, events of anemia (PT) were reported commonly (4.00% in the LCZ696 group), although less frequently as compared to enalapril treatment (4.75%). Incidence rate of thrombocytopenia (PT) was similar between LCZ696 and enalapril groups: 0.76% vs. 0.83% respectively. Incidence rates of neutropenia (PT) were also similarly low between LCZ696 and enalapril groups: 0.07% vs. 0.05% respectively.
Heart weights were decreased in mice and rats treated with LCZ696 and in rats treated with AHU377 or valsartan and may be related to the expected effects of sacubitril and valsartan in lowering blood pressure and afterload thereby decreasing the force of ventricular contraction resulting in decreased cardiac workload. No corresponding microscopic changes were present.	Heart weight decreases have been observed in animals with other compounds that interact with the RAAS. The preclinical studies were conducted in normal animals without cardiac hypertrophy. ARBs have been shown to reduce ventricular hypertrophy in patients with hypertension and heart failure (Yasunari et al 2005), this is a desirable effect. The effect of NEP inhibition is less well characterized. In a further mechanistic study conducted in patients with HFrEF: Following treatment initiation with sacubitril/valsartan, NT-proBNP concentration showed a statistically significant decrease from baseline as early as day 14, which persisted throughout the 12 months. All key echocardiographic measures of reverse cardiac remodeling (LVESVi, LVEDVi, LVEF, and LAVi) showed statistically significant improvement from baseline to Months 6 and 12. The improvements from baseline seen in all echocardiographic measures at 6 months were even greater at 12 months. Results for E/E' were consistent. Statistically significant correlations ($p<0.0001$) were shown between change from baseline in log transformed NT-proBNP concentration and all echocardiographic measures analyzed at 1 year (PROVE-HF).
Reproductive Toxicity Studies	
Fertility Neither LCZ696, sacubitril nor valsartan have been associated with effects on fertility in male or female rats.	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Embryo-fetal development Embryo-fetal development studies performed with LCZ696 in rats and rabbits indicate that LCZ696 is teratogenic in rabbits, and is associated with increased embryo-fetal toxicity, including embryo-fetal lethality in rats and rabbits. Both sacubitril and valsartan have been associated with fetotoxicity and embryo-fetal lethality in rabbits. A low incidence of hydrocephaly was observed in rabbit fetuses at LCZ696 doses ≥10 mg/kg, which was also associated with maternal toxicity. This finding is attributed to the valsartan component which produced similar fetal findings in rabbits (increased incidence of dilated brain ventricles) at equivalent maternally toxic doses (doses ≥5 mg/kg). Sacubitril administration in rabbits during embryo-fetal development was associated with delayed bone ossification (metacarpals) at doses associated with maternal toxicity (500 mg/kg/day); these slight generalized delays in development are not considered to have any functional implications.	There is a risk for embryo-fetal toxicity including embryo-fetal lethality and teratogenicity. Use of LCZ696 is contraindicated during pregnancy. Intrauterine exposure to RAAS blockers is associated with adverse fetal effects including oligohydramnios, renal failure, hypotension, pulmonary hypoplasia, cardiac defects, hypocalvaria, and limb defects, fetal growth restriction, cerebral complications and miscarriages or perinatal death, collectively termed the RAAS blockade syndrome. (Darby et al 2013).
Pre and post-natal development Pre- and post-natal development studies in rats with valsartan, but not sacubitril, indicate reductions in pup development and survival.	There is preclinical evidence for a risk of developmental toxicity, which is a known effect of RAAS blockade (see Section 8.3.1.5 and Section 8.3.1.6 on embryo-fetal toxicity/lethality and neonatal/infantile toxicity respectively).
Juvenile toxicity studies Kidney and bone were identified as potential targets in newborn and juvenile rats administered LCZ696 based on studies performed with valsartan and sacubitril. Treatment duration was from postpartum Day 7 through post-partum Day 70.	
Renal tubular and renal pelvic changes were observed in juvenile rats (doses ≥1 mg/kg/day) administered valsartan and represent an exaggerated pharmacological effect of angiotensin II receptor blockers.	Renal tubular and renal pelvic changes are expected pharmacological effects of angiotensin receptor blockers in rats treated during the first 13 days of life during which nephrogenesis is ongoing. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children less than 1 year of age cannot be excluded, while pre-clinical data do not indicate a safety concern for children older than 1 year.
Reduction in body weight gain, bone length and bone mineral density were observed in juvenile rats administered sacubitril from post-natal day (PND) 7 to PND 70 at doses ≥400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, at an LCZ696 pediatric clinical dose of 3.1 mg/kg twice daily). Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657. These bone findings do not appear to be related to on-target effects of neprilysin inhibition in the bone. Bone findings in juvenile animals were most prevalent on day 21 (corresponding to ~2 years of age) and coincide with times of highest	The mechanism underlying bone effects in rats and the translatability to pediatric patients are unknown. In the clinical pediatric study (CLCZ696B2319) no increased risk of fractures and altered growth (height and height Z-scores, BMI Z-scores, head circumference in <3-year-olds) was observed. Nonetheless, the duration of this clinical study may be too short to detect long-term changes in growth. The open-label extension study (CLCZ696B2319E1) confirmed the absence of negative effect on growth, bone growth and mineralization after long-term use in pediatric population.

Key Safety findings (from non-clinical studies)	Relevance to human usage
exposure to sacubitril/LBQ657 and decreased body weight changes. The decrease in body weight was transient from postnatal Day 10 to 20 and the effects for most bone parameters were reversible after treatment stopped. These changes would be most relevant during times of rapid bone growth. No evidence of compound-related increase in bone resorption, microscopic bone changes, or changes in intrinsic bone strength was observed in juvenile rat studies. No increase in fracture rates were observed in repeated dose studies performed with either LCZ696 or sacubitril in adult rats, mice, marmosets or monkeys.	
Following an oral dose (30 mg/kg) of [^{14}C] LCZ696 to lactating rats, transfer of LBQ657 (active metabolite) into milk was observed. The overall milk: plasma (M/P) concentration ratio of total radioactivity was 0.91 based on AUC0-∞ values. Projecting the rat data to humans, it is estimated that a breast-fed infant could be exposed to ~0.889% of an adult dose 400 mg (or 200 mg BID) by ingesting 1 L of milk daily. LBQ657 was the major drug-related compound in rat milk. After a single oral administration of 3 mg/kg [^{14}C] valsartan to lactating rats, transfer of valsartan into milk was observed.	LCZ696 and valsartan were excreted into breast milk of lactating rats. Many drugs are excreted in human milk, and therefore there may be a potential for adverse drug reactions in breastfed newborns/infants from LCZ696. A decision should be made whether to abstain from breast-feeding or to discontinue LCZ696 while breast-feeding, taking into account the importance of LCZ696 to the mother.
Genotoxicity/Mutagenicity Studies LCZ696 and sacubitril were each evaluated in two in vitro and one in vivo assay. Since sacubitril is converted to LBQ657 by esterases in the S9 fraction, the in vitro test systems were also exposed to both compounds. Furthermore, LBQ657 was evaluated in one in vitro assay which evaluated the clastogenic potential for extended duration in the absence of a metabolizing enzyme system. There was no indication of genotoxicity in the in vitro or in vivo systems. There was no evidence of mutagenicity or clastogenicity for valsartan. LCZ696, sacubitril, LBQ657, and valsartan are not genotoxic.	Pre-clinical evidence has demonstrated that LCZ696 is neither mutagenic, genotoxic nor clastogenic. Also, valsartan does not have any mutagenic, genotoxic, or clastogenic effects.
Carcinogenicity Studies The assessment of carcinogenicity potential of LCZ696 was based on carcinogenicity studies performed in rats and mice with sacubitril and with valsartan (previously completed). Carcinogenicity studies were not performed with LCZ696 based on the low exposure multiples which can be achieved with LCZ696 in the rat and mouse relative to human efficacious exposure. There was no evidence of carcinogenicity when sacubitril was administered by oral gavage, for a minimum of 104 weeks, to mice and rats at doses up to 1200 mg/kg/day and 400 mg/kg/day, respectively. There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively.	Pre-clinical data has demonstrated that neither sacubitril nor valsartan are carcinogenic.
General in vivo/in vitro safety pharmacology (Cardiovascular, Respiratory and Nervous system)	
The components of LCZ696 do not inhibit either ACE or amino peptidase P (APP) enzyme activity *in vitro*. Neither LBQ657, valsartan, nor the combination of the two potentiated bradykinin mediated paw swelling or	The rat model of angioedema showed a low potential for angioedema for LCZ696. However, in the PARADIGM-HF study, more events of angioedema were reported during the double-blind period after

