1. NAME OF THE MEDICINAL PRODUCT

SACUBASSEL 50mg (Sacubitril/Valsartan film-coated tablets)
SACUBASSEL 100mg (Sacubitril/Valsartan film-coated tablets)
SACUBASSEL 200mg (Sacubitril/Valsartan film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SACUBASSEL 50mg
Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex).

SACUBASSEL 100mg
Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex).

SACUBASSEL 200mg
Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex).

SACUBASSEL contains a salt complex of the anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2:5 respectively. Following oral administration, SACUBASSEL dissociates into sacubitril (which is further metabolized to LBQ657 [sacubitrilat]) and valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

SACUBASSEL 50mg
Off white to Light Pink, oval, biconvex film coated tablets, debossed with '5' on one side and plain on other side.

SACUBASSEL 100mg
Light Yellow color, oval, biconvex film coated tablets, debossed with '|' on one side and plain on other side

SACUBASSEL 200mg
Light pink to Pink, oval, biconvex film coated tablets, debossed with '2' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Heart failure
SACUBASSEL is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical efficacy and safety (section 5.1)].

SACUBASSEL is administered in combination with other heart failure therapies (e.g. beta blockers, diuretics and mineralocorticoid antagonists) as appropriate, in place of an ACE inhibitor or ARB [see Clinical efficacy and safety (section 5.1)].

Hypertension
SACUBASSEL is indicated for the treatment of essential hypertension.
SACUBASSEL should not be used as a first-line drug for the treatment of hypertension because of the risk of excessive decrease in blood pressure.

4.2 Posology and method of administration

Posology
Heart failure
The recommended starting dose of SACUBASSEL is one tablet of 100 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 200 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, hyperkalemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation of SACUBASSEL 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 angiotensin II receptor blocker (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, therefore a starting dose of 50 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended in these patients (see "Titration" in section 5.1).

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg (see section 4.4). A starting dose of 50 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg.

SACUBASSEL should not be co-administered with an ACE inhibitor or an 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 SACUBASSEL 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. Splitting or crushing of the tablets is not recommended.

Hypertension
The recommended starting dose of SACUBASSEL is 200 mg once daily. In patients whose blood pressure could not be adequately controlled with SACUBASSEL 200 mg once daily, the dose can be increased to 400 mg once daily. In hypertensive patients with heart failure, the heart failure dosing is recommended. SACUBASSEL may be used alone or in combination with other

antihypertensive agents except angiotensin- converting enzyme (ACE) inhibitors (see section 4.3) and angiotensin II receptor blockers (ARBs) (see section 4.4).

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 (Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 m^2) renal impairment.

A starting dose of 50 mg twice daily should be considered in heart failure patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2). As there is very limited clinical experience in heart failure patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) (see section 5.1) SACUBASSEL should be used with caution and a starting dose of 50 mg twice daily is recommended.

Safety and efficacy of SACUBASSEL in patients with essential hypertension and with severe renal impairment (eGFR <30 mL/min/1.73m^2) have not been established (see section 5.2)

Hepatic impairment
No dose adjustment is required when administering SACUBASSEL to patients with mild hepatic impairment (Child-Pugh A classification). 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. SACUBASSEL should be used with caution in these heart failure patients and the recommended starting dose is 50 mg twice daily (see section 4.4 and 5.2). A starting dose of 100 mg once daily is recommended for essential hypertensive patients with moderate hepatic impairment (Child-Pugh B classification). SACUBASSEL is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).

Paediatric population
The safety and efficacy of SACUBASSEL in children and adolescents aged below 18 years have not been established. No data are available.

Method of administration
Oral use.
SACUBASSEL may be administered with or without food (see section 5.2). The tablets must be swallowed with a glass of water.

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). SACUBASSEL 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 m^2) (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 m^2) (see sections 4.3 and 4.5).
- SACUBASSEL 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. Patients with SBP <100 mmHg were not studied (see section 5.1). Cases of symptomatic hypotension have been reported in 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.

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 (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).

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. 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).

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 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 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.

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 m^2) (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 events 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. SACUBASSEL may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins.

Co-administration of sacubitril/valsartan increased the Cmax 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 Cmax 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 drug-drug 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 Cmax 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.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
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.

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

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

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.

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

Heart failure
Summary of the safety profile
The most commonly reported adverse reactions 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).

A total of 6,622 heart failure patients were treated with sacubitril/valsartan in the PARADIGM-HF (vs. enalapril) and PARAGON-HF (vs. valsartan) clinical trials. Of these, 5,085 were exposed for at least 1 year.

