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.

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.

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*.

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 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hypotension Renal impairment Hyperkalemia Angioedema Embryo-fetal toxicity/lethality
Important potential risks	Neonatal/infantile toxicity through exposure from breast milk Hepatotoxicity Cognitive impairment Statin drug-drug interaction Long -term effects on growth, bone growth and mineralisation in the pediatric population
Missing information	Long term use of LCZ696 in HF patients Use in ACEI/ARB naïve HF patients

II.B: Summary of important risks

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

Table 2 Important identified risk Hypotension

Evidence for linking the risk to the medicine	Current evidence is based on adult (CLCZ696B2314) and pediatric (CLCZ696B2319) HF studies and mechanistic plausibility. The Entresto post-marketing data is consistent with the aforementioned information.

Risk factors and risk groups	Hypotension is most likely to occur in patients in whom the BP is highly dependent on Angiotensin II, including those with sodium or volume depletion (e.g., with diuretics). Concomitant use of aliskiren-containing products with LCZ696 in patients with diabetes is contraindicated because of the associated increased risks of hyperkalemia, renal impairment and hypotension with the combination of RAAS agents with aliskiren in this population. PDE-5 inhibitors such as sildenafil may have a more than additive effect of lowering blood pressure.
Risk minimization measures	**Routine risk minimization measures** To communicate the risk of hypotension and to reduce the risk of clinically significant hypotension. SmPC: Section 4.2, 4.4, 4.5, 4.8 and 4.9 **PL:** Sections 2, 3 and 4 **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2014: Non-interventional post-authorization European database safety study (Category 3).

Table 3 Important identified risk Renal impairment

Evidence for linking the risk to the medicine	Current evidence is based on adult (CLCZ696B2314) and pediatric (CLCZ696B2319) HF studies and mechanistic plausibility. The Entresto post-marketing data is consistent with the aforementioned information.
Risk factors and risk groups	Patients at greatest risk for renal impairment are those with CKD, those in whom the BP is highly dependent on Angiotensin II, including those with sodium or volume depletion (e.g., with diuretics), renovascular hypertension, and patients with bilateral renal artery stenosis or those treated with another RAAS agent. Concomitant use of aliskiren-containing products with LCZ696 in patients with diabetes mellitus is contraindicated because of the risk of renal impairment. Caution is required in patients under dual RAAS agent treatment.
Risk minimization measures	**Routine risk minimization measures** To communicate the risk of renal impairment and to reduce the risk of clinically significant renal impairment. SmPC: Section 4.2, 4.4, 4.5 and 4.8. PL: Sections 2, 3 and 4 **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2014: Non-interventional post-authorization European database safety study (Category 3).

Table 4 Important identified risk Hyperkalemia

Evidence for linking the risk to the medicine	Current evidence is based on adult (CLCZ696B2314) and pediatric (CLCZ696B2319) HF studies and mechanistic plausibility. The Entresto post-marketing data is consistent with the aforementioned information.
Risk factors and risk groups	Patients with severe renal impairment are more at risk for hyperkalemia. Furthermore, patients using potassium-sparing concomitant medications, mineral-corticoid antagonists, potassium supplements, or salt substitutes containing potassium are also at a higher risk for hyperkalemia.
Risk minimization measures	**Routine risk minimization measures** To communicate the risk of hyperkalemia and to reduce the risk of clinically significant hyperkalemia. SmPC: Section 4.2, 4.4, 4.5 and 4.8. PL: Sections 2, 3 and 4 **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2014: Non-interventional post-authorization European database safety study (Category 3).

Table 5 Important identified risk Angioedema

Evidence for linking the risk to the medicine	Current evidence is based on adult (CLCZ696B2314) and pediatric (CLCZ696B2319) HF studies and CLCZ696B2013 (US PMR, NIS) studies and mechanistic plausibility. The Entresto post-marketing data is consistent with the aforementioned information.
Risk factors and risk groups	A past medical history of angioedema and concomitant use of ACE inhibitors are considered to be risk factors for developing angioedema during LCZ696 treatment. African Americans are known to be at higher risk for ACE inhibitor induced angioedema as well as smokers. A history of seasonal allergies, antihistamine use, or corticosteroid use is associated with an increased risk of ACE inhibitor–associated angioedema. Smokers and former smokers are at increased risk of ACE inhibitor–associated angioedema, whereas patients with type 2 diabetes mellitus are at decreased risk. Immunosuppressant use, rheumatoid arthritis, and history of transplant have been associated with an increased risk of ACE inhibitor–associated angioedema.

