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Summary of the risk management plan (RMP) for Entresto (sacubitril/valsartan)

This is a summary of the risk management plan (RMP) for Entresto, which details the measures to be taken in order to ensure that Entresto is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Entresto, which can be found on Entresto's EPAR page.

Overview of disease epidemiology

Entresto is a medicine used to treat patients with chronic heart failure. Chronic heart failure is a complex disease that can result from weakened ability of the heart to pump sufficient blood to meet the needs of the body. When this happens, blood does not circulate efficiently and starts to back up, raising the pressure in the blood vessels and forcing fluid from the blood vessels into body tissues. The disease causes signs and symptoms such as shortness of breath, severe tiredness or fatigue, and swelling of the legs/ankles.

Heart failure is an important public health problem. In 2004, there were about 5.7 million new cases of heart failure worldwide. About 15 million patients suffer from heart failure in the European Union (EU) and close to 50% are expected to die within 5 years of their first hospital admission for heart failure. In the EU, 1.8 million patients are admitted to hospital each year due to heart failure, and up to 22% of them will need to be re-admitted. Heart failure is mainly a disease of the elderly, affecting about 10% of men and 8% of women aged over 60 years.

Entresto is used to treat *heart failure due to reduced ejection fraction* (also known as *systolic heart failure*), which occurs when the heart muscle does not contract forcefully enough to pump out enough blood for the body's needs.

Summary of treatment benefits

The active substances in Entresto are sacubitril and valsartan.

In the main study, Entresto was compared to enalapril, another medicine used for treating heart failure. Patients in the study had long-term heart failure with symptoms of the disease and reduced ejection fraction (the proportion of blood leaving the heart). In the group treated with Entresto, 21.8% (914 of 4,187) patients either died as a result of heart and circulation problems or were admitted to hospital with heart failure compared to 26.5% (1,117 of 4,212) patients treated with enalapril. In general, patients were monitored for about 27 months, during which they took the medicine for about 24 months on average. The study was stopped early because of compelling evidence that Entresto was more effective than enalapril.

Unknowns relating to treatment benefits

In the main clinical study, the majority of the patients were at least 64 years old and 19% were over 75 years old. There are few data on treatment benefits of Entresto in patients with severely reduced kidney function, severely reduced liver function and in children.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Low blood pressure (hypotension)	Symptoms of low blood pressure are very common, occurring in more than 1 out of 10 patients treated with Entresto.	Initially dose adjustment of medicines taken 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, doctors should reduce the dose of Entresto or stop it for a short period.
Kidneys do not work properly (renal impairment)	Use of Entresto may be associated with the kidneys working less well. Reduction in the working of kidneys is very common, occurring in more than 1 out of 10 patients taking Entresto.	Lowering the dose of Entresto should be considered in patients who develop important reduction in the working of kidneys. Patients with diabetes or those with moderate to severe reduction in the working of kidney should not take Entresto with aliskiren, a blood-pressure medicine.
High level of potassium in the blood (hyperkalaemia)	Use of Entresto may increase the level of potassium in the blood. A high potassium level in the blood is very common, occurring in more than 1 out of 10 patients treated with Entresto.	Medicines that increase potassium levels (e.g. potassium-sparing diuretics and potassium supplements) should be used carefully when taking Entresto. If blood levels of potassium increase, consideration should be given to adjusting medicines taken at the same time, taking measures such as reducing the amount of potassium in food or reducing the dose of Entresto for a short period. Regular checking of serum potassium is suggested, especially in patients who have risk factors such as severe reduction in the working of kidneys, diabetes or a high-potassium diet.
Rapid swelling of	Entresto may result in allergy-like	Entresto must not be taken with a type

Risk	What is known	Preventability
deeper skin tissues which can affect, for example the face, lips, and tongue and tissues around the throat, causing blockage of the windpipe (angioedema)	reaction with rapid swelling of deeper skin tissues including tissue in the face, lips and tongue. These reactions are uncommon, occurring in less than 1 out of 100 patients treated with Entresto. These reactions occurring in the windpipe may lead to death if prompt treatment is not given. Black patients have increased likelihood to develop angioedema.	of medicine called ACE inhibitors (for example enalapril, lisinopril and ramipril) which are used to treat high blood pressure or heart failure. These medicines can cause angioedema and their use with Entresto increases the risk. Patients taking an ACE inhibitor must not start taking Entresto for at least 36 hours after the last dose of an ACE inhibitor. Patients who stop Entresto must wait 36 hours after the last dose before starting an ACE inhibitor. Patients who have had angioedema while taking an ACE inhibitor or an angiotensin II receptor blocker must not take Entresto. Entresto should be used with special care in patients who have had angioedema. If angioedema occurs, the patient should be treated immediately. Entresto should not be taken again.
Harm to unborn babies and fetal death when used during pregnancy (embryo-fetal toxicity/lethality)	In animals, Entresto has caused serious permanent harm including death of 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).	Entresto should normally be stopped before pregnancy or as soon as pregnancy is discovered. The medicine is not recommended in early pregnancy and it must not be taken after the third month of pregnancy as it may cause serious harm to the baby.

Important potential risks

Risk	What is known
Harm to newborn babies and to infants who are breast-fed by mothers taking Entresto	In animal studies, normal growth and survival of newborn animals was affected when the mother was given the active substances in Entresto. Entresto is not recommended for mothers who are breastfeeding.
Liver injury (hepatotoxicity)	Very limited liver metabolism (i.e. breakdown by the liver) of individual active substances in Entresto, sacubitril and valsartan, suggests a low risk of liver injury. Animal studies also do not raise concerns about liver damage with Entresto. Data from clinical studies do not suggest the possibility of Entresto harming

Risk	What is known
	the liver.
Change in mental abilities (cognitive impairment)	In the target patient population of elderly patients with chronic heart failure, it is known that mental ability decreases quite frequently. It is not known if treatment with Entresto would have an effect on the onset of a decrease in mental abilities, and if so, by how much.
Increased levels of statin medicines in the body when taken with Entresto (statin drug-drug interaction)	Statins (e.g. atorvastatin and simvastatin) are used to lower high cholesterol levels. Entresto may increase the levels of statin medicines in the body, leading to side effects. Therefore, special care should be used when taking Entresto with statins.
Decrease in platelet count (thrombocytopenia)	Platelets play an important role in blood clotting. Entresto treatment may reduce the platelet count and thereby decrease the patient's ability to form blood clots and increase the risk of excessive bleeding.
Decrease in white blood cells (neutropenia)	Neutrophils, a type of white blood cells, are involved in defending the body from infections. Entresto treatment may decrease the neutrophil count in the blood.

Missing information

Risk	What is known
Use in children (paediatric patients)	Patients younger than 18 years have not been studied with Entresto; therefore use in these patients is not recommended.
Patients with severely reduced kidney function (patients with severe renal impairment)	There are few data on the use of Entresto in patients with severely decreased kidney function. Therefore, special care, with regular checks of the working of the kidneys, is recommended when using Entresto 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 minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Entresto can be found on Entresto's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
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 2017 or with the periodic safety update report in 2018 (1st interim report submission) Planned Q4 2022 (Final report submission)
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	Cognitive impairment	Planned	Planned March 2022 (Final report submission)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	chronic heart failure with preserved ejection fraction			
Cognitive function assessment in study CLCZ696D2301 (PARAGON HF study)	To evaluate cognitive function in patients with chronic heart failure with preserved ejection	Cognitive impairment	Started	Planned March 2020 (final report)
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 authorisation

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment

Not applicable.

This summary was last updated in 10-2015.