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 (≥1/1000 to <1/100) ; rare (≥1/10000 to <1/1000); very rare (<1/10000). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 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
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
Psychiatric disorders	Hallucinations**	Rare
	Sleep disorders	Rare
	Paranoia	Very rare

*See description of selected adverse reactions.
**Including auditory and visual hallucinations

Hypertension

Summary of the safety profile

The safety of sacubitril/valsartan in patients with essential hypertension was evaluated in clinical trials involving more than 7,000 hypertensive patients (over 3.500 treated with sacubitril/valsartan).

In a pooled group of short-term, double-blind, controlled studies, 3,272 patients were exposed to sacubitril/valsartan with median duration of 8 weeks, dizziness occurred at a higher frequency in patients treated with sacubitril/valsartan than in patients treated with olmesartan (see Table 2).
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.

Table 2 Adverse Drug Reactions in the pooled hypertension clinical studies

Adverse drug reactions	**sacubitril/valsartan**	**Olmesartan monotherapy**	**Frequency category**
	N = 3272 n (%)	**N = 1352 n (%)**	
Nervous system disorders			
Dizziness	49 (1.5)	12 (0.9)	Common

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.

In PARAGON-HF, no new adverse reactions were identified.

Laboratory Abnormalities
Hemoglobin and Hematocrit
Decreases in hemoglobin/hematocrit of > 20% were observed in approximately 5% of both sacubitril/valsartan- and enalapril-treated patients in the double-blind period in PARADIGM-HF. Decreases in hemoglobin/hematocrit of >20% were observed in approximately 7% of sacubitril/valsartan-treated patients and 9% of valsartan-treated patients in the double-blind period in PARAGON-HF.

Serum Creatinine
During the double-blind period in PARADIGM-HF, approximately 16% of both sacubitril/valsartan- and enalapril- treated patients had increases in serum creatinine of > 50%. During the double-blind period in PARAGON-HF, approximately 17% of sacubitril/valsartan-treated patients and 21% of valsartan-treated patients had increases in serum creatinine of > 50%.

Serum Potassium
During the double-blind period of PARADIGM-HF, approximately 16% of both sacubitril/valsartan- and enalapril- treated patients had potassium concentrations > 5.5 mEq/L. During the double-blind period of PARAGON-HF, approximately 18% of sacubitril/valsartan-treated patients and 20% of valsartan-treated patients had potassium concentrations > 5.5 mEq/L.

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 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 NTproBNP, 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. 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 PARAMOUNT, a randomized, double-blind, 36-week study in patients with heart failure with LVEF $\geq$ 45% comparing 200 mg of sacubitril/valsartan (n=149) to 160 mg of valsartan (n =152) twice-daily, sacubitril/valsartan decreased NT-proBNP by 17% while valsartan increased NT-proBNP by 8% at Week 12 (p = 0.005).

In PARAGON-HF, sacubitril/valsartan decreased NT-proBNP by 24% (Week 16) and 19% (Week 48) compared to 6% and 3% reductions on valsartan, respectively.
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

Heart failure

PARADIGM-HF
PARADIGM_HF, the pivotal phase 3 study, was a multinational, randomised, double-blind study of 8442 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) $\leq$ 40%, amended later to $\leq$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%). 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 (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).

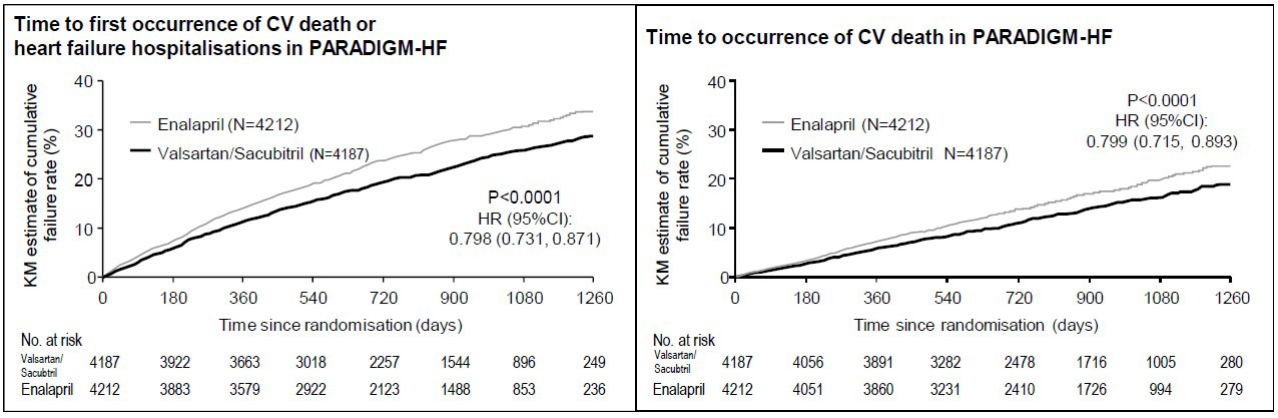
Table 3 Treatment effect for the primary composite endpoint, its components and all-cause mortality over a median follow-up of 27 months in PARADIGM-HF

