Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found
here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
http://www.gmc-uk.org/mobile/14327

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 prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Information for the healthcare professionals:

Sacubitril/valsartan 50 mg film-coated tablets
Sacubitril/valsartan 100 mg film-coated tablets
Sacubitril/valsartan 200 mg film-coated tablets

1 PATIENT POPULATION AND THERAPEUTIC 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 (see section 4).

2 INSTRUCTIONS FOR USE

The recommended starting dose of sacubitril/valsartan is 100 mg twice daily.

There is limited experience in patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB), therefore a starting dose of 50 mg twice daily is recommended when using sacubitril/valsartan in these patients. A starting dose of 50 mg twice daily should also be considered for patients previously taking low doses of ACE inhibitors or ARBs.

The dose of sacubitril/valsartan should be doubled every 2-4 weeks to the target dose of 200 mg twice daily, as tolerated by the patient (see section 6).

If a dose of sacubitril/valsartan is missed, the patient should take the next dose at the scheduled time.

Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, sacubitril/valsartan must not be started for at least 36 hours after discontinuing ACE inhibitor therapy (see section 2.1).

Sacubitril/valsartan should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of sacubitril/valsartan (see sections 31. and 3.2).

Patients with systolic blood pressure (SBP) <100 mmHg were not studied, therefore therapy should not be initiated until SBP is ≥100 mmHg (see section 3.1).

If patients experience tolerability issues (SBP ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medications, temporary down–titration or discontinuation of sacubitril/valsartan is recommended (see section 3.1).

Sacubitril/valsartan is intended for oral use and may be administered with or without food (see section 4).

Special populations

Elderly population
The dose should be in line with the renal function of the elderly patient.

Renal impairment
No dose adjustment is required in patients with mild or moderate (eGFR 30-90 ml/min/1.73 m^2) renal impairment. There is limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or end-stage renal disease. Therefore, caution is recommended when using sacubitil/valsaratan in these patients and a starting dose of 50 mg twice daily is recommended.

Hepatic impairment
No dose adjustment is required when administering sacubitil/valsaratan to patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in patients with moderate hepatic

impairment (Child-Pugh B classification) is 50 mg twice daily.

Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 1.1).

Paediatric population
The safety and efficacy of sacubitril/valsartan in paediatric patients aged below 18 years have not been established. No data are available.

2.1 Contraindications

- Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients listed in section 7.
- Concomitant use with ACE inhibitors (see sections 2, 3.1 and 3.2). Sacubitril/valsartan must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy (see section 6).
- Concomitant use with aliskiren-containing products in patients with diabetes mellitusor in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections 3.1 and 3.2).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see section 2).
- Pregnancy (see section 3.3).

3. SAFETY INFORMATION

3.1 Precautions for Use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

- The combination of sacubitril/valsartan with an ACE inhibitor is contra-indicated due to the increased risk of angioedema (see section 2.1). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 2, 2.1 and 3.2).

- The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 3.2). The combination of sacubitril/valsartan with aliskiren-containing products is contra-indicated in patients with type 2 diabetes or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections 2.1 and 3.2).

- Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing product (see sections 2 and 3.2).

Hypotension

Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Patients with SBP <100 mmHg were not studied (see section 4), therefore therapy should not be initiated until SBP is ≥100 mmHg. Hypotension adverse events occurred more frequently with sacubitril/valsartan (17.6%) than with enalapril (12.0%). When initiating therapy or during dose titration with sacubitril/valsartan, blood pressure should be monitored at an appropriate interval, in accordance with normal clinical practice. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended (see section 2). Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. Permanent discontinuation of therapy

is usually not required. Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with sacubitril/valsartan, however, such corrective action must be carefully weighed against the risk of volume overload.

Impaired renal function

Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension. There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2) including end-stage renal disease and these patients may be at greatest risk of hypotension (see section 2).

Worsening renal function

Use of sacubitril/valsartan may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs) (see section 3.2). Down-titration of sacubitril/valsartan should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalaemia

Use of sacubitril/valsartan may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists (see section 2). If patients experience clinically significant hyperkalaemia adjustment of concomitant medications, or temporary down–titration or discontinuation of sacubitril/valsartan is recommended. If serum potassium level is >5.4 mmol/l discontinuation of sacubitril/valsartan should be considered. In the clinical study PARADIGM-HF, the incidence of hyperkalaemia adverse events was 11.6% in the sacubitril/valsartan treated patients compared to 14% in the enalapril treated patients (see section 3.4).