Key Safety findings (from non-clinical studies)	Relevance to human usage
hemodynamic effect in rats, supporting a low potential for induction of angioedema.	LCZ696 treatment (0.45%) as compared to enalapril (0.24%). A US non-interventional Study LCZ696B2013 did not indicate an increased risk of angioedema among Black or non-Black patients initiating sacubitril/valsartan compared to patients initiating ACEI for HF. A non-interventional PASS LCZ696B2014 showed that overall number of angioedema cases was low, which is consistent with the real-world estimates from Study B2013, as well as from results from Study B2314 (PARADIGM-HF), and there was no increased risk identified compared to ACEIs.
In vitro studies with LCZ696 and AHU377 on human ether-a-go-go (hERG) channel current (a surrogate for IKr, the rapidly activating delayed rectifier potassium current) expressed in mammalian cells did not identify a risk for QT prolongation (IC50 >3 mM for LCZ696; >1 mM for AHU377). LCZ696 had no effect on EKG parameters in monkeys at doses up to 100 mg/kg. Slight blood pressure reductions were present at 100 mg/kg. Single oral dose administration sacubitril produced no changes in cardiovascular function including QT intervals in dogs.	There is no preclinical evidence of an increased risk for delayed cardiac conduction. The absence of cardiac risk is further supported by the results of the Thorough QT study (no effect on QT interval even after supra-therapeutic doses of LCZ696) and the observed morbidity and mortality benefits in the PARADIGM-HF study.
Changes in Amyloid beta (Aβ) levels in the Central Nervous System (CNS)	
The potential for LCZ696 to affect CNS Aβ levels was evaluated in a 2-week investigative toxicology study of LCZ696 in cynomolgus monkeys. Study results showed that treatment with LCZ696 at 50 mg/kg/day, a dose that produces clinically relevant systemic exposure, resulted in decreased clearance of Aβ42 following the first dose, with subsequent increased levels of Aβ42 in the CSF after 2-weeks treatment with LCZ696 (total CSF Aβ42 increased 33.5% on Day 15 relative to vehicle). CSF levels of Aβ40 and Aβ38 were also increased on day 15, relative to controls. It is important to note that by Day 15 elimination half- life of Aβ42 is similar to controls, and brain tissue concentrations of Aβ were not affected by LCZ696 compared to vehicle at this time point. Chronic (39 week) studies in young (2–4-year-old) cynomolgus monkeys did not show any compound-related microscopic brain changes or increases in brain or cerebral vascular Aβ staining or plaque formation as assessed by anti-Aβ immunostaining at doses up to 300 mg/kg (15X the Human Efficacious Dose assuming 400 mg and a 60 kg patient). The corresponding exposure to LBQ657 (Cmax) is 9X the 200 mg dose. Cynomolgus monkeys generally do not start to develop spontaneous Aβ plaques until much later in life (Kimura et al 2005, Oikawa et al 2010).	In contrast to the cynomolgus monkey study, administration of LCZ696 400 mg once daily for 14 days did not result in changes in CSF Aβ 1-40 and 1-42 concentrations in healthy subjects, despite having measurable concentrations of LBQ657 in the CSF sufficient to inhibit neprilysin. This suggests that enzymes and disposition pathways other than neprilysin appear to be more important in clearance of CSF amyloid-β in humans. CSF Aβ 1-38 concentrations were increased. The clinical significance of this observation is unknown, as Aβ 1-38 is not found in plaques, but there is no evidence in the literature that an isolated increase in this isoform would have clinical implications. Therefore, LCZ696 treatment in humans does not result in clinically meaningful increases in CSF Aβ. In the pivotal Phase 3 study PARADIGM-HF, the incidence of Dementia-related AEs (narrow SMQ Dementia) was low (less than 0.5%), and no imbalance was observed between treatment groups. This is consistent with the results of the analysis for the broad SMQ Dementia in pooled LCZ696 hypertension studies. Therefore, the clinical relevance of the preclinical findings is not known currently. For more details of the potential effects of LCZ696 on cognitive function, see Section 8.3.1.3.
Mechanisms for drug interactions	
Data from rats and marmosets treated with sacubitril alone and in combination with valsartan/ hydrochlorothiazide (valsartan-HCTZ) indicate a lack of pharmacokinetic drug-drug effects between sacubitril and valsartan.	No PK interaction between sacubitril and valsartan was observed in preclinical studies.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Inhibition studies indicated the likely involvement of P-glycoprotein (P-gp) in sacubitril transport; however, this is not predicted to have a significant effect on its oral absorption because a high absorption (>70%) was observed in animals. sacubitril, evaluated up to a concentration of 50 µM did not inhibit MRP2 or P-gp transporters and only very weakly inhibited BCRP transporter (<7% of the positive control).	There is preclinical evidence that there is a low potential for sacubitril to inhibit P-gp transporters, resulting in increased systemic concentrations of P-gp substrates (like digoxin).
Sacubitril has an in vitro inhibitory effect on OATP1B1 and OATP1B3 with IC50 of 1.91 ± 0.56 µM and 3.81 ± 2.2 µM, respectively. LBQ657 was shown to be an in vitro inhibitor of OATP1B1 (IC50 = 126 ± 26 µM) but not OATP1B.	There is preclinical evidence that there is a potential for increased concentrations of OATP1B1/3 substrates (e.g., statins, like atorvastatin, simvastatin, pravastatin, and pitavastatin) when co-administered with LCZ696. These effects may potentially be due to the OATP1B1 and OATP1B3 inhibitory effects of sacubitril. A clinical DDI study in healthy subjects showed that co-administration of LCZ696 increased the Cmax (maximum plasma concentration) of atorvastatin and its metabolites by 68% -108%, although the AUC was not significantly changed (<34%). Another DDI study in healthy subjects showed no significant impact of LCZ696 on pharmacokinetic exposure of simvastatin and its active metabolite simvastatin acid, which is a sensitive substrate of OATP1B1 and OATP1B3. Therefore, caution is recommended when co-administering LCZ696 with atorvastatin and other statins that are substrates of OATP1B1 and OATP1B3.
In vitro results suggested that active transport by OATP1B1 and OATP1B3 contribute to the systemic clearance of LBQ657 which may be altered when LBQ657 is co-administered with drugs that inhibit such transport.	There is preclinical evidence that there is a potential for increased concentrations of LCZ696 if co-administered with OATP1B1/3 inhibitors (like rifampin or cyclosporine).
Valsartan was found to be an in vitro substrate of OATP1B1, OATP1B3 (hepatic uptake transporter) and MRP2 (efflux transporter) in the test system of human hepatocytes and double transfected (OATP1B1/MRP2) MDCKII cells (Yamashiro et al 2006). Valsartan was found to be an in vitro substrate of hOAT1 and hOAT3. LBQ657 was found to be an in vitro substrate of hOAT3 but not hOAT1.	There is preclinical evidence that there is a potential for increased concentrations of valsartan if co-administered with hOAT1/3 inhibitors (like furosemide).
LBQ657 demonstrated weak inhibition potential of CYP2C9 (IC50 of about 40 µM) in in vitro assays. AHU377 and LBQ657 did not induce the expression and/or catalytic activities of CYP1A2, CYP2B6, CYP2C9, or CYP3A in primary human hepatocytes.	There is preclinical evidence to suggest any potential for increased concentrations of CYP2C9 substrates (like warfarin) when co-administered with LCZ696. However, this was refuted by the results of a clinical drug-drug interaction study with warfarin (Study LCZ696B2112).
Valsartan did not inhibit CYP enzymes 1A2, 2A6, 2C19, 2D6, 2E1, or 3A4 to any significant extent. It marginally inhibited CYP2C9 with a relatively high Ki value (135 µM) (Taavitsainen et al 2000). Valsartan did not induce the expression and/or catalytic activities of CYP1A2, CYP2B6, CYP2C9, or CYP3A in primary human hepatocytes. Sacubitril, LBQ657, and valsartan did not inhibit hepatic organic cation transporters 1 (OCT1) or renal OCT2 in the in vitro assays.	There is no preclinical evidence that there is a potential for altered concentrations of CYP1A2, CYP2B6, CYP3A or OCT 1/2 substrates when co-administered with LCZ696.
Other relevant topics based on the mechanism of action	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Based on findings from the literature (Jing et al 2013, Sengenès et al 2000), it cannot be excluded that inhibition of NEP by LCZ696 can increase systemic atrial natriuretic peptide (ANP) levels, resulting in stimulation of lipolysis. As a result, increase in free fatty acid content and muscle's cellular and hepatocellular uptake of free fatty acid may lead to deterioration in insulin sensitivity. However, there were no safety concerns related to stimulation of lipolysis or insulin resistance from the non-clinical studies.	The final results of a hyper-insulinaemic clamp study (LCZ696B2207) conducted in obese hypertensive patients confirmed that LCZ696 does not have any effect on insulin sensitivity. Furthermore, the PARADIGM-HF study did not show any between-treatment differences for new onset diabetes mellitus, changes from baseline for glucose levels or change from baseline lipids. Therefore, stimulation of lipolysis resulting in impaired insulin sensitivity is not considered to be a safety concern.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Clinical trial exposure to LCZ696 can be divided into heart failure, hypertension (HTN) and clinical pharmacology studies. Overall, in all these studies (ongoing and completed), the consolidated safety database for LCZ696 includes approximately 30,489 subjects who have been exposed to LCZ696 at varying doses and for varying treatment/study durations as of 27-Jan-2022.

In the 20 completed heart failure studies 24,499 patients were exposed to LCZ696 as of 27-Jan-2022. These studies are: Phase II studies - CLCZ696B2228 (TITRATION), CLCZ696B2214 (PARAMOUNT), Phase III and IV studies - CLCZ696B2314 (PARADIGM-HF), CLCZ696B2317 (PARADIGM-OLE), CLCZ696B2401 (TRANSITION), CLCZ696B3301 (OUTSTEP-HF), CLCZ696BCA02 (PARASAIL), CLCZ696BUS01 (PIONEER-HF), CLCZ696BUS08 (EVALUATE-HF), CLCZ696BUS13 (PROVE-HF), CLCZ696BUS14 (AWAKE-HF), CLCZ696D2301 (PARAGON-HF), CLCZ696D2302 (PARALLAX-HF), CLCZ696D1301E1 CLCZ696BDE01 (ACTIVITY-HF), CLCZ696B1301 (PARALLEL-HF), CLCZ696B1301E1, CLCZ696G2301 (PARADISE-MI), CLCZ696BCA03 (PARTHENON) and LCZ696BDE03. B1301E1, B2317 and D1301E1 are the extension studies of B1301, B2314 and D2301 respectively; patients are not double counted.

For HTN, the safety database consists of 3,704 patients (from 12 completed studies) who received LCZ696 (including short-term controlled studies which were pooled).

The completed clinical pharmacology studies had 1,251 subjects exposed to LCZ696.

HTN studies:

Phase II studies - CLCZ696A2201, CLCZ696A2219, CLCZ696A2219E1, CLCZ696A2216 (PARAMETER), CLCZ696A2223, CLCZ696A2224 and Phase III studies - CLCZ696A1304, CLCZ696A1305, CLCZ696A1306, CLCZ696A2315, CLCZ696A2316, CLCZ696A2318, and CLCZ696A2319

Pharmacology studies:

CLCZ696A1101, CLCZ696A2101, CLCZ696A2102, CLCZ696A2103, CLCZ696A2117, CLCZ696A2119, CLCZ696A2120, CLCZ696A2124, CLCZ696A2126, CLCZ696A2204, CLCZ696A2205, CLCZ696A2222, CLCZ696B2105, CLCZ696B2107, CLCZ696B2109, CLCZ696B2111, CLCZ696B2112, CLCZ696B2113, CLCZ696B2114, CLCZ696B2115, CLCZ696B2116, CLCZ696B2122, CLCZ696B2123, CLCZ696B2125, CLCZ696B2126, CLCZ696B2128, CLCZ696B2130, CLCZ696B2203, CLCZ696B2207, CLCZ696B2223, CLCZ696B2225, CLCZ696B2132, and CLCZ696F2130.