	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	914 (21.83)	1,117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002

failure hospitalisations*					
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



TITRATION
TITRATION was a 12-week safety and tolerability study in 538 patients with chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤35%) naïve to ACE inhibitor or ARB therapy or on varying doses of ACE inhibitors or ARBs prior to study entry. Patients received a starting dose of sacubitril/valsartan of 50 mg twice daily and were up-titrated to 100 mg twice daily, then to the target dose of 200 mg twice daily, with either a 3-week or a 6-week regimen.

More patients who were naïve to previous ACE inhibitor or ARB therapy or on low-dose therapy (equivalent to <10 mg enalapril/day) were able to achieve and maintain sacubitril/valsartan 200 mg when up-titrated over 6 weeks (84.8%) versus 3 weeks (73.6%). Overall, 76% of patients achieved and maintained the target dose of sacubitril/valsartan 200 mg twice daily without any dose interruption or down-titration over 12 weeks.

PARAGON-HF
PARAGON-HF, was a multicenter, randomized, double-blind trial comparing sacubitril/valsartan and valsartan in 4,796 adult patients with symptomatic heart failure with left ventricular ejection

fraction ≥ 45%, and structural heart disease [either left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)].
Patients with a systolic blood pressure of < 110 mmHg and patients with any prior echocardiographic LVEF < 40% at screening were excluded.

The primary objective of PARAGON-HF was to determine whether sacubitril/valsartan reduced the rate of the composite endpoint of total (first and recurrent) heart failure (HF) hospitalizations and cardiovascular (CV) death.

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single- blind run-in periods during which they received valsartan 80 mg twice-daily, followed by sacubitril/valsartan 100 mg twice-daily. Patients on prior low doses of an ACEi or ARB began the run-in period receiving valsartan 40 mg twice-daily for 1-2 weeks. Patients who successfully completed the sequential run-in periods were randomized to receive either sacubitril/valsartan 200 mg (N = 2,419) twice-daily or valsartan 160 mg (N = 2,403) twice-daily. The median follow-up duration was 35 months and patients were treated for up to 4.7 years.

The population was 81% Caucasian, 13% Asian, and 2% Black; the mean age was 73 years and 52% were female. At randomization, 77% of patients were NYHA Class II, 19% were NYHA Class III, and 0.4% were NYHA Class IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic etiology in 36% of patients. Furthermore, 96% had a history of hypertension, 23% had a history of myocardial infarction, 46% had an eGFR < 60 mL/min/1.73 m^2, and 43% had diabetes mellitus. Most patients were taking beta-blockers (80%) and diuretics (95%).

PARAGON-HF demonstrated that sacubitril/valsartan had a numerical reduction in the rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death, based on an analysis using a proportional rates model (rate ratio [RR] 0.87; 95% CI [0.75, 1.01], p = 0.06); see Table 4. The treatment effect was primarily driven by the reduction in total HF hospitalizations in patients randomized to sacubitril/valsartan (RR 0.85; 95% CI [0.72, 1.00]).