Risk minimization measures	**Routine risk minimization measures** To communicate the risk of angioedema and to reduce the risk of clinically significant angioedema. SmPC: Section 4.2, 4.3, 4.4, 4.5 and 4.8. PL: Sections 2 and 4 **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2014: Non-interventional post-authorization European database safety study (Category 3)

Table 6 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 7 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 8 Important potential risk Hepatotoxicity

Evidence for linking the risk to the medicine	The available current body of evidence (CT and post-marketing data) do not establish a potential causal association between Entresto and hepatotoxicity.
Risk factors and risk groups	Pre- existing liver conditions (metabolic, infectious, traumatic, neoplastic, immune-mediated, congenital, drug-mediated, alcohol-related) are all risk factors for liver toxicity. In clinical trials in patients with HF, the number of patients developing liver enzyme abnormalities and/or AEs during LCZ696 treatment was too small to identify risk factors. Heart failure in itself is a known risk factor for liver function abnormalities
Risk minimization measures	**Routine risk minimization measures** To communicate the risk of hepatotoxicity from LCZ696 use, especially in patients with hepatic impairment. SmPC: Section 4.2, 4.3, 4.5 and 5.2 PL: Sections 2 and 4 **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2014: Non-interventional post-authorization European database safety study (Category 3).

Table 9 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 10 Important potential risk Statin drug-drug interaction

Evidence for linking the risk to the medicine	The evidence of Entresto-statin DDI was from non-clinical studies, Study CLCZ696B2115, Study LCZ696B2314, and post-marketing data. Current cumulative data is not adequate to suggest a definitive interaction with concurrent Entresto and statin therapy leading to rhabdomyolysis. Additionally, no DDI has been observed with simvastatin in the dedicated DDI study.
Risk factors and risk groups	Patients with history of alcohol use, drug abuse, heat stroke, infections, trauma, metabolic disorders, strenuous activities and inflammatory myopathies are at increased risk of rhabdomyolysis. Patients with concomitant exposure to statins and sacubitril/valsartan.
Risk minimization measures	**Routine risk minimization measures** To warn about the risks associated with concomitant use of LCZ696 and statins. SmPC: Section 4.5. PL: Section 2 **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2015: Non-interventional post-authorization European database safety study (Category 3).

Table 11 Important potential risk Long-term effects on growth, bone growth and mineralisation in the pediatric population

Evidence for linking the risk to the medicine	Juvenile toxicity studies in rats showed reversible and transient reductions in body weight gain, bone length and bone mineral density, most prevalent on day 21 (corresponding to ~2 years of age in humans) and coinciding with times of highest exposure to sacubitril/LBQ657 and decreased body weight changes. No evidence of compound-related increase in bone resorption, microscopic bone changes, or changes in intrinsic bone strength was observed. In the 52-week pediatric HF study CLCZ696B2319 (PANORAMA-HF), there were 2 events each in sacubitril/valsartan and enalapril and the exposure-adjusted incidence rate of these AEs was similar in the sacubitril/valsartan and enalapril groups (1.080 (95% CI: 0.131, 3.901) vs. 1.116 (95% CI: 0.135, 4.031) per 100 patient-years). None of the events were drug-related or led to permanent discontinuation of study treatment. Mean change from baseline to week 52 in height and height z-score were comparable overall and across all three age groups.

Risk factors and risk groups	Heart Failure, nutrition, congenital disorders, genetic factors, race, physical activity, prematurity, steroid use.
Risk minimization measures	**Routine risk minimization measures:** To convey the relevant findings from preclinical and clinical studies. SmPC: 5.3 **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2319E1 (EU PASS Category 3): Multicenter, interventional study to evaluate long-term safety and tolerability of open-label sacubitril/valsartan in pediatric patients with HF.

Table 12 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

Table 13 Missing information Use in ACEI/ARB naïve HF patients

Risk minimization measures	**Routine risk minimization measures** To recommend caution by using a lower starting dose of LCZ696 when treating ACEI/ARB naive HF patients due to limited experience in clinical trials. SmPC: Section 4.2. PL: None. **Additional risk minimization measures** None
Additional pharmacovigilance activities	CLCZ696B2014: Non-interventional post-authorization European database safety study (Category 3).

II.C: Post-authorization development plan

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.

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

Table 14 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CLCZ696B2014	To further characterize specific safety outcomes (angioedema, hypotension, hyperkalemia, renal impairment, hepatotoxicity) in HF patients newly starting treatment with LCZ696 (regardless of prior use of ACEIs or ARBs) under real conditions.
CLCZ696B2015	To assess the risk of statin-related events associated with concomitant exposure to LCZ696 and statins compared to statin exposure alone in HF patients.
CLCZ696B2319E1	To evaluate long- term safety and tolerability of sacubitril/valsartan in pediatric HF subjects receiving open-label sacubitril/valsartan.