NOVARTIS

Drug Regulatory Affairs

Entresto

50 mg, 100 mg and 200 mg film-coated tablets

Summary of the Risk Management Plan (RMP) for Entresto® (sacubitril/valsartan)

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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 minimize 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“ 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“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Entresto®

Overview of disease epidemiology

Chronic heart failure (HF) is a complex disease that can result from any structural or functional heart disorder which weakens the heart’s ability to pump blood sufficiently to maintain blood flow and meet the needs of the body. When this happens, blood does not move efficiently through the circulatory system and starts to back up, raising the pressure in the blood vessels and forcing fluid from the blood vessels into body tissues. The disease is characterized by signs and symptoms such as shortness of breath, severe tiredness or fatigue, and swelling of the legs/ankles.

HF is an important public health problem. In 2004, there were an estimated 5.7 million new cases of heart failure worldwide. Twenty percent of subjects aged 40 years of age and older will develop heart failure later in life. An estimated 15 million patients suffer from heart failure in the European Union (EU). But, it is mainly a disease of the elderly affecting about 10% of men and 8% of women aged 60 years and older. In the EU, 1.8 million patients are hospitalized each year due to a sudden sign of heart failure, and up to 22% of them will need to be re-hospitalized for a similar event. Of the 15 million patients in the EU suffering from heart failure, close to 50% are expected to die within 5 years after their first hospital admission due to heart failure.

There are various diseases and life-style reasons which can increase the risk of developing heart failure. The most important ones are listed below:

- High blood pressure (hypertension)
- Coronary heart disease (disease of the heart caused by the blockage of the blood vessels that supply blood to the heart muscle, which includes chest pain or previous heart attack)
- Diabetes

- Diseases of the heart valves
- Overweight (obesity)
- Smoking
- Low physical activity

There are two different types of HF: **HF due to reduced ejection fraction** (HFrEF) also known as HF due to non-working of the left ventricular systolic or **systolic heart failure**, which occurs when the heart muscle doesn't contract with enough force, so there is less oxygen-rich blood that is pumped throughout the body; and **HF with preserved ejection fraction** (HFpEF) also known as **diastolic heart failure**, which occurs when the heart contracts normally, but the ventricles do not relax properly or are hard, and less blood enters the heart during normal filling. The diagnosis has to be made by an experienced doctor.

Summary of treatment benefits

Entresto® is used to treat HFrEF in adults. The main clinical study PARADIGM-HF (CLCZ696B2314) was a randomized (assigned to a group by chance), double-blind (both researchers and the participants in the clinical study did not know what drug the participant was receiving), international study of 8442 patients with HF. It compared how well the treatment worked, safety and tolerability of Entresto® to enalapril, another type of medicine used to treat HF called angiotensin converting enzyme inhibitor. The results of PARADIGM-HF proved that Entresto® reduced the risk of dying from cardiovascular (CV) reasons and the risk of being hospitalized due to HF more than enalapril. Entresto® also reduced the risk of dying from any reason and was found to be better than enalapril in reducing the symptoms and physical limitations of HF, and slowing disease progression.

Unknowns relating to treatment benefits

In the main clinical study (PARADIGM-HF), the majority of the patients were at least 64 years of age and 19% were 75 years of age or older. There are few data related to treatment benefits of Entresto® in patients with severe kidney function damage, severe liver function damage and in children.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Low blood pressure (Hypotension)	Experiencing symptoms of low blood pressure is very common, occurring in more than 1 out of 10 patients treated with Entresto®.	Initially dose adjustment of drugs taken together with Entresto® should be considered and treatment of other causes of low blood pressure (e.g. low body fluid volume) should be considered. If low blood pressure continues despite such measures, reduce the dose or stop Entresto® for a short period of time.
Kidneys do not work	Use of Entresto® may	Lowering the dose of Entresto® should be

Risk	What is known	Preventability
properly (Renal impairment)	be associated with reduced working of the kidneys. Reductions in the working of kidneys is very common, occurring in more than 1 out of 10 patients treated with Entresto®.	considered in patients who develop a notable reduction in the working of kidneys. Patients with severe renal impairment with eGFR <10 ml/minute/1.73 m^2 should not take Entresto®. HF patients with diabetes or those with moderate to severe reduction in the working of kidney should not take Entresto® along with aliskiren.
High level of potassium in the blood (Hyperkalemia)	Use of Entresto® may be associated with an increased risk of high level of potassium in the blood. High potassium levels in the blood is very common, occurring in more than 1 out of 10 patients treated with Entresto®.	Medicinal products known to increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used carefully when taking along with Entresto®. In case of increased blood levels of potassium, consideration should be given to adjustment of medications taken at the same time, measures such as reducing the amount of potassium included in food or to reduce the dose of Entresto® for a short period of time. Regular checking of serum potassium is recommended, especially in patients who have risk factors as severe reduction in the working of kidneys, diabetes or who are on a high potassium diet.
Swelling mainly of the face, lips, tongue and/or throat (Angioedema)	Entresto® may result in increased allergic reaction like swelling mainly of the face, lips, tongue and/or throat. These reactions are uncommon, occurring in less than 1 out of 100 patients treated with Entresto®. These allergic reactions occurring in the windpipe may lead to death if prompt treatment is not taken. Black patients may have increased likelihood to develop angioedema.	Entresto® must not be taken along with another type of medicine called ACE inhibitors (for example enalapril, lisinopril, ramipril) which are used to treat high blood pressure or heart failure. Patients taking an ACE inhibitor must wait for at least 36 hours after taking the last dose before starting to take Entresto®. Patients who stop taking Entresto® must wait 36 hours after taking the last dose before starting an ACE inhibitor. Entresto® must not be taken by patients with a known history of angioedema related to previous ACE inhibitor or Angiotensin Receptor Blocker (ARB) therapy. Entresto® should be used with special care in patients with a known history of angioedema. If angioedema occurs, Entresto® should be immediately stopped and the patient should be treated immediately. Entresto® should not be taken again.
Harm to unborn babies and fetal death when	In animal, Entresto® has caused serious	Women who can become pregnant must use contraception that works very well during treatment