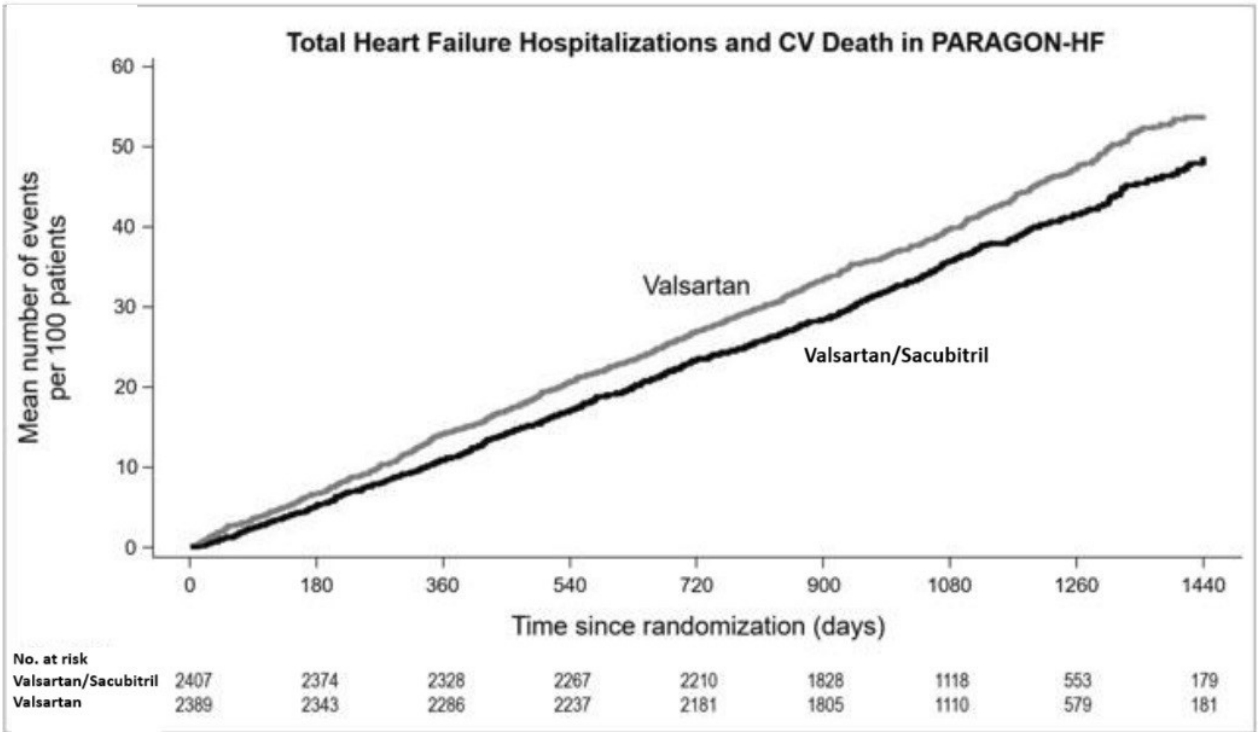
Table 4: Treatment Effect for the Primary Composite Endpoint and its Components in PARAGON-HF

	sacubitril/valsartan N = 2,407		**Valsartan N = 2,389**		**Effect Size (95% CI)**
Efficacy Endpoints	**n**	**Event Rate[a]**	**n**	**Event Rate[a]**	
Composite of total (first and recurrent) HF hospitalizations and CV death	894	12.8	1,009	14.6	RR = 0.87 (0.75, 1.01) *p*-value 0.06
Total HF Hospitalizations	690	9.9	797	11.6	RR = 0.85 (0.72, 1.00)
CV Death[b]	204	2.9	212	3.1	HR = 0.95 (0.79, 1.16)

Abbreviations: RR = rate ratio, HR = hazard ratio
[a]Event rate per 100 patient-years
[b]Includes patients who had CV death following HF hospitalization event

