Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sacubitril/Valsartan Clonmel 49 mg/51 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sacubitril sodium and valsartan disodium equivalent to 48.6 mg sacubitril and 51.4 mg valsartan.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pink, biconvex, oval film-coated tablet debossed with "S7V" on one side and "M2" on the other side. Approximate tablet dimensions: 12 mm x 5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult heart failure

Sacubitril/Valsartan Clonmel is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1) who are taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) which is equivalent to ≥10 mg of enalapril per day until switching to treatment with Sacubitril/Valsartan Clonmel.

4.2 Posology and method of administration

Posology

General considerations
Sacubitril/Valsartan Clonmel should not be co-administered with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB). Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy (see sections 4.3, 4.4 and 4.5).

The valsartan contained within Sacubitril/Valsartan Clonmel is more bioavailable than the valsartan in other marketed tablet formulations (see section 5.2).

If a dose is missed, the patient should take the next dose at the scheduled time.

Adult heart failure
The recommended starting dose of Sacubitril/Valsartan Clonmel is one tablet of 49 mg/51 mg twice daily. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient (see section 5.1).

If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of Sacubitril/Valsartan Clonmel is recommended (see section 4.4).

In PARADIGM-HF study, sacubitril/valsartan was administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB (see section 5.1). There is limited experience in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products (equivalent <10 mg Enalapril per day.
Sacubitril/Valsartan Clonmel is not intended for this patient group.

Treatment should not be initiated with Sacubitril/Valsartan Clonmel in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg (see section 4.4). Sacubitril/Valsartan Clonmel is not intended for patients with SBP ≥100 to 110 mmHg.

Special populations
Elderly
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 (eGFR 60-90 ml/min/1.73 m^2) renal impairment.
Sacubitril/Valsartan Clonmel is not intended for patients with moderate and severe renal impairment.

There is no experience in patients with end-stage renal disease and use of Sacubitril/Valsartan Clonmel is not recommended.

Hepatic impairment
No dose adjustment is required when administering Sacubitril/Valsartan Clonmel to patients with mild hepatic impairment (Child-Pugh A classification).

Sacubitril/Valsartan Clonmel is not intended for patients with moderate hepatic impairment.

Sacubitril/Valsartan Clonmel is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).

Method of administration

Oral use.
Sacubitril/Valsartan Clonmel may be administered with or without food (see section 5.2). The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Concomitant use with ACE inhibitors (see sections 4.4 and 4.5). Sacubitril/Valsartan Clonmel 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 4.4).
- Hereditary or idiopathic angioedema (see section 4.4).
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2) (see sections 4.4 and 4.5).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see section 4.2).
- Second and third trimesters of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

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

- The combination of sacubitril/valsartan with an ACE inhibitor is contraindicated due to the increased risk of angioedema (see section 4.3). 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 4.2, 4.3 and 4.5).
- The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 4.5). The combination of sacubitril/valsartan with aliskiren- containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2) (see sections 4.3 and 4.5).
- Sacubitril/Valsartan Clonmel contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product (see sections 4.2 and 4.5).

Hypotension

Treatment should not be initiated unless SBP is ≥100 mmHg for adult patients. Patients with SBP below these values were not studied (see section 5.1). Cases of symptomatic hypotension have been reported in adult patients treated with sacubitril/valsartan during clinical studies (see section 4.8), especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). When initiating therapy or during dose titration with sacubitril/valsartan, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended (see section 4.2). Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. 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.

Renal impairment

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 (see section 4.2). There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2) and these patients may be at greatest risk of hypotension (see section 4.2). Sacubitril/Valsartan Clonmel is not intended for patients with moderate and severe renal impairment. There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended.

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 4.5). Down-titration should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is >5.4 mmol/l in adult patients. Use of sacubitril/valsartan may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur (see section 4.8). 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 4.2). If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered.

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. It 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 contraindicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema (see section 4.3).

Black patients have an increased susceptibility to develop angioedema (see section 4.8).

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, sacubitril/valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Patients with renal arterystenosis

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 New York Heart Association (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 5.1).

Patients with hepatic impairment

There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In these patients, exposure may be increased and safety is not established. Caution is therefore recommended when using it in these patients (see section 4.2 and 5.2). Sacubitril/Valsartan Clonmel is not intended for patients with moderate hepatic impairment. Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).