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan. If angioedema occurs, sacubitril/valsartan should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Sacubitril/valsartan must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, e.g. adrenaline solution 1 mg/1 ml (0.3-0.5 ml), and/or measures necessary to ensure a patent airway, should be promptly administered.

Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if sacubitril/valsartan is used in these patients. Sacubitril/valsartan is contra-indicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy (see section 2.1).

Black patients have an increased susceptibility to develop angioedema (see section 3.4).

Patients with renal artery stenosis

Sacubitril/valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. Caution is required in patients with renal artery stenosis and monitoring of renal function is recommended.

Patients with NYHA functional classification IV

Caution should be exercised when initiating sacubitril/valsartan in patients with NYHA functional classification IV due to limited clinical experience in this population.

B-type natriuretic peptide (BNP)

BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate (see section 4).

Effects on ability to drive and use machines

No studies of the effects on the ability to drive have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

3.2 Usage with other Medicines

Interactions resulting in a contraindication

ACE inhibitors
The concomitant use of sacubitril/valsartan with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema.

Sacubitril/valsartan must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 2 and 2.1).

Aliskiren
The concomitant use of sacubitril/valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see section 2.1). The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 3.1).

Interactions resulting in concomitant use not being recommended

Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing product (see section 3.1).

Interactions requiring precautions

Statins
In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. Sacubitril/valsartan may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of sacubitril/valsartan increased the C_{max} of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Therefore, caution should be exercised when co-administering sacubitril/valsartan with statins.

PDE5 inhibitors including sildenafil
Addition of a single dose of sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril/valsartan alone. Therefore, caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with sacubitril/valsartan.

Potassium

Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if sacubitril/valsartan is co-administered with these agents (see section 3.1).

Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors
In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of sacubitril/valsartan and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly (see section 3.1).

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Drug interactions between sacubitril/valsartan and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Furosemide

Co-administration of sacubitril/valsartan and furosemide had no effect on the pharmacokinetics of sacubitril/valsartan but reduced C_{max} and AUC of furosemide by 50% and 28%, respectively. While there was no relevant change in urine volume, the urinary excretion of sodium was reduced within 4 hours and 24 hours after co-administration of furosemide and sacubitril/valsartan. The average daily dose of furosemide was unchanged from baseline until the end of the PARADIGM-HF study in patients treated with sacubitril/valsartan.

Nitroglycerine

There was no drug-drug interaction between sacubitril/valsartan and intravenously administered nitroglycerin with regards to blood pressure reduction. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone.

Transporters
The active metabolite of sacubitril (LBQ657) and valsartan are OATP1B1, OATP1B3, OAT1 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MPR2 (e.g. ritonavir) may increase the systemic exposure to LBQ657 or valsartan, respectively. Exercise appropriate care when initiating or ending concomitant treatment with such medicinal products.

Metformin

Co-administration of sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. The clinical relevance of these findings is unknown. Therefore, when initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

<u>No significant interaction</u>

No clinically meaningful drug-drug interaction was observed when sacubitril/valsartan was co-administered with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol. No interaction is expected with atenolol, indomethacin, glyburide or cimetidine.

CYP 450 interactions
In vitro metabolism studies indicate that potential for CYP 450-based drug interactions is low since there is limited metabolism of sacubitril/valsartan via CYP450 enzymes. Sacubitril/valsartan does not induce or inhibit

CYP450 enzymes.

3.3 Use during pregnancy and lactation

As for other medicinal products that act directly on the RAAS, sacubitril/valsartan must not be used during pregnancy as a risk to the foetus cannot be excluded. If pregnancy is confirmed during therapy, sacubitril/valsartan should be discontinued as soon as possible.

It is not known whether sacubitril/valsartan is excreted in human milk. Because of the potential risk for adverse reactions in breast-fed newborns/infants, sacubitril/valsartan is not recommended during breast-feeding. A decision should be made whether to abstain from breast-feeding or to discontinue sacubitril/valsartan while breast-feeding, taking into account the importance of sacubitril/valsartan to the mother.

3.4 Adverse Reactions

Summary of the safety profile

Discontinuation of therapy due to an adverse event in the double-blind period of the PARADIGM-HF study occurred in 450 sacubitril/valsartan-treated patients (10.71%) and 516 enalapril-treated patients (12.20%). The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalaemia and renal impairment.