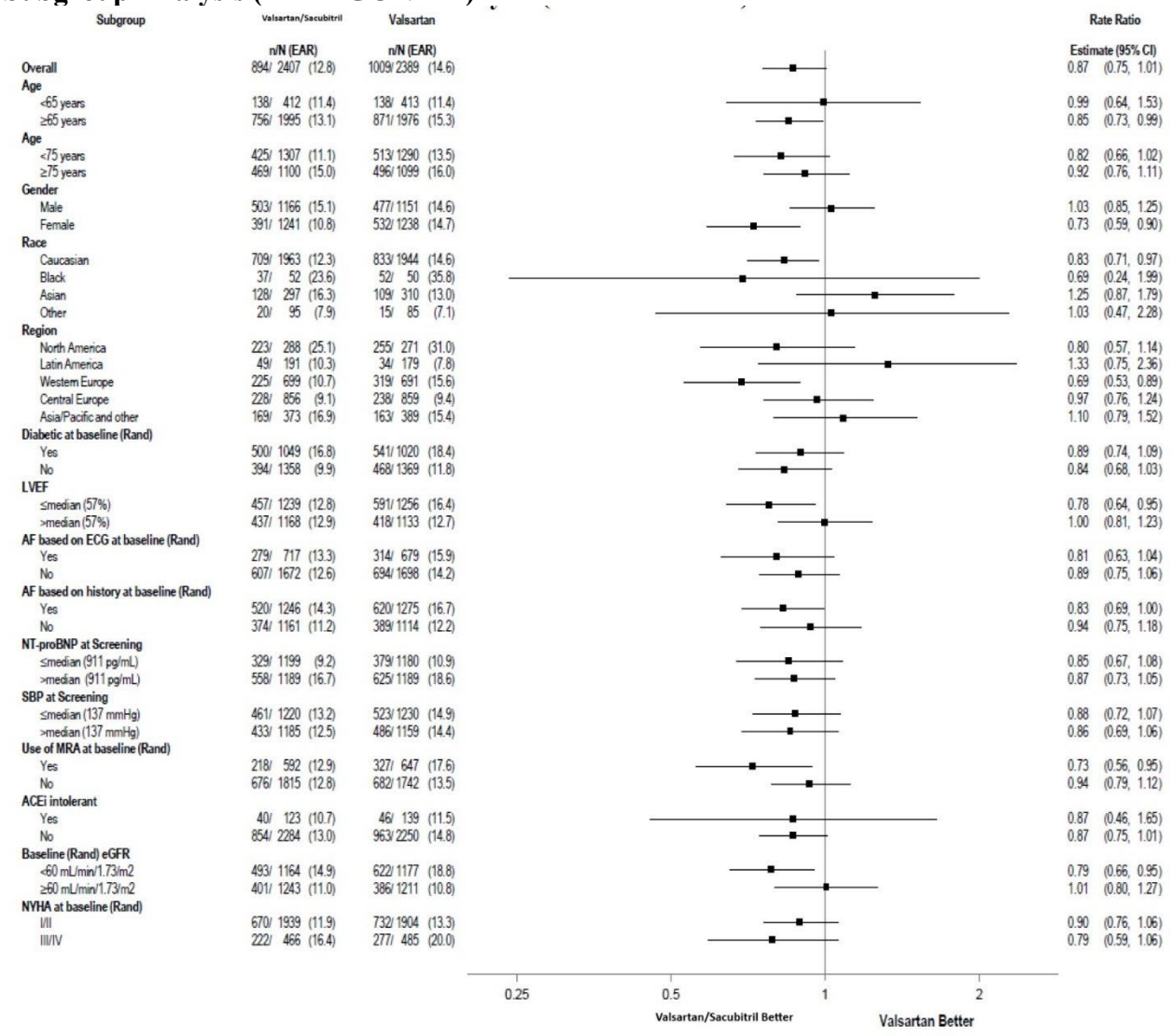
Figure 2 shows the mean number of composite endpoint events of total HF hospitalizations and CV death over time.

Figure 2: Mean Number of Events Over Time for the Primary Composite Endpoint of Total HF Hospitalizations and CV Death



A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes (Figure 3).

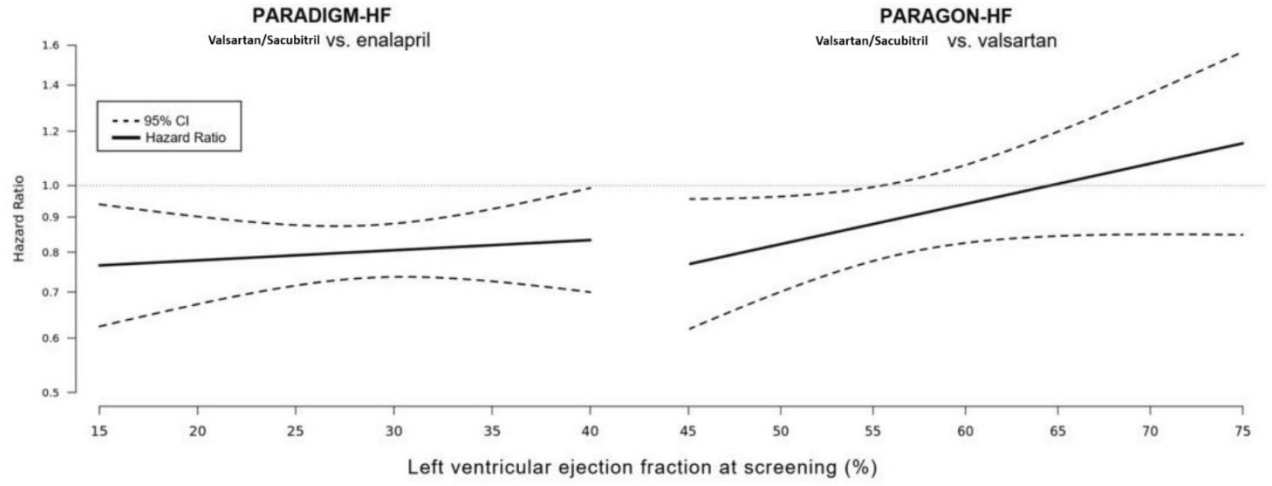
Figure 3: Primary Composite Endpoint of Total HF Hospitalizations and CV Death – Subgroup Analysis (PARAGON-HF)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors.