Psychiatric disorders

Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 4.2 and 4.3).

Aliskiren
The concomitant use of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2) (see section 4.3). The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 4.4). Combination of sacubitril/valsartan with aliskiren is potentially associated with a higher frequency of adverse reactions such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) (see sections 4.3 and 4.4).

Interactions resulting in concomitant use not being recommended
Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product (see section 4.4).

Interactions requiring precautions

OATP1B1 and OATP1B3 substrates, e.g. 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. Caution should be exercised when

co-administering sacubitril/valsartan with statins. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered.

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 PDE5 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 4.4).

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 4.4).

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 including sacubitril/valsartan. 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. The average daily dose of furosemide was unchanged from baseline until the end of the PARADIGM-HF study in patients treated with sacubitril/valsartan.

Nitrates, e.g. nitroglycerine
There was no interaction between sacubitril/valsartan and intravenously administered nitroglycerin with regard 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. A similar effect on the heart rate may occur when sacubitril/valsartan is co- administered with sublingual, oral or transdermal nitrates. In general no dose adjustment is required.

OATP and MRP2 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 MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised 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.

No significant interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Valsartan
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with ARBs, similar risks may exist for this class of medicinal product. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ARBs should be stopped immediately and, if appropriate, alternative therapy should be started. Exposure to ARBs therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to ARBs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension (see section 4.3).

Sacubitril
There are no data from the use of sacubitril in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Sacubitril/valsartan
There are no data from the use of sacubitril/valsartan in pregnant women. Animal studies with sacubitril/valsartan have shown reproductive toxicity (see section 5.3).

Breast-feeding

Limited data show that sacubitril and its active metabolite LBQ657 are excreted in human milk in very low amounts with an estimated relative infant dose of 0.01% for sacubitril and 0.46% for the active metabolite LBQ657 when administered to breast-feeding women at a dose of 24 mg/26 mg sacubitril/valsartan, twice daily. In the same data, valsartan was under the limit of detection. There is insufficient information on the effects of sacubitril/valsartan in newborns/infants. Because of the potential risk for adverse reactions in breast-fed newborns/infants, Sacubitril/Valsartan Clonmel is not recommended in women who are breast-feeding.

Fertility

There are no available data on the effect of sacubitril/valsartan on human fertility. No impairment of fertility was demonstrated in studies with it in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Sacubitril/valsartan has a minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in adults during treatment with sacubitril/valsartan were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%) (see section 4.4). Angioedema was reported in patients treated with sacubitril/valsartan (0.5%) (see description of selected adverse reactions).

Tabulated list of adverse reactions

Adverse 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); not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 2: List of adverse reactions

System organ class	Preferred term	Frequency category
Blood and lymphatic system disorders	Anaemia	Common
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalaemia*	Very common
	Hypokalaemia	Common
	Hypoglycaemia	Common
	Hyponatraemia	Uncommon
Psychiatric disorders	Hallucinations**	Rare
	Sleep disorders	Rare
	Paranoia	Very rare
Nervous system disorders	Dizziness	Common
	Headache	Common
	Syncope	Common
	Dizziness postural	Uncommon
	Myoclonus	Not known
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension*	Very common
	Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastro intestinal disorders	Diarrhoea	Common
	Nausea	Common
	Gastritis	Common
	Intestinal angioedema	Very rare
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Angioedema*	Uncommon
Renaland urinary disorders	Renal impairment*	Very common
	Renal failure (renal failure, acute renal failure)	Common
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common

* See description of selected adverse reactions.

** Including auditory and visual hallucinations

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 4.4).

Hyperkalaemia and serum potassium

In PARADIGM-HF, hyperkalaemia and serum potassium concentrations >5.4 mmol/l were reported in 11.6% and 19.7% of sacubitril/valsartan-treated patients and 14.0% and 21.1% of enalapril-treated patients, respectively.

Blood pressure

In PARADIGM-HF, hypotension and clinically relevant low systolic blood pressure (<90 mmHg and decrease from baseline of > 20 mmHg) were reported in 17.6% and 4.76% of sacubitril/valsartan- treated patients compared with 11.9% and 2.67% of enalapril-treated patients, respectively.

Renal impairment

In PARADIGM-HF, renal impairment was reported in 10.1% of sacubitril/valsartan-treated patients and 11.5% of enalapril-treated patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Limited data are available with regard to overdose in humans. A single dose of 583 mg sacubitril/617 mg valsartan and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) were studied in healthy adult 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.