The overall incidence of adverse drug reactions (ADRs) to sacubitril/valsartan in heart failure patients was comparable to that seen with enalapril. The pattern of the ADRs is consistent with the pharmacology of sacubitril/valsartan and the patients' underlying conditions.

The overall frequency of adverse reactions was not related to gender, age or race.

Tabulated list of adverse reactions

Adverse drug reactions are ranked by System Organ Class and then by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

List of adverse reactions in clinical studies

Blood and lymphatic system disorders	
Anaemia	Common
Immune system disorders	
Hypersensitivity	Uncommon
Metabolism and nutrition disorders	
Hyperkalaemia*	Very common
Hypokalaemia	Common
Hypoglycaemia	Common
Nervous system disorders	

Dizziness	Common
Headache	Common
Syncope	Common
Dizziness postural	Uncommon
Ear and labyrinth disorders	
Vertigo	Common
Vascular disorders	
Hypotension*	Very common
Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Gastrointestinal disorders	
Diarrhoea	Common
Nausea	Common
Gastritis	Common
Skin and subcutaneous tissue disorders	
Pruritus	Uncommon
Rash	Uncommon
Angioedema	Uncommon
Renal and urinary disorders	
Renal impairment*	Very common
Renal failure (renal failure, acute renal failure)	Common
General disorders and administration site conditions	
Fatigue	Common
Asthenia	Common

*In PARADIGM-HF, hyperkalaemia, renal impairment and hypotension were reported in 11.6%, 10.1% and 17.6% of patients treated with Sacubitril/valsartan, compared with 14.0%, 11.5% and 11.9% of patients treated with enalapril, respectively.

Description of selected adverse reactions

Angioedema
Angioedema has been reported in patients treated with sacubitril/valsartan. In PARADIGM-HF, angioedema was reported in 0.5% of patients treated with sacubitril/valsartan, compared with 0.2% of patients treated with enalapril. A higher incidence of angioedema was observed in Black patients treated with sacubitril/valsartan (2.4%) and enalapril (0.5%) (see section 3.1).

3.5 Overdose

Limited data are available with regard to overdose in humans. A single dose of sacubitril/valsartan 1200 mg and multiple doses of 900 mg (14 days) were studied in healthy volunteers and were well tolerated.

Hypotension is the most likely symptom of overdose due to the blood pressure lowering effects of Sacubitril/valsartan. Symptomatic treatment should be provided.

Sacubitril/valsartan is unlikely to be removed by haemodialysis due to high protein binding.

4 CLINICAL PHARMACOLOGY

Mechanism of action

Sacubitril/valsartan exhibits the novel mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits of sacubitril/valsartan in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan.

Sacubitril/valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because BNP is a neprilysin substrate (see section 3.1). NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

In a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1200 mg sacubitril/valsartan had no effect on cardiac repolarisation.

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of sacubitril/valsartan 400 mg once daily for two weeks to healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo; there were no changes in concentrations of CSF Aβ1-40 and 1-42. The clinical relevance of this finding is not known (see section 12).

Pharmacokinetics

The valsartan contained within sacubitril/valsartan is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in sacubitril/valsartan is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.

Absorption

Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657. These reach peak plasma concentrations in 2 hours, 1 hour, and 2 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60% and 23%, respectively.

Following twice daily dosing of sacubitril/valsartan, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1.6-fold. Administration of sacubitril/valsartan with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. sacubitril/valsartan can be administered with or without food.

Distribution

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94-97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volume of distribution of valsartan and sacubitril were 75 litres to 103 litres, respectively.

Biotransformation

Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolised to a significant

extent. Valsartan is minimally metabolised, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite of valsartan has been identified in plasma at low concentrations (<10%).

Since CYP450-enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with medicinal products that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

Elimination

Following oral administration, 52-68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37-48% of sacubitril (primarily as LBQ657) and 86% of valsartan and its metabolites are excreted in faeces.

Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life ($T_{½}$) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Linearity/non-linearity

The pharmacokinetics of sacubitril, LBQ657 and valsartan were linear over an sacubitril/valsartan dose range of 24 mg sacubitril/26 mg valsartan to 194 mg sacubitril/206 mg valsartan.

Use in Specific Populations

Elderly population
LBQ657 and valsartan exposure are increased in subjects over 65 years of age by 42% and 30%, respectively, compared to younger subjects.

