NOVARTIS

Regulatory Affairs

Entresto

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Sacubitril/Valsartan
Product(s) concerned (brand name(s)):	Entresto®
Document status:	Final
Version number of the RMP Public Summary:	9.0
Date of final sign off of the RMP Public Summary	28-04-2025

Template version 2.2 Sep 2023

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”.

Table of contents

Summary of the risk management plan for Entresto (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, 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 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	
Important identified risks	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

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 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 embryofetal lethality, protect unborn children from exposure to LCZ696. SmPC: Section 4.3 and 4.6. PL: Section 2 **Additional risk minimization measures** None

Table 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 preclinical 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 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 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

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

There are no studies required for Entresto.