Regulatory Affairs

Drug generic name

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	*Sacubitril/valsartan*
Product(s) concerned (brand name(s)):	*Entresto®*
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Entresto® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Entresto® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Entresto®.

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Summary of the risk management plan for Entresto®
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, all 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 to reduce the risk of cardiovascular mortality and morbidity in adult patients with symptomatic chronic heart failure (CHF) with reduced ejection fraction (HFrEF). (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 as 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 analyzed, 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	
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
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 CLCZ696B2314 study and the 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 CLCZ696B2314 study and the 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 CLCZ696B2314 study and the 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 CLCZ696B2314 study and the 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 (Kostis JB et al 2005). 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 (Kostis WJ et al 2018).
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) CLCZ696B2013: Non-interventional US PMR database study.

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 preclinical 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
Additional pharmacovigilance activities	None

Table 7: Important identified 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
Additional pharmacovigilance activities	None

Table 8: Important identified 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 identified 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. In clinical study CLCZ696D2301, 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 sacubitril/valsartan and valsartan groups. Adding to the strength of evidence are studies CLCZ696B2314 and CLCZ696D2301, where the incidence of cognitive issues was similar between exposed to Entresto and unexposed. In

	addition, in study CLCZ696D2301 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 sacubitril/valsartan and valsartan groups.
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
Additional pharmacovigilance activities	Multicenter, randomized, double-blind, active-controlled study CLCZ696B2320 (PERSPECTIVE) (Category 3)

Table 10: Important identified 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: Missing information: Long term use of LCZ696 in HF patients	
Evidence for linking the risk to the medicine	**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 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.
Risk factors and risk groups	Patients with long term exposure (> 5 years) to treatment with Entresto.
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
Additional pharmacovigilance activities	CLCZ696B2015: Non-interventional post-authorization European database safety study (Category 3).

Table 12: Missing information: Use in ACEI/ARB-naive HF patients	
Evidence for linking the risk to the medicine	**Population in need of further characterization:** Clinical studies supporting the approval of LCZ696 mainly included patients who were previously receiving either an ACEI or ARB, as this is standard of care for HF patients. There are over 760 ACEI/ARB-naive patients in the 4 studies [33 in study CLCZ696B2314, 459 in CLCZ696BUS01, 241 in CLCZ696B2401 and 33 in CLCZ696B2228 study]. **Anticipated risk/consequence of the missing information:** No new safety findings were found during clinical development program that can alter the characterization of missing information of 'Use in ACEI/ARB-naive patients'. The available cumulative data does not suggest a change to the benefit-risk for Entresto.
Risk factors and risk groups	Clinical studies supporting the approval of Entresto mainly included patients who were previously receiving either an ACEI or ARB, as this is standard of care for HF patients. There were only few ACEI/ARB-naive patients of HFrEF in the clinical program, which constitutes the risk group
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 13: Other studies in post-authorization development plan

Study short name	Rationale and study objectives
PERSPECTIVE (CLCZ696B2320)	To evaluate the effects of LCZ696 compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and brain amyloid plaque deposition as assessed by PET imaging in patients with chronic heart failure with preserved ejection fraction.
CLCZ696B2013 – US PMR	To assess the risk of serious angioedema in association with sacubitril/valsartan use in Black heart failure patients in the United States.
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.