4.1.1 Clinical trial exposure from Heart failure studies:

For HF, the safety database consists of more than 24,499 patients who have been exposed to LCZ696, the majority of whom were enrolled in study CLCZ696B2314 (including the CLCZ696B2314 run-in period). The cumulative exposure data from completed HF studies

includes 23,503 from HF studies presented in Table 4-1 and 996 patients from CLCZ696BCA03 (CLCZ696BCA03 Clinical study report).

Table 4-1 Duration of exposure to study drug - Completed adult HF studies (Safety Set)

Duration of exposure	LCZ696 200mg BID N=23503	Enalapril 10mg BID N=12318	Valsartan 160mg BID N=6490	Ramipril 5mg BID N=2816	Placebo N=163
Any exposure - n (%)	23503 (100)	12318 (100)	6490 (100)	2816 (100)	163 (100)
Cumulative exposure – n (%)					
>= 1 month	17492 (74.42)	6421 (52.13)	3343 (51.51)	2572 (91.34)	154 (94.48)
>= 3 months	13506 (57.47)	4723 (38.34)	3010 (46.38)	2467 (87.61)	147 (90.18)
>= 6 months	11096 (47.21)	3993 (32.42)	2369 (36.50)	2363 (83.91)	2 (1.23)
>= 9 months	10151 (43.19)	3808 (30.91)	2163 (33.33)	2291 (81.36)	0
>= 1 year	9022 (38.39)	3648 (29.62)	2094 (32.27)	2091 (74.25)	0
>= 2 years	5776 (24.58)	2220 (18.02)	1855 (28.58)	1008 (35.80)	0
>= 3 years	2749 (11.70)	935 (7.59)	916 (14.11)	260 (9.23)	0
>= 4 years	675 (2.87)	72 (0.58)	144 (2.22)	1 (0.04)	0
>= 5 years	148 (0.63)	16 (0.13)	0	0	0
Exposure in days					
N	23503	12318	6490	2816	163
Mean	407.35	291.08	379.02	598.37	155.56
SD	466.580	411.975	497.494	358.164	42.556
Minimum	1.00	1.00	1.00	1.00	1.00
Q1	30.00	16.00	14.00	364.00	166.00
Median	173.00	35.00	34.00	599.00	169.00
Q3	720.00	546.00	892.00	831.00	170.00
Maximum	2416.00	1956.00	1724.00	1465.00	233.00
Person-time (person-years)	26212.31	9876.72	6734.76	4613.33	69.42

Duration is calculated from the first day taking study drug, including run-in, DB, and extension as applicable.
- Person-years: summed up from all patients of respective treatment, over the entire study including run-in, DB, and extension treatment phases. The duration in each treatment phase is defined from the first dose to the last dose; any temporary treatment discontinuation during the phase is not excluded.
- Completed clinical adult HF studies of LCZ696 are B1301, B1301E1, B2214, B2314, B2317, B2228, BCA02, B2401, B3301, D2301, D2302, D1301E1, BUS01, BUS08, BUS13, BUS14, BDE01, BDE03 and G2301.
- B1301E1, B2317 and D1301E1 are the extension of B1301, B2314 and D2301 respectively; patients are not double counted.

Table 4-2 Duration of exposure to study drug –LCZ696B2319 (Pediatric study-Safety Set)

Duration of exposure	LCZ696 3.1 mg/kg BID N=187	Enalapril 0.2 mg/kg N=188
Any exposure - n (%)	187 (100)	188 (100)
Cumulative exposure – n (%)		
>= 1 month	183 (97.86)	182 (96.81)
>= 3 months	177 (94.65)	170 (90.43)

Duration of exposure	LCZ696 3.1 mg/kg BID N=187	Enalapril 0.2 mg/kg N=188
>= 6 months	168 (89.84)	159 (84.57)
>= 9 months	163 (87.17)	152 (80.85)
>= 1 year	85 (45.45)	70 (37.23)
Exposure in days		
N	187	188
Mean	339.31	318.99
SD	95.629	110.749
Minimum	4.00	7.00
Q1	357.00	317.00
Median	365.00	364.00
Q3	376.00	371.00
Maximum	497.00	515.00
Person-time (person-years)	173.72	164.19

- Duration is calculated from the first day taking study drug in the double-blind period. PK/PD dose are not included.
- Person-years: summed up from all patients of respective treatment, over the DB period from the first dose to the last dose; any temporary treatment discontinuation during the DB period is not excluded.

Table 4-3 Exposure by age group and gender - Completed adult HF studies (Safety Set)

Gender	Treatment*	Any age n (pt-y)	Age <65 years n (pt-y)	Age 65-74 years n (pt-y)	Age 75-84 years n (pt-y)	Age 85+ years n (pt-y)
Overall						
	LCZ696 200mg BID	23503 (26212.31)	9332 (10857.97)	7746 (8735.98)	5613 (5940.12)	812 (678.23)
	Enalapril 10mg BID	12318 (9816.72)	5902 (4929.11)	3883 (3050.53)	2315 (1706.23)	218 (130.85)
	Valsartan 160mg BID	6490 (6734.76)	1102 (1231.49)	2389 (2539.33)	2557 (2514.51)	442 (449.43)
	Ramipril 5mg BID	2816 (4613.33)	1444 (2490.09)	866 (1353.28)	457 (712.40)	49 (57.56)
	Placebo	163 (69.42)	27 (10.96)	63 (27.04)	66 (28.17)	7 (3.25)
	Total	45290 (47446.54)	17807 (19519.62)	14947 (15706.18)	11008 (10901.43)	1528 (1319.31)
Male						
	LCZ696 200mg BID	16236 (18359.56)	7264 (8500.93)	5263 (6003.12)	3266 (3459.41)	443 (396.10)
	Enalapril 10mg BID	9456 (7609.03)	4718 (4002.95)	2927 (2298.53)	1669 (1227.43)	142 (89.12)
	Valsartan 160mg BID	3092 (3214.40)	639 (713.66)	1183 (1238.00)	1073 (1092.07)	197 (170.65)
	Ramipril 5mg BID	2121 (3596.21)	1203 (2093.67)	610 (992.59)	285 (484.77)	23 (25.19)
	Placebo	68 (28.15)	12 (4.43)	27 (11.29)	25 (10.57)	4 (1.85)
	Total	30973 (32807.35)	13836 (15315.65)	10010 (10534.54)	6318 (6274.25)	809 (682.91)

Gender	Treatment*	Any age n (pt-y)	Age <65 years n (pt-y)	Age 65-74 years n (pt-y)	Age 75-84 years n (pt-y)	Age 85+ years n (pt-y)
Female						
	LCZ696 200mg BID	7267 (7852.74)	2068 (2357.04)	2483 (2732.86)	2347 (2480.71)	369 (282.13)
	Enalapril 10mg BID	2862 (2207.69)	1184 (926.17)	956 (761.00)	646 (478.80)	76 (41.73)
	Valsartan 160mg BID	3398 (3520.36)	463 (517.82)	1206 (1301.33)	1484 (1422.44)	245 (278.77)
	Ramipril 5mg BID	695 (1017.12)	241 (396.42)	256 (360.70)	172 (227.63)	26 (32.38)
	Placebo	95 (41.28)	15 (6.53)	36 (15.76)	41 (17.60)	3 (1.39)
	Total	14317 (14639.89)	3971 (4203.98)	4937 (5171.64)	4690 (4627.18)	719 (636.40)

- *includes patients who were treated with respective study medication in the study including run-in, DB, and extension as applicable.
- Pt-y: the total duration in person-years, summed up from all patients of respective treatment, over the entire study including run-in, DB and extension treatment phases. The duration in each treatment phase is defined from the first dose to the last dose; any temporary treatment discontinuation during the phase is not excluded.
-Completed clinical adult HF studies of LCZ696 are B1301, B1301E1, B2214, B2314, B2317, B2228, BCA02, B2401, B3301, D2301, D2302, D1301E1, BUS01, BUS08, BUS13, BUS14, BDE01, BDE03 and G2301.
- B1301E1, B2317 and D1301E1 are the extension of B1301, B2314 and D2301 respectively; patients are not double counted.

Table 4-4 Exposure by age group and gender - LCZ696B2319 (Pediatric study-Safety Set)

Gender	Treatment*	Any age n (pt-y)	Age 1 month to <2 years n (pt-y)	Age 2 years to <6 years n (pt-y)	Age 6 years to <18 years n (pt-y)
Overall					
	LCZ696 3.1 mg/kg BID	187 (173.72)	31 (29.85)	47 (45.21)	109 (98.66)
	Enalapril 0.2 mg/kg BID	188 (164.19)	39 (34.07)	38 (35.78)	111 (94.35)
	Total	375 (337.91)	70 (63.92)	85 (80.99)	220 (193.01)
Male					
	LCZ696 3.1 mg/kg BID	89 (81.27)	12 (10.88)	19 (17.70)	58 (52.68)
	Enalapril 0.2 mg/kg BID	93 (83.14)	17 (14.58)	22 (21.00)	54 (47.56)
	Total	182 (164.41)	29 (25.46)	41 (38.71)	112 (100.24)
Female					
	LCZ696 3.1 mg/kg BID	98(92.45)	19 (18.97)	28 (27.51)	51 (45.98)
	Enalapril 0.2 mg/kg BID	95 (81.05)	22 (19.49)	16 (14.77)	57 (46.79)
	Total	193 (173.50)	41 (38.45)	44 (42.28)	108 (92.77)

- *includes patients who were treated with respective study medication in the study during the double-blind period. PK/PD dose are not included.
- Person-years: summed up from all patients of respective treatment, over the DB period from the first dose to the last dose; any temporary treatment discontinuation during the DB period is not excluded.