Impaired renal function
A correlation was observed between renal function and systemic exposure to LBQ657 in patients with mild to severe renal impairment, and to valsartan exposure in patients with severe renal impairment. In patients with mild and moderate renal impairment (30 ml/min/1.73 m^2 ≤ eGFR <90 ml/min/1.73 m^2), the AUC for LBQ657 was up to 2-fold higher. A 2.9-fold higher AUC for LBQ657 and a 1.6-fold higher AUC for valsartan were observed in patients with severe renal impairment (15 ml/min/1.73 m^2 ≤ eGFR <30 ml/min/1.73 m^2). There are limited data in patients with severe renal impairment. No studies have been performed in patients undergoing dialysis. However, LBQ657 and valsartan are highly bound to plasma protein and therefore unlikely to be effectively removed by dialysis.

Impaired hepatic function
In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, LBQ657 increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects. In patients with mild to moderate hepatic impairment, the exposures of free concentrations of LBQ657 increased by 1.47- and 3.08-fold, respectively, and the exposures of free concentrations of valsartan increased by 1.09-fold and 2.20-fold, respectively, compared to matching healthy subjects. sacubitril/valsartan has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis.

5 NONCLINICAL TOXICOLOGY

Non-clinical data (including studies with sacubitril and valsartan components and/or Sacubitril/valsartan) reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility.

Fertility, reproduction and development

Sacubitril/valsartan treatment during organogenesis resulted in increased embryofoetal lethality in rats at doses ≥49 mg sacubitril/51 mg valsartan/kg/day (≤0.72-fold the maximum recommended human dose [MRHD] on the basis of AUC) and rabbits at doses ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). Sacubitril/valsartan is teratogenic based on a low incidence of foetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at an sacubitril/valsartan dose of ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day. The adverse embryofoetal effects of sacubitril/valsartan are attributed to the angiotensin receptor antagonist activity (see section 3.3).

Sacubitril treatment during organogenesis resulted in embryo-foetal lethality and embryo-foetal toxicity (decreased foetal body weights and foetal ossification delays) in rabbits at doses associated with maternal toxicity (500 mg/kg/day; 5.7-fold the MRHD on the basis of LBQ657 AUC). Sacubitril is not teratogenic in rats and rabbits. No evidence of embryo-foetal toxicity or teratogenicity was observed in rats treated with sacubitril. The embryo-foetal no-observed adverse effect level (NOAEL) for sacubitril was at least 750 mg/kg/day in rats and 200 mg/kg/day in rabbits (2.2-fold the MRHD on the basis of LBQ657 AUC).

Pre- and postnatal development studies in rats conducted with sacubitril at high doses up to 750 mg/kg/day (2.2-fold the MRHD on the basis of AUC) and valsartan at doses up to 600 mg/kg/day (0.86-fold the MRHD on the basis of AUC) indicate that treatment with sacubitril/valsartan during organogenesis, gestation and lactation may affect pup development and survival.

Other preclinical findings

The effects of sacubitril/valsartan on amyloid-β concentrations in CSF and brain tissue were assessed in young (2-4 years old) cynomolgus monkeys treated with sacubitril/valsartan (24 mg sacubitril/26 mg valsartan/kg/day) for two weeks. In this study sacubitril/valsartan reduced CSF Aβ clearance in cynomolgus monkeys, increasing CSF Aβ1-40, 1-42 and 1-38 levels; there was no corresponding increase in Aβ levels in the brain. Increases in CSF Aβ1-40 and 1-42 were not observed in a two-week healthy volunteer study in humans (see section 4). Additionally, in a toxicology study in cynomolgus monkeys treated with sacubitril/valsartan at 146 mg sacubitril/154 mg valsartan/kg/day for 39 weeks, there was no evidence for the presence of amyloid plaques in the brain. Amyloid content was however not measured quantitatively in this study.

In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation. A study in adult rats showed only a minimal transient inhibitory effect on bone mineral density but not on any other parameters relevant for bone growth, suggesting no relevant effect of sacubitril on bone in adult patient populations under normal conditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults cannot be excluded.

In juvenile rats treated with valsartan (postnatal days 7 to 70), doses as low as 1 mg/kg/day produced persistent irreversible kidney changes consisting of tubular nephropathy (sometimes accompanied by tubular epithelial necrosis) and pelvic dilatation. These kidney changes represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans.

