Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	Sacubitril/valsartan
Condition Full indication	Sacubitril/valsartan is indicated to reduce the risk of cardiovascular mortality and morbidity in adult patients with symptomatic heart failure and reduced ejection fraction.
Company	Novartis Pharmaceuticals UK Ltd
EAMS number	**00101/0002**

Introduction
The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to doctors who may wish to prescribe the unlicensed medicine under their own responsibility. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine. The General Medical Council's guidance on prescribing unlicensed medicines can be found here: http://www.gmc-uk.org/mobile/news/14327

What is Sacubitril/valsartan?
Sacubitril/valsartan is a fixed combination of the new chemical entity sacubitril and the angiotensin II receptor antagonist valsartan. It is available as immediate-release tablets in three different strengths: 50 mg, 100 mg and 200 mg.

What is Sacubitril/valsartan used to treat?
Sacubitril/valsartan is used to treat adult patients with symptomatic heart failure and reduced left ventricle ejection fraction (when the heart cannot pump blood adequately and the percentage of blood leaving the heart each time it contracts is lower than normal).

How is Sacubitril/valsartan used?
Treatment with Sacubitril/valsartan may start with 100 mg twice daily. However, for patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker, a lower starting dose of 50 mg twice daily is recommended. The same low starting dose of 50 mg twice daily should also be considered for patients previously taking low doses of an ACE inhibitor or an angiotensin II receptor blocker. The dose of sacubitril/valsartan may be doubled every 2 to 4 weeks up to the maximum dose of 200 mg twice daily, if the patient can tolerate it. Sacubitril/valsartan should not be taken together with an ACE inhibitor.

How does Sacubitril/valsartan work?
The valsartan component is a known angiotensin II receptor blocker which has been used for many years in the treatment of certain patients with heart failure. It reduces the actions of aldosterone in the body (a hormone produced in the adrenal glands) and acts on blood vessels and kidneys to help relieve the heart's workload. The sacubitril component has a new target. It increases the level of several naturally occurring peptides produced in the chambers of the heart which also act on blood vessels and kidneys but through different routes. The two drugs work together to open up blood vessels, decrease salt and water retention, and reduce the strain on the heart.

How has Sacubitril/valsartan been studied?
The effects of sacubitril/valsartan were studied in a large trial (PARADIGM-HF) that evaluated its efficacy and safety profile in 8,442 patients with heart failure and reduced ejection fraction. Sacubitril/valsartan was compared with enalapril (an established ACE inhibitor in the treatment of heart failure) with approximately half of the patients receiving one of the two treatments (in random order). Most patients received the study drugs for over 2 years. The main measures of effectiveness (how well the medicine worked) were the number of deaths from cardiovascular causes or hospitalizations (admissions to hospital) due to heart failure with sacubitril/valsartan compared to enalapril.

What benefits and risks has Sacubitril/valsartan shown during the studies?
Benefits
The PARADIGM-HF trial found that in the group of patients receiving sacubitril/valsartan the percentage of patients who either died from cardiovascular causes or were admitted to hospital because of their heart failure (21.8%) was significantly lower than in the group of patients who received enalapril (26.5%). Also in general fewer patients among those who received sacubitril/valsartan (17%) died from any cause compared with those who received enalapril (19.8%).

Risks
Sacubitril/valsartan may cause a significant drop in blood pressure (hypotension) which may result in dizziness, light-headedness or fainting. Older patients and those who already have low blood pressure are at higher risk of hypotension. Sacubitril/valsartan has also been associated with some impairment of kidney function and an increase in the level of potassium in the blood. It may be necessary to check the amount of potassium in blood at regular intervals. There is also a small risk of a serious allergic reaction called angioedema which causes swelling of the face, lips, tongue and/or throat and may lead to difficulties in breathing or swallowing. This requires immediate medical attention.

Why has Sacubitril/valsartan been given a positive Early Access to Medicine Scientific opinion?
Heart failure is a life threatening and debilitating chronic condition. Despite different available treatment options patients with heart failure, especially those with reduced ejection fraction, have a poor prognosis and admissions to hospital are common. Therefore, there is a significant need for more effective therapies that can prevent deaths and help patients have a more normal life out of hospital. Sacubitril/valsartan has been shown to reduce mortality and hospital admissions and the MHRA considered that it has the potential to offer significant benefits for patients with heart failure over current treatments.
With regard to the medicine's side effects, the most frequent were mild to moderate in severity and sacubitril/valsartan was generally well tolerated. The MHRA therefore concluded that, based on the current evidence, the benefits of sacubitril/valsartan in patients with symptomatic heart failure and reduced left ventricle ejection fraction are greater than its risks and eligible patients should be offered an early access to this new therapy.

What are the uncertainties?
The effects of sacubitril/valsartan were studied mostly in patients with heart failure who were treated with and were able to tolerate an ACE inhibitor or angiotensin II receptor blocker. There is limited experience in patients who had not previously received any of those two classes of medicines. Therefore, special attention is required when starting therapy with sacubitril/valsartan is such patients as there may be higher risk of side effects. Also there is some uncertainty about the long-term effects of sacubitril/valsartan during chronic use.

Are there on-going clinical studies?
Several studies are ongoing in different groups of patients. The largest ongoing study is evaluating the efficacy and safety of sacubitril/valsartan in patients with heart failure and preserved ejection fraction. Other studies are assessing the effect of sacubitril/valsartan in patients with hypertension.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that sacubitril/valsartan is used as safely as possible. Based on this plan, the company that makes sacubitril/valsartan must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including possible side effects and recommendations for preventing or minimising these side effects.
Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the Company to report adverse effects experienced by patients receiving sacubitril/valsartan through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the Company.
Patients in the Early Access to Medicines Scheme will also receive an alert card from their doctor summarising the important risks with the medicine. Patients should carry the card with them in case they need treatment or advice from a healthcare professional who is not familiar with sacubitril/valsartan treatment.

Other information about Sacubitril/valsartan – see EAMS Treatment Protocol