Table 4-5 Exposure by age group and race - Completed adult HF studies (Safety Set)

Race	Treatment*	Any age n (pt-y)	Age <65 years n (pt-y)	Age 65-74 years n (pt-y)	Age 75-84 years n (pt-y)	Age 85+ years n (pt-y)
Overall						
	LCZ696 200mg BID	23503 (26212.31)	9332 (10857.97)	7746 (8735.98)	5613 (5940.12)	812 (678.23)
	Enalapril 10mg BID	12318 (9816.72)	5902 (4929.11)	3883 (3050.53)	2315 (1706.23)	218 (130.85)
	Valsartan 160mg BID	6490 (6734.76)	1102 (1231.49)	2389 (2539.33)	2557 (2514.51)	442 (449.43)
	Ramipril 5mg BID	2816 (4613.33)	1444 (2490.09)	866 (1353.28)	457 (712.40)	49 (57.56)
	Placebo	163 (69.42)	27 (10.96)	63 (27.04)	66 (28.17)	7 (3.25)
	Total	45290 (47446.54)	17807 (19519.62)	14947 (15706.18)	11008 (10901.43)	1528 (1319.31)
Caucasian						
	LCZ696 200mg BID	17413 (19417.69)	5960 (7158.38)	6084 (6818.97)	4694 (4900.63)	675 (539.71)
	Enalapril 10mg BID	8277 (6413.44)	3354 (2843.48)	2885 (2138.90)	1864 (1318.82)	174 (112.24)
	Valsartan 160mg BID	5276 (5523.75)	801 (921.52)	1960 (2117.20)	2162 (2122.87)	353 (362.15)
	Ramipril 5mg BID	2129 (3581.08)	1034 (1855.59)	674 (1088.82)	380 (594.54)	41 (42.13)
	Placebo	140 (59.20)	19 (7.18)	54 (23.39)	61 (25.84)	6 (2.78)
	Total	33235 (34995.16)	11168 (12786.15)	11657 (12187.29)	9161 (8962.70)	1249 (1059.02)
Black						
	LCZ696 200mg BID	1287 (1010.26)	853 (661.78)	300 (250.81)	111 (79.11)	23 (17.56)
	Enalapril 10mg BID	782 (455.39)	545 (311.59)	175 (109.80)	54 (29.42)	8 (4.59)
	Valsartan 160mg BID	137 (128.52)	33 (30.38)	58 (49.55)	36 (43.13)	10 (5.46)
	Ramipril 5mg BID	40 (69.38)	25 (42.73)	10 (15.79)	5 (10.86)	0
	Placebo	2 (0.96)	1 (0.48)	0	1 (0.48)	0
	Total	2248 (1664.51)	1457 (1047.95)	543 (425.95)	207 (163.00)	41 (27.61)
Asian						
	LCZ696 200mg BID	3161 (3992.03)	1744 (2184.12)	893 (1131.79)	465 (612.50)	59 (63.62)
	Enalapril 10mg BID	2023 (1966.33)	1346 (1235.78)	495 (539.26)	174 (187.36)	8 (3.92)
	Valsartan 160mg BID	784 (850.42)	201 (228.00)	279 (305.76)	256 (263.30)	48 (53.36)

Race	Treatment*	Any age n (pt-y)	Age <65 years n (pt-y)	Age 65-74 years n (pt-y)	Age 75-84 years n (pt-y)	Age 85+ years n (pt-y)
	Ramipril 5mg BID	473 (702.39)	282 (427.23)	131 (178.56)	54 (84.16)	6 (12.44)
	Placebo	15 (6.52)	7 (3.30)	6 (2.27)	2 (0.95)	0
	Total	6456 (7517.69)	3580 (4078.45)	1804 (2157.63)	951 (1148.27)	121 (133.34)
Native American						
	LCZ696 200mg BID	338 (360.05)	159 (150.46)	97 (117.51)	69 (72.94)	13 (19.14)
	Enalapril 10mg BID	226 (167.05)	121 (89.88)	64 (51.71)	34 (23.07)	7 (2.38)
	Valsartan 160mg BID	76 (68.92)	16 (16.92)	21 (15.62)	32 (31.89)	7 (4.49)
	Ramipril 5mg BID	45 (70.62)	24 (36.91)	14 (24.59)	7 (9.12)	0
	Placebo	2 (0.92)	0	1 (0.46)	0	1 (0.46)
	Total	687 (667.56)	320 (294.17)	197 (209.89)	142 (137.03)	28 (26.47)
Pacific Islander						
	LCZ696 200mg BID	9 (0.88)	5 (0.57)	3 (0.22)	1 (0.08)	0
	Enalapril 10mg BID	5 (2.45)	3 (2.07)	1 (0.16)	1 (0.22)	0
	Valsartan 160mg BID	2 (1.80)	0	1 (1.36)	1 (0.44)	0
	Ramipril 5mg BID	4 (6.10)	2 (1.81)	2 (4.29)	0	0
	Total	20 (11.23)	10 (4.45)	7 (6.03)	3 (0.74)	0
Other						
	LCZ696 200mg BID	1237 (1394.61)	586 (686.08)	350 (405.04)	259 (265.29)	42 (38.20)
	Enalapril 10mg BID	982 (807.13)	519 (443.48)	260 (210.23)	182 (145.70)	21 (7.72)
	Valsartan 160mg BID	212 (160.84)	51 (34.66)	69 (49.83)	68 (52.38)	24 (23.98)
	Ramipril 5mg BID	105 (151.88)	65 (103.02)	28 (32.87)	10 (13.01)	2 (2.98)
	Placebo	3 (1.39)	0	2 (0.93)	1 (0.46)	0
	Total	2539 (2515.85)	1221 (1267.24)	709 (698.90)	520 (476.83)	89 (72.88)
Unknown						
	LCZ696 200mg BID	48 (34.55)	24 (15.36)	14 (10.45)	10 (8.74)	0
	Enalapril 10mg BID	12 (2.36)	8 (1.43)	3 (0.48)	1 (0.46)	0

Race	Treatment*	Any age n (pt-y)	Age <65 years n (pt-y)	Age 65-74 years n (pt-y)	Age 75-84 years n (pt-y)	Age 85+ years n (pt-y)
	Valsartan 160mg BID	3 (0.50)	0	1 (0.01)	2 (0.49)	0
	Ramipril 5mg BID	20 (31.87)	12 (22.80)	7 (8.36)	1 (0.71)	0
	Placebo	1 (0.44)	0	0	1 (0.44)	0
	Total	84 (69.72)	44 (39.58)	25 (19.30)	15 (10.84)	0
Missing						
	LCZ696 200mg BID	10 (2.24)	1 (0.22)	5 (1.19)	4 (0.84)	0
	Enalapril 10mg BID	11 (2.58)	6 (1.41)	0	5 (1.17)	0
	Total	21 (4.83)	7 (1.63)	5 (1.19)	9 (2.01)	0

- *including patients who were treated with respective study medication in the study including run-in, DB and extension as applicable.
- Pt-y: the total duration in person-years, summed up from all patients of respective treatment, over the entire study including run-in, DB, and extension treatment phases.
The duration in each treatment phase is defined from the first dose to the last dose; any temporary treatment discontinuation during the phase is not excluded.
- Completed clinical adult HF studies of LCZ696 are B1301, B1301E1, B2214, B2314, B2317, B2228, BCA02, B2401, B3301, D2301, D2302, D1301E1, BUS01, BUS08, BUS13, BUS14, BDE01, BDE03 and G2301.
- B1301E1, B2317 and D1301E1 are the extension of B1301, B2314 and D2301 respectively; patients are not double counted.

Table 4-6 Exposure by age group and race - LCZ696B2319 (Pediatric study-Safety Set)

Race	Treatment*	Any age n (pt-y)	Age 1 month to <2 years n (pt-y)	Age 2 years to <6 years n (pt-y)	Age 6 years to <18 years n (pt-y)
Overall					
	LCZ696 3.1 mg/kg BID	187 (173.72)	31 (29.85)	47 (45.21)	109 (98.66)
	Enalapril 0.2 mg/kg BID	188 (164.19)	39 (34.07)	38 (35.78)	111 (94.35)
	Total	375 (337.91)	70 (63.92)	85 (80.99)	220 (193.01)
Caucasian					
	LCZ696 3.1 mg/kg BID	87 (80.72)	12 (11.47)	16 (15.37)	59 (53.88)
	Enalapril 0.2 mg/kg BID	93 (86.09)	19 (16.61)	13 (13.26)	61 (56.22)
	Total	180 (166.82)	31(28.09)	29 (28.63)	120 (110.10)
Black					
	LCZ696 3.1 mg/kg BID	23 (20.94)	4 (3.21)	4 (4.19)	15 (13.54)
	Enalapril 0.2 mg/kg BID	25 (19.60)	1 (1.13)	6 (6.17)	18 (12.30)
	Total	48 (40.54)	5 (4.34)	10 (10.35)	33 (25.84)

Race	Treatment*	Any age n (pt-y)	Age 1 month to <2 years n (pt-y)	Age 2 years to <6 years n (pt-y)	Age 6 years to <18 years n (pt-y)
Asian					
	LCZ696 3.1 mg/kg BID	57 (52.12)	10 (9.96)	23 (21.68)	24 (20.48)
	Enalapril 0.2 mg/kg BID	45 (37.19)	11 (8.85)	11 (9.52)	23 (18.82)
	Total	102 (89.31)	21 (18.81)	34 (31.20)	47 (39.30)
Native American					
	LCZ696 3.1 mg/kg BID	3 (3.01)	0	2 (2.00)	1 (1.00)
	Enalapril 0.2 mg/kg BID	2 (2.01)	1(1.01)	0	1 (1.00)
	Total	5 (5.02)	1 (1.01)	2 (2.00)	2 (2.00)
Other					
	LCZ696 3.1 mg/kg BID	9 (8.85)	2 (2.28)	2 (1.97)	5 (4.60)
	Enalapril 0.2 mg/kg BID	17 (14.63)	4 (3.94)	8 (6.83)	5 (3.86)
	Total	26 (23.49)	6 (6.22)	10 (8.80)	10 (8.47)
Unknown					
	LCZ696 3.1 mg/kg BID	8 (8.07)	3 (2.91)	0	5 (5.16)
	Enalapril 0.2 mg/kg BID	6 (4.66)	3 (2.52)	0	3 (2.14)
	Total	14 (12.74)	6 (5.44)	0	8 (7.30)

- *includes patients who were treated with respective study medication in the study during the double-blind period. PK/PD dose are not included.
- Person-years: summed up from all patients of respective treatment, over the DB period from the first dose to the last dose; any temporary treatment discontinuation during the DB period is not excluded.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Pregnant women	LCZ696 is teratogenic, embryo-fetotoxic and embryo-fetolethal.	No	Included as contraindication
Breastfeeding women	LCZ696 is excreted into breast milk of lactating rats and LCZ696 has a risk of developmental toxicity. Therefore, there may be a potential for adverse events in breastfed newborns/infants from LCZ696.	No	Included as important potential risk in RMP and reflected in section 4.6 of the SmPC.
Patients with a history of hypersensitivity to sacubitril/valsartan or to drugs of similar chemical classes	Increased risk of anaphylaxis.	No	Included as contraindication.
Patients with a known history of angioedema	Angioedema is a known class effect	No	Included as contraindication.
Patients with evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), bilirubin >1.5 mg/dl	Greater risk of increased exposure to the active components of LCZ696 (sacubitril, LBQ657 and valsartan).	No	Severe hepatic impairment, biliary cirrhosis and cholestasis included as contraindication.
Patients with severe renal impairment as defined by: eGFR <30 mL/min/1.73m2 as calculated by the Modification in Diet in Renal Disease formula	Precautionary measures to preclude enrolling patients who might be at risk after LCZ696 exposure.	No	Included under the important identified risk ‘Renal Impairment’ and reflected as a cautionary statement in the posology section of the SmPC (Section 4.2).
Pediatric patients (< 1 month)	Due to the concern that use of a RAAS blocker may affect kidney development based on pre-clinical rat toxicity studies, children < 1 month old (full term	No	Indication does not include pediatric patients < 1 month.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	infant) (or < 44 weeks post conception for pre-term infant) were excluded from the study.		