6 CLINICAL STUDIES

PARADIGM-HF

PARADIGM-HF was a multinational, randomised, double-blind study of 8,442 patients comparing sacubitril/valsartan to enalapril, both given to adult patients with chronic heart failure, NYHA class II-IV and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤40%, amended later to ≤35%) in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalisation for heart failure (HF). Patients with SBP <100 mmHg, severe renal impairment (eGFR <30 ml/min/1.73 m^2) and severe hepatic impairment were excluded at screening and therefore not

prospectively studied.

Prior to study participation, patients were well treated with standard of care therapy which included ACE inhibitors/ARBs (>99%), beta blockers (94%), mineralocorticoid antagonists (58%) and diuretics (82%).

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and enter a sequential single-blind run-in period during which they received treatment with enalapril 10 mg twice daily, followed by single-blind treatment with sacubitril/valsartan 100 mg twice daily, increasing to 200 mg twice daily. They were then randomised to the double-blind period of the study, during which they received either sacubitril/valsartan 200 mg or enalapril 10 mg twice daily [sacubitril/valsartan (n=4209); enalapril (n=4233)].

Sacubitril/valsartan was superior to enalapril, reducing the risk of cardiovascular death or heart failure hospitalisations to 21.8% (914/4187) compared to enalapril treated patients (1117/4212; 26.5%). The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalisation, 3.1% for CV death alone, and 2.8% for first HF hospitalisation alone. The relative risk reduction was 20% (hazard ratio [HR]: 0.80, 95% CI [0.73; 0.87], 1-sided p=0.0000002) versus enalapril (see Table 2). This effect was observed early and was sustained throughout the duration of the study (see Figure 1). Both components contributed to the risk reduction. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in sacubitril/valsartan -treated patients compared to enalapril-treated patients (HR 0.80, p=0.0082). Pump failure accounted for 26% of cardiovascular deaths and was reduced by 21% in sacubitril/valsartan -treated patients compared to enalapril-treated patients (HR 0.79, p=0.0338).

This risk reduction was consistently observed across subgroups including: gender, age, race, geography, NYHA class, ejection fraction, renal function, history of diabetes or hypertension, prior heart failure therapy, and atrial fibrillation.

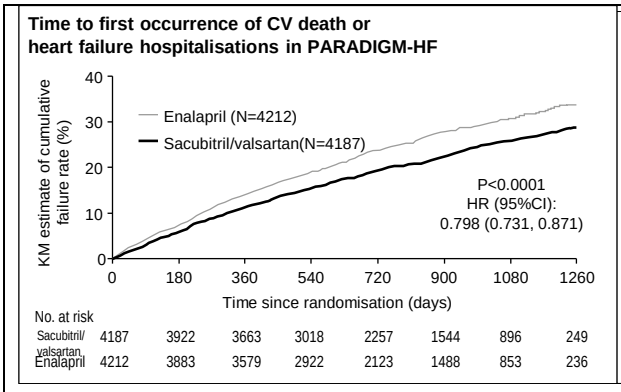
Sacubitril/valsartan improved survival with a significant reduction in all-cause mortality of 2.8% (sacubitril/valsartan: 711/4187, 17%, enalapril 835/4212, 19.8%). The relative risk reduction was 16% compared with enalapril (HR 0.84; 95% CI [0.76 to 0.93], 1-sided p=0.0005) (see Table 1).

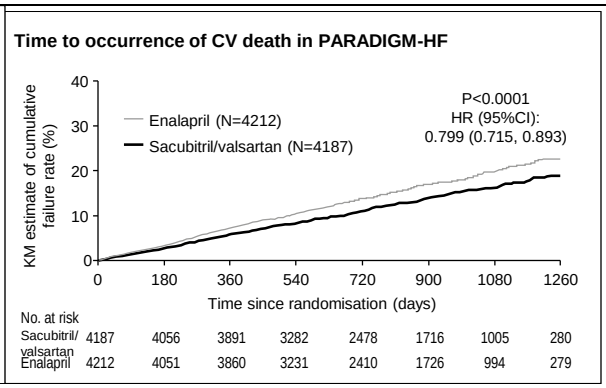
Table 1 Treatment effect for the primary composite endpoint, its components and all-cause mortality over a median follow-up of 27 months