In an analysis of the relationship between LVEF and outcome in PARADIGM-HF and PARAGON- HF, patients with LVEF below normal treated with sacubitril/valsartan experienced greater risk reduction (Figure 4).

Figure 4: Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by
LVEF in PARADIGM-HF and PARAGON-HF



Hypertension
The antihypertensive effect of sacubitril/valsartan was evaluated in two randomized, double-blind, active- controlled, 8-week studies evaluating the efficacy and safety of sacubitril/valsartan in comparison to olmesartan (CLCZ696A2315 and CLCZ696A1306) in more than 2,500 adult patients of which more than 1,700 patients received sacubitril/valsartan . Both studies demonstrated non-inferiority as well as superiority of the mean sitting systolic blood pressure (msSBP) lowering effect of both sacubitril/valsartan 200mg once daily (2.3 and 5.0 mmHg in each study, respectively) and sacubitril/valsartan 400mg once daily (3.5 and 7.0 mmHg) compared to olmesartan 20mg once daily. Consistent results were observed in mean diastolic BP.

Additionally, persistency of blood pressure lowering effect was demonstrated in a 52-week, safety, tolerability and efficacy, open-label, extension study (CLCZ696A2219E1) in which 341 patients were received sacubitril/valsartan as a monotherapy or in combination with amlodipine and hydrochlorothiazide

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.

<u>Absorption</u>
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. Following once daily dosing of sacubitril/valsartan, steady state levels of sacubitril, LBQ657 (sacubitrilat) and valsartan are achieved in 5 days with no accumulation in sacubitril and valsartan and 1.2-fold accumulation in sacubitrilat. 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 (T½) 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 patients
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. 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.
Safety and efficacy of sacubitril/valsartan in patients with essential hypertension and with severe renal impairment have not been established.

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. 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. In patients with moderate hepatic impairment (Child-Pugh B classification), a starting dose of 50 mg twice daily is recommended in patients with heart failure and 100 mg once daily in hypertensive patients. 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.

Race/Ethnicity
The pharmacokinetics of sacubitril/valsartan (sacubitril, sacubitrilat and valsartan) are comparable across different race and ethnic groups (Caucasians, Blacks, Asians, Japanese and others).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SACUBASSEL 50
Microcrystalline Cellulose (PH 102), L-HPC(LH-11), Crospovidone (kollidon CL), Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Titanium dioxide, Macrogol, Talc, Iron oxide red and Black iron oxide

SACUBASSEL 100
Microcrystalline Cellulose (PH 102), L-HPC(LH-11), Crospovidone (kollidon CL), Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Titanium dioxide, Macrogol, Talc, Iron oxide red, Iron oxide yellow and Black iron oxide

SACUBASSEL 200
Microcrystalline Cellulose (PH 102), L-HPC(LH-11), Crospovidone (kollidon CL), Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Titanium dioxide, Macrogol, Talc, Iron oxide red and Black iron oxide

6.2 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from moisture.

6.3 Pack size

SACUBASSEL 50mg – Alu-Alu blisters of 10's tablets OR 14’s tablets. Three blisters of 10's OR Two blisters of 14’s in a carton.

SACUBASSEL 100mg – Alu-Alu blisters of 10's tablets OR 14’s tablets. Two blisters of 14’s OR Six blisters of 10's in a carton.
SACUBASSEL 200mg – Alu-Alu blisters of 7's tablets OR 10’s tablets. Eight blisters of 7’s OR Six blisters of 10's in a carton.

7. PRODUCT REGISTRATION HOLDER
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STRATA OFFICE, NO. 3, JALAN BANGSAR, KL ECO CITY,
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MALAYSIA

8. MANUFACTURER
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54 & 83, Bachupally Village,
Bachupally Mandal, Medchal-
Malkajgiri District,
Telangana State 500090, India

9. DATE OF REVISION
August 2026