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Table 5-2 Limitations of ADR detection common to clinical trial development programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are very rare	In the adult HF studies, approximately 23081 patients received sacubitril/valsartan (Section 4.1) and in the single pediatric HF study, 187 patients received sacubitril/valsartan.	The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions
Due to prolonged exposure	The overall median duration of treatment in PARADIGM-HF was 27 months with 16 months additional median duration exposure in the PARADIGM-HF OLE study (CLCZ696B2317). The maximum durations in PARADIGM-HF and PARADIGM-HF-OLE study were 51 months and 32 months, respectively. The number of patients with greater than 5 years exposure to sacubitril/valsartan was 148 (Section 4.1). The median duration of treatment in the pediatric PANORAMA-HF study (CLCZ696B2319) was 365 days. While in the long-term extension PANORAMA-HF OLE study (CLCZ696B2319E1), the median duration of treatment was 911 days.	Data collected to date do not suggest an adverse effect of long-term exposure in adult and pediatric population.
Due to cumulative effects	The maximum accumulation observed was 1.6-fold for LBQ657 following multiple dosing of LCZ696 bid while no significant accumulation of sacubitril and valsartan was observed.	None.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-3 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	These patients have been excluded from clinical trials. LCZ696 is teratogenic, embryo-fetotoxic and embryo-fetolethal. The literature describes the RAAS syndrome after intrauterine exposure. LCZ696 is contraindicated during pregnancy.
Breastfeeding women	These patients have been excluded from clinical trials. LCZ696 is excreted into breast milk of lactating rats and has a risk of developmental toxicity.

Type of special population	Exposure
Patients with relevant comorbidities	
Patients with hepatic impairment	The safety of LCZ696 in patients with various stages of hepatic impairment was studied in the clinical development program in the form of a pharmacokinetic study in patients with mild or moderate hepatic impairment. Patients with mild and moderate hepatic impairment were included in PARADIGM-HF study. Patients with severe hepatic impairment were excluded from PARADIGM-HF study. LCZ696 is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child Pugh C classification).
Patients with renal impairment	The safety of LCZ696 in patients with various stages of renal impairment was studied extensively in the clinical development program. More than 4200 heart failure patients with mild renal impairment (eGFR at baseline between 60 and 90 mL/min/1.73m2), more than 3000 HF patients with moderate renal impairment (eGFR at baseline between 30 and 60 mL/min/1.73m2), and 25 patients with severe renal impairment (eGFR at baseline lower than 30 mL/min/1.73m2) have been studied in the PARADIGM-HF study (patients with severe renal impairment were excluded from the study. However, patients could develop severe renal impairment during the study). The safety profile is further supported by two dedicated clinical pharmacology studies and a study in the hypertension program. There is no experience in patients with end-stage renal disease.
ACEI/ARB naïve patients	Relatively small numbers of ACEI/ARB-naive patients have been studied in the LCZ696 HF program as below: ● TITRATION (CLCZ696B2228): 33 patients ● TRANSITION (CLCZ96B2401): 241 patients ● PIONEER-HF (CLCZ696BUS01): 459 patients. The general safety profile of LCZ696 in these patients is similar to the overall patient population in which LCZ696 demonstrated a positive benefit/risk profile and LCZ696 has been recommended for use in ACEI/ARB-naïve patients. 2021 ESC HF guidelines (September 2021): Two studies have examined the use of ARNI in hospitalized patients, some of whom had not been previously treated with ACE-I. Initiation in this setting appears safe and reduces subsequent CV death or HF hospitalizations by 42% compared to enalapril. As such, initiation of sacubitril/valsartan in ACE-I naive (i.e. de novo) patients with HFrEF may be considered (class of recommendation IIb, level of evidence B). AHA/ACC/HFSA guidelines (April 2022): Trial data have included ACEi/ARB-naïve patients before ARNi initiation (53% in the PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial and 24% in the TRANSITION (Comparison of Pre- and Post-discharge Initiation of Sacubitril/Valsartan Therapy in HFrEF Patients After an Acute Decompensation Event] trial) and have shown similar efficacy and safety in treatment-naïve patients. The PIONEER-HF trial showed that ARNi reduced NT-proBNP levels in patients hospitalized for acute decompensated HF without increased rates of adverse events (worsening renal function, hyperkalemia, symptomatic hypotension, angioedema) when compared with enalapril. Additional outcome analyses suggested reduction in all-cause mortality and re-hospitalization for HF but were only hypothesis-generating as exploratory study endpoints. In the open-label TRANSITION trial, patients with HFrEF hospitalized with worsening HF were randomized to start ARNi either before or after discharge. Safety outcomes were similar for both arms, suggesting that early initiation may simplify management (rather than initiating and uptitrating ACEi first and then switching to ARNi). ARNi should be initiated de novo in patients hospitalized with acute HFrEF before discharge in the absence of contraindications. ARNi may be initiated de novo in patients with chronic

Type of special population	Exposure
	symptomatic HFrEF to simplify management, although data are limited.
Population with relevant different ethnic origin and Subpopulations carrying relevant genetic polymorphisms	Included in the clinical development program and were adequately represented. Overall, patients across all racial subgroups showed favorable efficacy outcomes with LCZ696 treatment and safety profile was generally similar to overall population. However, effects of genetic polymorphisms have not been studied in HF patients.
Other	
Pediatric patients (< 1 month)	These patients have been excluded from clinical trials due to the concern that use of RAAS blocker may affect kidney development based on pre-clinical rat toxicity studies.

Source: Attachment to Annex 7

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The patient exposure estimate is calculated based on worldwide sales volume of film-coated tablets/ granules in capsules sold and the recommended frequency for taking LCZ696. As it is recommended to take LCZ696 BID, the estimated exposure calculation is the total number of tablets sold during the reporting interval divided by two; to report this in patient-treatment-years (PTY), it is further divided by 365.25.

6.1.2 Part II Module SV.1.2. Exposure

Estimate of post-authorization (non-CT) exposure based on worldwide sales data

Table 6-1 Estimated cumulative post-marketing (non-clinical trial) exposure

Formulation	Number of Tablets sold	Estimated exposure (PTY)
Film-coated tablets	14,641,775,579 2	20,043,498 0
Granules in capsules	290, 879	398
Total	14,642, 066,458	20,043,897

Patient-treatment-years (PTY): exact number is taken into consideration when calculating totals, which may account for discrepancies (i.e. ± 1) in the total columns.
Data cut-off: 31-Jul-2024

Table 6-2 Estimated cumulative post-marketing (non-CT) exposure, per region

Formulation	EEA (including EU) (PTY)	USA and Canada (PTY)	Japan (PTY)	ROW* (PTY)
Film-coated tablets	4,040,633	CCI	CCI	10,951,535
Granules in capsules	359	CCI	CCI	30

EEA: European Economic Area; EU: European Union; ROW: Rest of the World; USA: United States of America
Patient-Treatment-Years (PTY): exact number is taken into consideration when calculating totals, which may account for discrepancies (i.e. ± 1) in the total columns.

*Sales from the United Kingdom are considered under ROW.
[PSUR]: Data cut-off: 31-Jul-2024

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Treatment with LCZ696 is unlikely to result in drug abuse or dependency because of low blood-brain barrier penetration of LBQ657 and low binding affinity of sacubitril, LBQ657 and valsartan to targets associated with abuse liability. Due to the complementary role of neprilysin and aminopeptidase N in enkephalin inactivation and the high selectivity of LBQ657 for neprilysin, no clinically relevant anti-nociceptive effects are expected with LCZ696 (Noble et al 1992). In addition, there is no preclinical, clinical, or post-marketing evidence suggestive of abuse liability potential in association with valsartan administration. Therefore, no risk minimization activities are proposed.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable; the RMP was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Changes for RMP version 9.0 from RMP version 8.0:

In line with the GVP Module V (Rev.2) guidance and the accumulated clinical trial and post-marketing experience with sacubitril/valsartan, including two completed PASS LCZ696B2014 and LCZ696B2015, Novartis proposes the removal of the following risks from the list of safety concerns:

Important Identified Risks (LCZ696B2014)

- Angioedema
- Hypotension
- Hyperkalemia
- Renal impairment

Important Potential Risk (LCZ696B2014)

- Hepatotoxicity

Missing information (LCZ696B2014)

- Use in ACEI/ARB-naïve HF patients

Important Potential Risk (LCZ696B2015)

- Statin drug-drug interaction

The rationale for the removal is provided in Table 8-1.

Table 8-1 Rationale for the removal of selected safety concern from the sacubitril/valsartan RMP

Topic Safety concern type	Risk management	Rationale for removal
Hypotension Important identified risk	Routine PV No additional risk minimization activities No additional PV activities	Well-characterized risk and appropriately communicated in the CDS/SmPC. The cumulative experience in clinical trials and post-marketing does not indicate a change in nature/frequency of this risk. Study B2014 complements the current knowledge of the risk of hypotension as was observed from clinical trials. The IR of hypotension in sacubitril/valsartan-treated patients in Study B2014 was of a similar magnitude as was observed in clinical trials.