The medicinal product is unlikely to be removed by haemodialysis due to high protein binding (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II receptor blockers (ARBs), other combinations, ATC code: C09DX04

Mechanism of action

Sacubitril/valsartan exhibits the 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. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

Pharmacodynamic effects

The pharmacodynamic effects of sacubitril/valsartan were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure, and are consistent with simultaneous neprilysin inhibition and RAAS blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of sacubitril/valsartan resulted in an initial increase in natriuresis, increased urine cGMP, and decreased plasma levels of mid-regional pro-atrial natriuretic peptide (MR-proANP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) compared to valsartan. In a 21-day study in HFrEF patients, sacubitril/valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. The AT1-receptor was also blocked as evidenced by increased plasma renin activity and plasma renin concentrations. In the PARADIGM-HF study, sacubitril/valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. In the PANORAMA-HF study, a reduction in NT-proBNP was observed at weeks 4 and 12 for sacubitril/valsartan (40.2% and 49.8%) and enalapril (18.0% and 44.9%) compared to baseline. The NT-proBNP levels continued to decrease over the duration of the study with a reduction of 65.1% for sacubitril/valsartan and 61.6% for enalapril at week 52 compared to baseline. BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because BNP is a neprilysin substrate (see section 4.4). 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 sacubitril/valsartan 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg 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 194 mg sacubitril/206 mg valsartan 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 5.3).

Clinical efficacy and safety

The 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg strengths are in some publications referred to as 50, 100 or 200 mg.

PARADIGM-HF
PARADIGM-HF, the pivotal phase 3 study, 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 m2) 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%). The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

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 (see section 4.8 for discontinuations during this period). 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=4 209); enalapril (n=4 233)].

The mean age of the population studied was 64 years of age and 19% were 75 years of age or older. At randomisation, 70% of patients were NYHA class II, 24% were class III and 0.7% were class IV. The mean LVEF was 29% and there were 963 (11.4%) patients with a baseline LVEF >35% and ≤40%.

In the sacubitril/valsartan group, 76% of patients remained on the target dose of 200 mg twice daily at the end of the study (mean daily dose of 375 mg). In the enalapril group, 75% of patients remained on the target dose of 10 mg twice daily at the end of the study (mean daily dose of 18.9 mg).

Sacubitril/valsartan was superior to enalapril, reducing the risk of cardiovascular death or heart failure hospitalisations to 21.8% compared to 26.5% for enalapril treated patients. 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% versus enalapril (see Table 3). 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 (hazard ratio [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 (II/III), 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, 17%, enalapril, 19.8%). The relative risk reduction was 16% compared with enalapril (see Table 3).

Table 3: Treatment effect for the primary composite endpoint, its components and all-cause mortality over a median follow-up of 27 months

	Sacubitril/ valsartan N=4,187# n (%)	**Enalapril N=4,212# n (%)**	**Hazard ratio (95% CI)**	**Relative risk reduction**	**p-value*** **
Primary composite endpoint of CV death and heart failure hospitalisations*	914 (21.83)	1,117 (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