Risk	What is known	Preventability
used during pregnancy (Embryo-fetal and infantile toxicity/lethality)	permanent harm including death of the unborn babies in the womb. There have been reports of injury to the unborn baby when pregnant women have taken valsartan (one of the active component of Entresto®).	and for one week after their last dose of Entresto®. Entresto® must not be used during pregnancy. If a woman has become pregnant during therapy, Entresto® should be stopped as soon as possible.

Important potential risks

Risk	What is known
Harm to new born babies and to infants who are breast fed by mothers taking Entresto	In animal studies, normal growth and survival of new born animals was affected when the mother was given the active substances in Entresto®.
Liver injury (Hepatotoxicity)	Very limited liver metabolism (i.e. breakdown by the liver) of individual components of Entresto®, sacubitril and valsartan, suggests a low risk of liver injury. Animal studies also do not raise concerns with respect to liver damaging potential for Entresto® or its active components. Data from clinical studies do not suggest the possibility for Entresto® to harm the liver.
Increased levels of statin drugs in the body when taken along with Entresto® (Statin Drug-drug interaction)	Entresto® may increase the exposure of statins drugs in the body. Statins are used to lower high cholesterol levels (e.g. atorvastatin). Therefore special care should be used when taking Entresto® along with statin drugs.
Change in mental abilities (Cognitive impairment)	In the target patient population of elderly patients with chronic heart failure, it is known that decrease in mental abilities occurs quite frequently. Currently, it is unknown if treatment with Entresto® would have an effect on the onset of a decrease in mental abilities, and if so, by how much.

Missing information

Risk	What is known
Use in children (Pediatric patients)	Patients younger than 18 years have not been studied with Entresto®; therefore use in these patients is not recommended at this time.
Patients with severely decreased functioning of the kidneys (Patients with severe renal impairment)	There are few data in HF patients with severely decreased functioning of the kidneys, therefore special care is recommended when using Entresto® in these patients and periodic checks of the functioning of the kidney is suggested. Entresto® is contraindicated in patients with severe renal impairment with eGFR <10 ml/minute/1.73 m^2.
Patients with severely decreased functioning of the liver	No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification), biliary

Risk	What is known
(Patients with severe hepatic impairment)	cirrhosis or cholestasis so how well the treatment works, and safety in these patients are unknown. The use of Entresto® is not suggested in these patients.
Patients who have not previously used an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) (use in ACEI/ARB naïve patients)	Only a few patients with heart failure (about 75) who had not previously used ACE inhibitor or ARB class of medicines were included in studies on Entresto. The safety and tolerability of Entresto in these patients were generally similar to other patients treated with Entresto.

Summary of risk minimization activities by safety concern

All medicines have a Product Information which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. A shortened version of this information in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measure.

This medicine has no additional risk minimization measures like educational materials.

Post authorization development plan

List of studies in post authorization development plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
Multicenter, randomized, double-blind, active-controlled study (CLCZ696B2320)	To evaluate the effects of Entresto® 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	Cognitive impairment	Planned	Planned March 2022 (Final report submission)
Cognitive function assessment in study CLCZ696D2301	To evaluate cognitive function in patients with chronic heart	Cognitive impairment	Started	Planned March 2020 (final report)

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
(PARAGON HF study)	failure with preserved ejection			
Non-interventional post-authorization European database safety study	To further characterise specific safety outcomes (angioedema, hypotension, hyperkalaemia, renal impairment, hepatotoxicity) in heart failure patients newly starting treatment with Entresto (regardless of prior use of ACE inhibitors or ARBs)	Angioedema Use in patients who have previously been treated with either an ACE inhibitor or an ARB Hypotension Hyperkalaemia Renal impairment Hepatotoxicity	Planned	Planned Q4 2022 (Final report submission)
Non-interventional post-authorization European database safety study	To assess the risk of statin-related events associated with concomitant use of Entresto and statins compared to statin alone in patients with heart failure	Statin drug-drug interaction	Planned	Planned Q2 2020 (Final report submission)
Observational US database study	To assess the risk of serious angioedema in association with Entresto use in black patients with heart failure in the United States	Angioedema in black patients in US	Planned	Planned Q3 2019 (final report)

Studies which are a condition of the marketing authorization

None.

Summary of changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in December 2016.