		The post-marketing exposure-adjusted reporting rates (EARR) of hypotension have steadily decreased across multiple reporting intervals. The same is true for the EARR of fatal and life-threatening cases, as well as those cases reported along with syncope, renal impairment, TIA, stroke, and fall, whose EARR have become extremely low over time. Hypotension will continue to be monitored and reviewed in the next PSUR.
Angioedema Important identified risk	Routine PV No additional risk minimization activities No additional PV activities	Well-characterized risk and appropriately communicated in the CDS/SmPC. The cumulative experience in clinical trials and post-marketing does not indicate a change in nature/frequency of this risk. Study B2014 confirms the previous understanding of the risk of angioedema. It had overall low number of angioedema cases, which is consistent with the real-world estimates from Study B2013, as well as from results from Study B2314 (PARADIGM-HF). The post-marketing EARR of angioedema have steadily decreased across multiple reporting intervals. The same is true for the EARR of fatal and life-threatening cases, as well as those cases reporting hospitalization due to angioedema, whose EARR have become extremely low over time. Angioedema will continue to be monitored and reviewed in the next PSUR.
Hyperkalemia Important identified risk	Routine PV No additional risk minimization activities No additional PV activities	Well-characterized risk and appropriately communicated in the CDS/SmPC. The cumulative experience in clinical trials and post-marketing (including the results from study CLCZ696B2014) does not indicate a change in nature/frequency of this risk. The IR of hyperkalemia in sacubitril/valsartan-treated patients in Study B2014 was of a similar magnitude as was observed in clinical trials. The post-marketing EARR of hyperkalemia have steadily decreased across multiple reporting intervals. The same is true for the EARR of fatal and life-threatening cases, whose EARR have become extremely low over time. Hyperkalemia will continue to be monitored and reviewed in the next PSUR.
Renal impairment Important identified risk	Routine PV No additional risk minimization activities No additional PV activities	Well-characterized risk and appropriately communicated in the CDS/SmPC. The cumulative experience in clinical trials and post-marketing (including the results from study CLCZ696B2014) does not indicate a change in nature/frequency of this risk. In study B2014, the incidence of renal impairment in patients treated with sacubitril/valsartan was higher when compared to patients treated with ACEI, regardless of prior exposure to ACEI/ARBs or in ACEI/ARB-naïve patients. However, the higher HF severity of the sacubitril/valsartan users, as well as morbidities usually associated with HF and potentially detection bias, likely contributed to that difference in incidence rates. The post-marketing EARR of renal impairment have steadily decreased across multiple reporting intervals. The same is true for the EARR of fatal and life-threatening cases, as well as those requiring dialysis or renal transplant, whose EARR have become extremely low over time. Renal impairment will continue to be monitored and reviewed in the next PSUR.
Hepatotoxicity Important potential risk	Routine PV No additional risk minimization activities No additional PV activities	This safety concern was thoroughly assessed in study B2014, which demonstrated no evidence of an association between the exposure to sacubitril/valsartan and the occurrence of hepatotoxicity. The same observation can be derived from the cumulative experience from clinical trials and post-marketing reports. The post-marketing EARR of hepatotoxicity have steadily decreased across multiple reporting intervals and have become extremely low over time.

		The risk is appropriately communicated in the CDS/SmPC. This is considered sufficient to minimize it. There are currently no additional risk minimization or PV activities in place for this safety concern. Hepatotoxicity will continue to be monitored and reviewed in the next PSUR.
Statin drug-drug interaction Important potential risk	Routine PV No additional risk minimization activities No additional PV activities	This safety concern was thoroughly assessed in study B2015, which demonstrated no evidence of an association between the concomitant exposure to sacubitril/valsartan and a statin and the occurrence of myotoxicity, hepatotoxicity or pancreatitis. This finding is in line with the cumulative clinical trials and post-marketing experience. The post-marketing EARR of statin drug-drug interaction cases have steadily decreased across multiple reporting intervals and have become extremely low over time. This is also true for cases of rhabdomyolysis with and without interaction with a statin. The risk is appropriately communicated in the CDS/SmPC. This is considered sufficient to minimize it. There are currently no additional risk minimization or PV activities in place for this safety concern. Statin DDI will continue to be monitored and reviewed in the next PSUR.
Use in ACEI/ARB-naïve HF patients Missing information	Routine PV No additional risk minimization activities No additional PV activities	This safety concern was assessed in study B2014, which demonstrated that the safety profile of sacubitril/valsartan in ACEI/ARB-naïve initiators is similar to that of non-naïve counterparts. Cumulative clinical trials and post-marketing experience is aligned with that observation. The risk is appropriately addressed in the CDS/SmPC (Dosage regimen and administration). It will continue to be monitored and reviewed in the next PSUR.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

Clinical data for the important identified and important potential risks detailed in this section are based on the randomized, double-blind epoch of the pivotal Phase III clinical study CLCZ696B2314 (PARADIGM-HF) in adults for the HFrEF indication and CLCZ696B2319 (PANORAMA-HF) for chronic heart failure in pediatrics (adolescents and children).

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Identified Risk: Embryo-fetal toxicity/lethality

AEs of ‘Embryo-fetal toxicity/lethality’ in clinical trial data are defined by the SMQ (narrow) ‘Foetal disorders’, SMQ (narrow) ‘Neonatal disorders’ and SMQ ‘Termination of pregnancy and risk of abortion’.

Table 8-2 Important identified risk embryo-fetal toxicity/lethality: Other details

Embryo-fetal toxicity/lethality	Details
Potential mechanisms	Although the exact mechanism is unclear, drugs that block the RAAS are contraindicated in pregnancy as the RAAS seems to be necessary for normal fetal development.
Evidence sources and strength of evidence	Current evidence is based on mechanistic plausibility and pre-clinical findings.
Characterization of the risk	In the adult HF study LCZ696B2314 (PARADIGM) no cases of congenital anomaly were observed. Five pregnancy-related cases were reported with spontaneous

Embryo-fetal toxicity/lethality	Details
	abortions in two cases, a healthy baby in one case (mother counted as one case) and medical termination of pregnancy in the fifth case. None of the events were considered serious or suspected to be related to the study medication by the investigator. Crude incidence rate of developmental toxicity (SMQ Pregnancy and neonatal topics) was comparable between Entresto (0.26%) and enalapril (0.45%). EAIR (per 100 PTY) for Entresto was 0.116 (0.058, 0.207) and enalapril was 0.202 (0.122, 0.315). No pregnancy-related events have been reported in the HTN studies. The pediatric population is expected to be less exposed to this identified risk. No case related to embryo-fetal toxicity/lethality were reported in the pediatric study CLCZ696B2319 and from the post-marketing data.
Risk factors and risk groups	Women of childbearing potential. Exposure to ACEI, folic acid deficiency, advanced maternal age.
Preventability	Women of childbearing potential must use contraception during treatment and for one week after their last dose of LCZ696. As for any drug that also acts directly on the RAAS, LCZ696 must not be used during pregnancy. If pregnancy is detected during therapy, LCZ696 should be discontinued as soon as possible.
Impact on the benefit-risk balance of the product	Despite the mechanistic plausibility and considering the paucity of related reports received, which reflects the low expected frequency of this risk if the recommendations to mitigate it are followed, its impact on the benefit-risk balance is deemed limited.
Public health impact	Considering the HF population is elderly and the majority of the female patients are past child-bearing age, the expected frequency of this risk in the HF population is naturally low. Therefore, its impact on public health is expected to be low as it is manageable through the existing information in the current SmPC.

8.3.1.2 Important potential Risk: Neonatal/infantile toxicity through exposure from breast milk

AEs of 'Neonatal/infantile toxicity through exposure from breast milk' in clinical trial data are defined by the SMQ 'Neonatal exposures via breast milk'.

Table 8-3 Important potential risk Neonatal/infantile toxicity through exposure from breast milk: Other details

Neonatal/infantile toxicity through exposure from breast milk	Details
Potential mechanisms	Although the exact mechanism is unclear, drugs that block the RAAS may affect the growth/development of infants as the RAAS seems to be necessary for normal infant growth.
Evidence sources and strength of evidence	Currently, there is no evidence to support the existence of this risk. In a pre-clinical study, sacubitril and valsartan were excreted in the milk of lactating rats. However, it is not known whether LCZ696 is excreted in human milk.
Characterization of the risk	No events related to neonatal/infantile toxicity through exposure from breast milk have been reported in the adult HF or hypertension clinical studies. The pediatric population is expected to be less exposed to this potential risk. No case related to neonatal toxicity through exposure from breast milk were reported in the pediatric study CLCZ696B2319.
Risk factors and risk groups	Breastfed infants of women taking LCZ696.
Preventability	Because of the potential risk for adverse reactions in breast-fed newborns/infants from LCZ696, it is not recommended during breastfeeding. A decision should be made whether to abstain from breast-feeding or to abstain from using the

Neonatal/infantile toxicity through exposure from breast milk	Details
	medicinal product, taking into account the importance of the medicinal product to the mother.
Impact on the benefit-risk balance of the product	As it is not clear whether LCZ696 is excreted in human milk and, because currently there is no data to suggest neonatal/infantile toxicity through breast milk, no impact to the existing benefit-risk assessment is contemplated.
Public health impact	The public health impact is currently unknown. However, it is considered low, because the HF population is elderly and potentially past breast-feeding age.

8.3.1.3 Important potential Risk: Cognitive impairment

AEs of 'Cognitive impairment' in clinical trial data are defined by the SMQ (narrow) 'Dementia'.