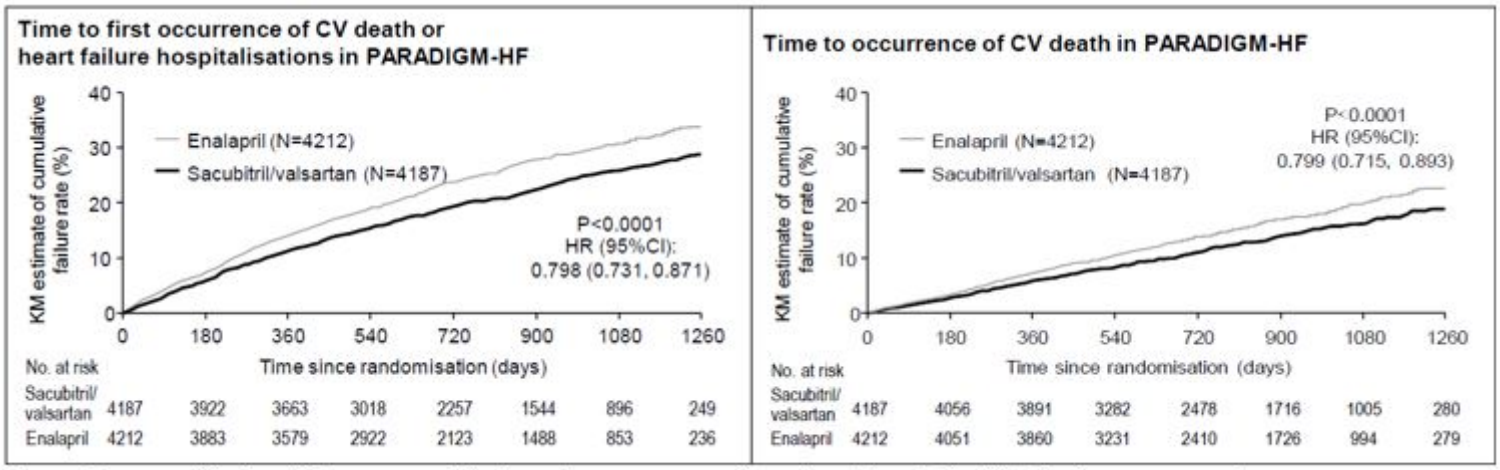

Figure 1: Kaplan-Meier curves for the primary composite endpoint and the CV death component

5.2 Pharmacokinetic properties

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.

Adult population

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 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 carboxylesterases 1b and 1c; 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.

In vitro metabolism studies indicate that potential for CYP450-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.

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 approximately linear over a sacubitril/valsartan dose range of 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan.

Special populations

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

Renal impairment
A correlation was observed between renal function and systemic exposure to LBQ657 in patients with mild to severe renal impairment. The exposure of LBQ657 in patients with moderate (30 ml/min/1.73 m^2 ≤ eGFR <60 ml/min/1.73 m^2) and severe renal impairment (15 ml/min/1.73 m^2 ≤ eGFR <30 ml/min/1.73 m^2) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60 ml/min/1.73 m^2 ≤ eGFR <90 ml/min/1.73 m^2), the largest group of patients enrolled in PARADIGM-HF. The exposure of valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild 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.

Hepatic impairment
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. However, 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 (see sections 4.3 and 4.4).

Effect of gender
The pharmacokinetics of sacubitril/valsartan (sacubitril, LBQ657 and valsartan) are similar between male and female subjects.

5.3 Preclinical safety data

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). It is teratogenic based on a low incidence of foetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril/valsartan dose of ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day. Cardiovascular abnormalities (mainly cardiomegaly) were observed in rabbit foetuses at a maternally non-toxic dose (1.46 mg sacubitril/1.54 mg valsartan/kg/day). A slight increase in two foetal skeletal variations (misshapen sternebra, sternebra bipartite ossification) was observed in rabbits at a 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 4.6).

Sacubitril treatment during organogenesis resulted in embryo-foetal lethality and embryo-foetal toxicity (decreased foetal body weights and skeletal malformations) in rabbits at doses associated with maternal toxicity (500 mg/kg/day; 5.7-fold the MRHD on the basis of LBQ657 AUC). A slight generalised delay in ossification was observed at doses of >50 mg/kg/day. This finding is not considered adverse. 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

Sacubitril/valsartan
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 CSF Aβ clearance in cynomolgus monkeys was reduced, 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 5.1). 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 not, however, measured quantitatively in this study.

Sacubitril
In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation at approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657. The mechanism for these findings in juvenile rats is unknown. 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.

Valsartan
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. Functional renal maturation is an ongoing process within the first year of life in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Hydroxypropylcellulose, low-substituted
Crospovidone, type A and type B
Talc
Silica, colloidal anhydrous
Magnesium stearate

Film coating

Poly(vinyl alcohol) - partially hydrolysed
Titanium dioxide
Macrogol
Talc
Iron oxide red (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

oPA/Al/PVC-Al blisters

Blister packs containing 14, 20, 28, 56, 168 or 196 film-coated tablets and multipacks containing 168 (3 packs of 56) or 196 (7 packs of 28) film-coated tablets.
Unit-dose blister packs containing 14x1, 20x1, 28x1, 56x1, 168x1 or 196x1 film-coated tablets and multipacks of 168 (3 packs of 56x1) or 196 (7 packs of 28x1) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/384/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6^{h} July 2026

10 DATE OF REVISION OF THE TEXT