	Sacubitril/valsartan N=4187[♯] n (%)	**Enalapril N=4212[♯] n (%)**	**Hazard ratio (95% CI)**	**Relative risk reduction**	**p-value *****
Primary composite endpoint of CV death and heart failure hospitalisations*	914 (21.83)	1117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual components of the primary composite endpoint					
CV death**	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	0.00004
First heart failure hospitalisation	537 (12.83)	658 (15.62)	0.79 (0.71, 0.89)	21%	0.00004
Secondary endpoint					
All-cause mortality	711 (16.98)	835 (19.82)	0.84 (0.76, 0.93)	16%	0.0005

*The primary endpoint was defined as the time to first event of CV death or hospitalisation for HF.
**CV death includes all patients who died up to the cut-off date irrespective of previous hospitalisation.
***One-sided p-value
[♯] Full analysis set

Figure 1 Kaplan-Meier curves for the primary composite endpoint and the CV death component





Fewer patients experienced deterioration in heart failure symptoms, including dyspnoea and fatigue, and physical limitations as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), when compared to enalapril. There was a beneficial effect on severity of heart failure as measured by New York Heart Association (NYHA) classification.

7 PHARMACEUTICAL INFORMATION

50mg film-coated tablet: Pale Violet ovaloid biconvex film-coated tablet with bevelled edges, debossed with "NVR" on one side and "LZ" on the other side.

100mg film-coated tablet: Pale yellow ovaloid biconvex film-coated tablet with bevelled edges, debossed with "NVR" on one side and "L1" on the other side.

200mg film-coated tablet: Light pink ovaloid biconvex film-coated tablet with bevelled edges, debossed with "NVR" on one side and "L11" on the other side.

Qualitative and quantitative compostion

Each 50 mg film-coated tablet contains 24 mg sacubitril and 26 mg valsartan as sodium salt complex.

Each 100 mg film-coated tablet contains 49 mg sacubitril and 51 mg valsartan as sodium salt complex.

Each 200 mg film-coated tablet contains 97 mg sacubitril and 103 mg valsartan as sodium salt complex.

List of excipients

Tablet core

Cellulose, microcrystalline
Low-substituted hydroxypropylcellulose
Crospovidone
Magnesium stearate (vegetable origin)
Talc
Silica, colloidal anhydrous

Film coating
50mg:
Hypromellose
Titanium dioxide (E171)
Macrogol 4000

Talc
Iron oxide red (E172)
Iron oxide black (E172)

100mg:
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Talc
Iron oxide red (E172)
Iron oxide yellow (E172)

200mg:
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Talc
Iron oxide red (E172)
Iron oxide black (E172)

Incompatibilities

Not applicable.

8 HOW SUPPLIED/STORAGE AND HANDLING

Sacubitril/valsaratan is provided in HDPE bottles with induction seals and child-resistant caps. Each bottle contains 70 film-coated tablets.

Special precautions for storage
Do not store above 25°C.
Protect from moisture. Store in original package.

Shelf life
50 mg: 24 months
100 mg: 48 months
200 mg: 48 months

9 SCIENTIFIC OPINION HOLDER

Novartis Pharmaceuticals UK Limited
Frimley Business Park, Frimley
Camberley GU167SR
United Kingdom

10 EAMS NUMBER

00101/0002

11 DATE OF SCIENTIFIC OPINION

27/08/2015

Additional information:

• Each prescribing physician will be provided with a **physician pack** containing all the relevant documents needed to manage patients receiving sacubitril/valsartan under EAMS.

• As each patient gives **informed consent**, they must be issued with a **Patient Alert Card**. This is credit-card sized and patients must be instructed to carry it with them at all times. It summarises the symptoms of angioedema and gives advice on what to do if they develop. In addition it alerts any other healthcare professional that may treat them, that the patient is receiving sacubitril/valsartan through an early access scheme and provides details of their physician, their out of hours contact details and the Company's contact details.

• Prescribers will be provided with training and guidance documents on the safety reporting requirements and processes. All adverse events experienced by patients in the sacubitril/valsartan EAMS should be reported to Novartis from the start of treatment and at regular intervals using an electronic reporting tool. The training must be completed before a patient commences the EAMS.

• On completion of the training prescribers will need to submit a short **Patient Treatment Request Form** to register individual patients and sign a **Terms of Supply of Product Form** to ensure eligibility within the scheme.

• Following approval by Novartis, pharmacists must submit an **EAMS Supply Form** and confirmation of patient visits in the electronic reporting tool every 3 months to receive continuing supplies of sacubitril/valsartan.

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