Table 8-4 Clinical trial data of cognitive impairment in double-blind period – CLCZ696B2314 (Adult HF study-Safety set)

	LCZ696 200mg bid N=4203 n(%) 95% CI	Enalapril 10mg bid N=4229 n(%) 95% CI	LCZ696 vs Enalapril RR 95% CI
Number of patients with at least one event	12 (0.29)	15 (0.35)	0.80 (0.38, 1.72)
IR per 100 PTY	0.13 (0.07, 0.22)	0.16 (0.09, 0.26)	
Maximum severity			
Mild	5 (0.12)	10 (0.24)	
Moderate	5 (0.12)	2 (0.05)	
Severe	2 (0.05)	3 (0.07)	
SAEs	4 (0.10)	2 (0.05)	2.01 (0.37,10.98)
AEs requiring dose adjustment or interruption	0	1 (0.02)	0
AEs leading to permanent disc of therapy	3 (0.07)	1 (0.02)	3.02 (0.31,29.01)

- n (%): number (percentage) of patients with events.
- IR/100 PTY: exposure-adjusted incidence rate per 100 person-years is calculated by n (number of patients with events)/ total exposure time (in 100 years) of double-blind treatment, summed up from all patients in the treatment group. Exposure time is the duration from Day 1 to the 1st event for patients with at least one event or the duration of treatment in double-blind period for patients with no event reported.
Source: [SCS-Appendix 1- Table 14.3.1-5.1]

Table 8-5 Clinical trial data of cognitive impairment in double-blind period – (Safety set)

	B2320 HFpEF (randomized treatment epoch)		
	LCZ696 200mg bid N=295 n(%)	Valsartan 160mg bid N=297 n(%)	Total N=592 n(%)
Number of patients with at least one event	1 (0.34)	1 (0.34)	2 (0.34)
IR per 100 PTY	0.12	0.12	0.12
Maximum severity			
Mild	0	0	0

Moderate	1 (0.34)	0	1 (0.17)
Severe	0	1 (0.34)	1 (0.17)
SAEs	0	0	0
AEs requiring dose adjustment or interruption	0	0	0
AEs leading to permanent disc of therapy	0	1 (0.34)	1 (0.17)

- n (%): number (percentage) of patients with events.
- IR/100 PTY: exposure-adjusted incidence rate per 100 person-years is calculated by n (number of patients with events)/ total exposure time (in 100 years) of double-blind treatment, summed up from all patients in the treatment group.
Exposure time is the duration from Day 1 to the 1st event for patients with at least one event or the duration of treatment in double-blind period for patients with no event reported.
Source: [LCZ696B2320 CSR-Table 14.3.1-1.8, Table 14.3.1-1.13, Table 14.3.1-1.14, Table 14.3.1-1.16, Table 14.3.1-1.17, Table 14.3.1-1.18]

Table 8-6 Clinical trial data of cognitive impairment in double-blind period by sub-group – CLCZ696B2314 (Adult HF study)

Subgroup	LCZ696 200mg BID N=4203 n/m(%)	Enalapril 10mg BID N=4229 n/m(%)
Age group		
< 65 years	1/2120 (0.05)	0/2174 (0.00)
>= 65 years	11/2083 (0.53)	15/2055 (0.73)
< 75 years	4/3417 (0.12)	2/3446 (0.06)
>= 75 years	8/786 (1.02)	13/783 (1.66)
Gender		
Male	9/3316 (0.27)	10/3270 (0.31)
Female	3/887 (0.34)	5/959 (0.52)
Race		
Caucasian	12/2777 (0.43)	13/2796 (0.46)
Black	0/213 (0.00)	0/214 (0.00)
Asian	0/757 (0.00)	1/750 (0.13)
Native American	0/84 (0.00)	0/88 (0.00)
Pacific Islander	0	0/1 (0.00)
Other	0/372 (0.00)	1/380 (0.26)
Unknown	0	0
History of stroke		
Yes	1/357 (0.28)	1/370 (0.27)
No	11/3846 (0.29)	14/3859 (0.36)
History of AFib and/or documented AFib at screening ECG		
Yes	7/1527 (0.46)	7/1587 (0.44)
No	5/2676 (0.19)	8/2642 (0.30)

- % = 100*n/m, where n is the number of patients with an event of interest, m is the number of patients at risk in corresponding subgroup within the treatment.

Table 8-7 Clinical trial data of cognitive impairment in double-blind period – (by subgroup)

	B2320	
Subgroup	LCZ696 200mg BID N=295 n/m (%)	Valsartan 160mg BID N=297 n/m (%)
Age group		
<65	0/41 (0.00)	0/45 (0.00)
>=65	1/254 (0.39)	1/252 (0.40)
<75	1/186 (0.54)	0/180 (0.00)
>=75	0/109 (0.00)	1/117 (0.85)
Gender		
Male	0/161 (0.00)	1/154 (0.65)
Female	1/134 (0.75)	0/143 (0.00)
Race		
Caucasian	1/273 (0.37)	1/271 (0.37)
Black	0/6 (0.00)	0/9 (0.00)
Asian	0/11 (0.00)	0/12 (0.00)
Native American	0/2 (0.00)	0
Other	0/2 (0.00)	0/3 (0.00)
Unknown	0/1 (0.00)	0/2 (0.00)
History of stroke		
Yes	0/25 (0.00)	0/23 (0.00)
No	1/270 (0.37)	1/274 (0.36)
History of Atrial Fibrillation		
Yes	1/137 (0.73)	1/146 (0.68)
No	0/158 (0.00)	0/151 (0.00)
LVEF at screening		
<= 60%	1/227 (0.44)	0/212 (0.00)
> 60%	0/68 (0.00)	1/84 (1.19)

- % = 100*n/m, where n is the number of patients with an event of interest (per electronic Case Retrieval Strategy), m is the number of patients at risk in corresponding subgroup within the treatment.

Table 8-8 Important potential risk Cognitive impairment: Other details

Cognitive impairment	Details
Potential mechanisms	*In vitro* and non-clinical data suggest that neprilysin is involved in the degradation of soluble Aβ in the CSF. However, it is unknown whether pharmacological increase of Aβ in the CSF could result in cognitive impairment. The human genetic data for neprilysin (GWAS studies) and neprilysin SNPs associated with differences in neprilysin activity reveal no association with Alzheimer's Disease (AD) (Debiec et al 2004, Hamilton et al 2012; Miners et al 2012). RAAS inhibition has been positively related with moderating cognitive decline (Gorelick et al 2011).
Evidence sources and strength of evidence	In pre-clinical studies, Entresto had an effect on CSF amyloid-β clearance, increasing CSF amyloid-β in young cynomolgus monkeys treated with Entresto 50 mg/kg/day for two weeks. A healthy volunteer study showed that Entresto had no significant effect on CSF levels of the amyloid-β species 1-42 or 1-40 compared with placebo, whereas a 42% increase in CSF AUEC0-36h of soluble amyloid-β 1-38 was observed, compared with placebo. The clinical relevance of increased CSF levels of amyloid-β 1-38 is unknown but is considered unlikely to be associated with toxicity.

Cognitive impairment	Details
	Clinical studies CLCZ696B2314 and CLCZ696D2301 and PASS CLCZ696B2320 studies showed no evidence of increased risk of cognitive impairment with Entresto. Post-marketing data was consistent with the CT data.
Characterization of the risk:	In the pivotal the adult HF study CLCZ696B2314, incidence rates of Dementia (broad SMQ) were the same in both treatment groups (2.0% each, AER 0.9 vs. 0.9 per 100 PYs, RR 1.0, CI 0.8-1.4). Incidence rates were 0.3% vs. 0.4%, corresponding to 12 and 15 patients in the LCZ696 and enalapril groups respectively, AER 0.1 vs. 0.2 per 100 PYs, RR 0.8, CI 0.3-1.8). Most frequently reported events by PT for Dementia (narrow SMQ) were dementia (0.14% vs. 0.24%, corresponding to 6 and 10 patients in the LCZ696 and the enalapril groups, respectively), dementia Alzheimer's type (0.05% vs. 0.05%, 2 patients in each group), vascular dementia (0.05% vs. 0.02%, 2 vs. 1 patient, respectively) and senile dementia (0% vs. 0.05%, 0 vs. 2 patients, respectively). Most events related to dementia (narrow SMQ) were either mild or moderate in severity; severe events were reported for 0.05% and 0.07% of patients, corresponding to two and three patients in the LCZ696 and enalapril groups, respectively. In the completed adult HF study CLCZ696D2301 (PARAGON HF), changes in cognition over time as assessed by a repeated measures analysis of the mean MMSE remained stable from baseline to week 96 with no significant difference between the LCZ696 and valsartan groups. There were fewer AEs of cognitive impairment reported in the LCZ696group compared to the valsartan group (narrow SMQ (Dementia): 1.28% vs 1.83%, respectively; broad SMQ (Dementia): 5.25% vs 5.83% respectively). These results are further supported by the incidence of cognitive impairment reported as SAEs (narrow SMQ: 0.21% vs 0.25% respectively; broad SMQ: 1.24% vs 1.50%, respectively) or those that cause permanent discontinuation of study drug (narrow SMQ: 0.04% vs 0.25% respectively; broad SMQ: 0.25% vs 0.54% respectively), which were numerically lower in the LCZ696 group compared to the valsartan group, respectively. The pediatric population is expected to be less exposed to this potential risk. No case related to cognitive impairment were reported in the LCZ696 arm of the pediatric study CLCZ696B2319. Study CLCZ696B2320 (Interventional PASS), in adults demonstrated that LCZ696 does not lead to a significant decrease in cognitive function compared to valsartan, as assessed up to 3 years using the CogState comprehensive battery of neuropsychological tests, which include a longitudinal evaluation of key cognitive domains such as memory, executive function, and attention. There was no significant treatment difference between LCZ696 and valsartan at Month 36 from baseline in change in CogState GCCS ($p > 0.05$, left boundary of 95% CI for Cohen's $D > -0.3$), confirming that changes in cognitive function were comparable in patients in the 2 treatment groups. LCZ696 did not lead to significant changes compared to valsartan over 3 years in performing activities of daily living and to function independently, as assessed using Functional activities questionnaire (FAQs). In addition, LCZ696 did not lead to a significant increase in Aβ deposition in the brain compared to valsartan over 3 years, confirmed by analysis of Aβ accumulation using florbetapir (^{18}F) PET imaging. Cognitive impairment-related AEs ('cognitive impairment' narrow SMQ: dementia) in this study were reported for 1 patient each in the LCZ696 group (EAIR: 0.118 per 100 patient-years) and the valsartan group (EAIR: 0.121 per 100 patient-years) and both were events of Alzheimer's type dementia. However, the event in the LCZ696 arm was non-serious, moderate in severity and did not lead to permanent discontinuation of study treatment whereas the event in valsartan arm was serious, severe and led to permanent discontinuation of study treatment. Also, cognitive impairment-related AEs ('cognitive impairment' broad SMQ were reported in a lower proportion of patients in the LCZ696 arm compared with the valsartan arm (3.73% vs. 6.73%). Post-marketing data is consistent with the clinical trial data with no new safety finding.
Risk factors and risk groups	Unknown
Preventability	Unknown

Cognitive impairment	Details
Impact on the benefit-risk balance of the product	Currently there is no clinical evidence to suggest a causal association between LCZ696 and cognitive impairment. Hence, the impact of this risk in this benefit-risk balance is deemed low.
Public health impact	The impact on public health is linked to the likely low impact on the individual patient.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 8-9 Missing information: Long term use of LCZ696 in HF patients

Long term use of LCZ696 in HF patients	Details
Evidence source	Population in need of further characterization: CLCZ696B2317, a Phase 3b, multicenter and single-arm study was conducted to continue to evaluate the safety and tolerability of LCZ696 in adult HF patients with reduced EF as an open-label follow-up, to the completed Study PARADIGM-HF (CLCZ696B2314). Anticipated risk/consequence of the missing information: LCZ696 was safe and well tolerated over long-term use and the overall safety profile was similar between patients who had previously received either LCZ696 or Enalapril in PARADIGM-HF. The incidence of angioedema remains low and appears to be unchanged over long-term use of LCZ696. Based on the results presented, the benefit risk profile of LCZ696 after long-term use remains positive.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risk	Embryo-fetal toxicity/lethality
Important potential risks	Neonatal/infantile toxicity through exposure from breast milk Cognitive impairment
Missing information	Long term use of LCZ696 in HF patients

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific AE follow-up checklist will be used to collect additional data to help further characterize and/or closely monitor the safety concern specified below. Targeted follow-ups with specific checklist are applicable only for serious adverse events for the risk mentioned below:

- Cognitive impairment

Other forms of routine pharmacovigilance activities:

Not applicable.

10.2 Part III.2. Additional pharmacovigilance activities

None.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
None.				
Category 3 - Required additional pharmacovigilance activities				

11 Part IV: Plans for post-authorization efficacy studies

None.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risk	
Embryo-fetal toxicity/lethality	**Routine risk communication:** The routine risk minimization measures are addressed in the SmPC in the following sections: Section 4.3 and 4.6 **PL:** Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** Prescription only medicine. Medicinal product subject to restricted medical prescription.
Important Potential risks	
Neonatal/infantile toxicity through exposure from breast milk	**Routine risk communication:** The routine risk minimization measures are addressed in the SmPC in the following section: Section 4.6 **PL:** Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** Prescription only medicine. Medicinal product subject to restricted medical prescription.
Cognitive impairment	**Routine risk communication:** The SmPC mentions the relevant findings from clinical and preclinical studies: Section 5.1 and 5.3 **PL:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** Prescription only medicine. Medicinal product subject to restricted medical prescription.
Missing information	
Long term use of LCZ696 in HF patients	**Routine risk communication:** Currently available data do not support the need for risk minimization for long-term use in HF patients. Should routine pharmacovigilance activities uncover additional data; any significant safety concern will be communicated through the IB, and SmPC and additional risk minimization activities may be proposed if necessary. **PL:** None

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** Prescription only medicine. Medicinal product subject to restricted medical prescription.

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Embryo-fetal toxicity/lethality	Routine risk minimization measures: The routine risk minimization measures are addressed in the SmPC in the following sections: Section 4.3 and 4.6 PL: Section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risks		
Neonatal/infantile toxicity through exposure from breast milk	Routine risk minimization measures: The routine risk minimization measures are addressed in the SmPC in the following sections: Section 4.6 PL: Section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Cognitive impairment	Routine risk minimization measures: The routine risk minimization measures are addressed in the SmPC in the following sections: Section 5.1 and 5.3 PL: None. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities: None
Missing information		
Long term use of LCZ696 in HF patients	Routine risk minimization measures: None. Additional risk minimization	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	measures: None	Additional pharmacovigilance activities: None.

13 Part VI: Summary of the risk management plan for Entresto®, Neparvis® (sacubitril/valsartan)

This is a summary of the risk management plan (RMP) for Entresto. The RMP details important risks of Entresto, how these risks can be minimized, and how more information will be obtained about Entresto's risks and uncertainties (missing information).

Entresto's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Entresto should be used.

This summary of the RMP for Entresto should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Entresto's RMP.

13.1 Part VI: I. The medicine and what it is used for

Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction and in children and adolescents patients aged one year and older with symptomatic chronic heart failure with left ventricular systolic dysfunction (see SmPC for the full indication). It contains sacubitril and valsartan as the active substances and it is given orally.

Further information about the evaluation of Entresto's benefits can be found in Entresto's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link: https://www.ema.europa.eu/en/medicines/human/EPAR/entresto

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Entresto, together with measures to minimize such risks and the proposed studies for learning more about Entresto's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Entresto, these measures are supplemented with additional *risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Entresto are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Entresto. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risk	Embryo-fetal toxicity/lethality
Important potential risks	Neonatal/infantile toxicity through exposure from breast milk Cognitive impairment
Missing information	Long term use of LCZ696 in HF patients

13.2.2 Part VI: II.B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 13-2 Important identified risk Embryo-fetal toxicity/lethality

Evidence for linking the risk to the medicine	Current evidence is based on the mechanistic plausibility and pre-clinical findings.
Risk factors and risk groups	Women of childbearing potential. Exposure to ACEI, folic acid deficiency, advanced maternal age.
Risk minimization measures	**Routine risk minimization measures** To communicate the risk of teratogenicity, embryo-fetotoxicity and embryo-fetal lethality, protect unborn children from exposure to LCZ696. SmPC: Section 4.3 and 4.6. PL: Section 2 **Additional risk minimization measures** None

Table 13-3 Important potential risk Neonatal/infantile toxicity through exposure from breast milk

Evidence for linking the risk to the medicine	Currently, there is no evidence to support the existence of this risk. In pre-clinical study, sacubitril and valsartan were excreted in the milk of lactating rats. However, it is not known whether LCZ696 is excreted in human milk.
Risk factors and risk groups	Breast fed infants of women taking LCZ696. No events related to neonatal/infantile toxicity through exposure from breast milk have been reported in the HF or hypertension clinical studies.

Risk minimization measures	**Routine risk minimization measures** To communicate the potential risk of ADRs in breastfed newborns/infants. SmPC: Section 4.6 PL: Section 2 **Additional risk minimization measures** None

Table 13-4 Important potential risk Cognitive impairment

Evidence for linking the risk to the medicine	In preclinical studies, Entresto had an effect on CSF amyloid-β clearance, increasing CSF amyloid-β in young cynomolgus monkeys treated with Entresto 50 mg/kg/day for two weeks. A healthy volunteer study showed that Entresto had no significant effect on CSF levels of the amyloid-β species 1-42 or 1-40, compared with placebo, whereas a 42% increase in CSF AUEC0-36h of soluble amyloid-β 1-38 was observed, compared with placebo. The clinical relevance of increased CSF levels of amyloid-β 1-38 is unknown but is considered unlikely to be associated with toxicity. Clinical studies CLCZ696B2314 and CLCZ696D2301 and PASS CLCZ696B2320 studies showed no evidence of increased risk of cognitive impairment with Entresto. Post-marketing data was consistent with the CT data.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures** To convey the relevant findings from clinical and preclinical studies. SmPC: Section 5.1 and 5.3 PL: None. **Additional risk minimization measures** None

Table 13-5 Missing information Long term use of LCZ696 in HF patients

Risk minimization measures	**Routine risk minimization measures** Currently available data do not support the need for risk minimization for long-term use in HF patients. **Additional risk minimization measures** None

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Entresto.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-6 Other studies in the post-authorization development plan

There are no studies required for Entresto.

Annex 4 - Specific adverse drug reaction follow-up forms

Cognitive impairment

Targeted Follow-up Checklist sacubitril/valsartan: Dementia-related events (Version 2.1/ Sep-2020)

1. Family and medical history			
1A	Is there a relevant medical history of dementia?	No Unknown Yes, please specify: …	
1B	Is there a family history of dementia?	No Unknown Yes, please specify: …	
2. Action with current treatment			
2A	For the current event, **was treatment with valsartan/sacubitril discontinued?**		
	No Unknown Yes – please go to Question 2B		
	2B	If Yes, did the symptoms resolve when valsartan/sacubitril was discontinued?	
		No Unknown Yes	
3. Event details			
3A	For the current event, **did the patient experience any of the following signs and/or symptoms?**		
	Yes, please, check all that apply:		
	3B	Cognitive disorder Confusional state Disorientation Impaired reasoning Memory impairment	
	No – please go to Question 3C		
3C	**Was the diagnosis of Dementia established?**		
	No – no need to further complete the questionnaire Yes – please, go to Question 3D		
	3D	If yes, please **specify who made the diagnosis**:	
		Diagnosis was made by a **Physician**:	Psychiatrist Neurologist Geriatrician Other, please specify: …
		Diagnosis was made by a **Non-physician**:	Psychologist Nurse practitioner Other, please specify: …
	3E	Can the person who established the diagnosis be	No Yes, please provide contact
		Name:	Contact:
	3F	**When was the diagnosis of Dementia established**? Date (d/ M/ yyyy): .... /….. . /……	
	3G	Please, **provide the primary diagnostic classification**:	
		Probable Alzheimer's disease Possible Alzheimer's disease Vascular dementia Lewy Body Parkinson's disease Pick's disease Frontal lobe dementia	
	The following questions only need to be completed if the diagnosis of Dementia was established.		

	4A	Was the patient **assessed using cognitive tests** to support the diagnosis?				
		No Yes, please provide the results:				
			Test	*Date (d/ M/*	*Result abnormal?*	*If abnormal, please specify the results*
		4B	Global Deterioration Scale:	.. / .. .. .. /	No Yes	…
		4C	Neuropsychiatric Inventory	.. / .. .. .. /	No Yes	…
		4D	Cognitive battery	.. / .. .. .. /	No Yes	…
		4E	ADAS cognitive behavior	.. / .. .. .. /	No Yes	…
		4F	Activities of daily living inventory	.. / .. .. .. /	No Yes	…
		4G	Clinical dementia rating	.. / .. .. .. /	No Yes	…
		4H	Other, please specify: …….	.. / .. .. .. /	No Yes	…
	4I	Was the patient **assessed using cerebral imaging** to support the diagnosis?				
		☐ No ☐ Yes, please provide the results:				
			Test	*Date (d/ M/*	*Result abnormal?*	*If abnormal, please specify the results*
		4J	☐ Magnetic resonance imaging	.. / .. .. .. /	No Yes	…
		4K	Positron emission tomography	.. / .. .. .. /	No Yes	…
		4L	Other, please specify:	.. / .. .. .. /	No Yes	…

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.