1. NAME OF THE MEDICINAL PRODUCT

Savagen 24mg/26mg Film Coated Tablets
Savagen 49mg/51mg Film Coated Tablets
Savagen 97mg/103mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Savagen Film Coated Tablets are available in 3 strengths:

Savagen 24mg/26mg Film Coated Tablets: Each tablet contains 25.60mg of Sacubitril Sodium equivalent to 24.30mg of Sacubitril and 28.30mg of Valsartan Disodium equivalent to 25.70 mg of Valsartan. This has been rounded up to 24mg/26mg throughout the document.

Savagen 49mg/51mg Film Coated Tablets: Each tablet contains 51.195mg of Sacubitril Sodium equivalent to 48.60mg of Sacubitril and 56.59mg of Valsartan Disodium equivalent to 51.40 mg of Valsartan. This has been rounded up to 49mg/51mg throughout the document.

Savagen 97mg/103mg Film Coated Tablets: Each tablet contains 102.39mg of Sacubitril Sodium equivalent to 97.20mg of Sacubitril and 113.18mg of Valsartan Disodium equivalent to 102.80 mg of Valsartan. This has been rounded up to 97mg/103mg throughout the document.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablets.

Savagen 24mg/26mg Film Coated Tablets: White colored ovaloid shaped biconvex tablets, debossed with "N3" on one side and plain on another side.

Savagen 49mg/51mg Film Coated Tablets: Light yellow colored ovaloid shaped biconvex tablets, debossed with "N2" on one and plain on another side.

Savagen 97mg/103mg Film Coated Tablets: Pink colored ovaloid shaped biconvex tablets, debossed with "N1" on one and plain on another side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Heart failure
Savagen 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.

Savagen 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.

Hypertension
Savagen is indicated for the treatment of essential hypertension.
Savagen 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 Savagen is one tablet of 49mg/51mg 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 97mg/103mg twice daily, as tolerated by the patient.

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 Savagen is recommended.

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). 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 24mg/26mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended in these patients.

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg. A starting dose of 24mg/26mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg.

Savagen 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.

The valsartan contained within Savagen is more bioavailable than the valsartan in other marketed tablet formulations.

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 Savagen is 97mg/103mg once daily. In patients whose blood pressure could not be adequately controlled with Savagen 97mg/103mg once daily, the dose can be increased to 2 tablets of 97mg/103mg once daily. In hypertensive patients with heart failure, the heart failure dosing is recommended. Savagen may be used alone or in combination with other antihypertensive agents except angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

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 24mg/26mg 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) Savagen should be used with caution and a starting dose of 24mg/26mg twice daily is recommended.

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

Hepatic impairment
No dose adjustment is required when administering Savagen 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. Savagen should be used with caution in these heart failure patients and the recommended starting dose is 24mg/26mg twice daily. A starting dose of 49mg/51mg once daily is recommended for essential hypertensive patients with moderate hepatic impairment (Child-Pugh B classification). Savagen is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).

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

Method of administration
Oral use.
Savagen may be administered with or without food. The tablets must be swallowed with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients.
- Concomitant use with ACE inhibitors. Sacubitril/Valsartan must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema.
- 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).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimesters of pregnancy.

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. 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.
- The combination of Sacubitril/Valsartan with direct renin inhibitors such as aliskiren is not recommended. 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).
- Savagen contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product.

Hypotension

Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Sacubitril/Valsartan, 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. 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. 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.

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). 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. 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. 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.
Black patients have an increased susceptibility to develop angioedema.

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.

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

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.

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). The combination of Sacubitril/Valsartan with direct renin inhibitors such as aliskiren is not recommended. 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).

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.

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.

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.

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 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 (sacubitrilat)) 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 (sacubitrilat) 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.

<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

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.

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.

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.

Breastfeeding

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

Fertility

There are no available data on the effect of Sacubitril/Valsartan on human fertility.

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
The most commonly reported adverse reactions during treatment with Sacubitril/Valsartan were hypotension, hyperkalaemia and renal impairment. Angioedema was reported in patients treated with Sacubitril/Valsartan.

Tabulated list of adverse reactions

Adverse reactions are ranked by System organ class and by frequency: very common; common; uncommon; rare; very rare. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

System organ class	Preferred term	Frequency category
Blood and lymphatic system disorders	Anaemia	Common
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalemia*	Very common
	Hypokalemia	Common
	Hypoglycaemia	Common
Nervous system disorders	Dizziness	Common

System organ class	Preferred term	Frequency category
	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
Tabulated list of adverse reactions

System organ class	Preferred term	Frequency category
Nervous system disorders	Dizziness	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%).

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.

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 (sacubitrilat), 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 (sacubitrilat) 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. BNP is not a suitable biomarker of heart failure in patients treated with Sacubitril/Valsartan because BNP is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

In PARAMOUNT study in patients with heart failure with LVEF ≥ 45% comparing 200 mg of Sacubitril/Valsartan to 160 mg of valsartan twice-daily, Sacubitril/Valsartan decreased NT-proBNP by 17% while valsartan increased NT-proBNP by 8% at Week 12.

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 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.

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.

Hypertension

The antihypertensive effect of Sacubitril/Valsartan was evaluated in a study evaluating the efficacy and safety of Sacubitril/Valsartan in comparison to olmesartan (CLCZ696A2315 and CLCZ696A1306). 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 study (CLCZ696A2219E1) in which patients were received Sacubitril/Valsartan as a monotherapy or in combination with amlodipine and hydrothiazide.

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.

Absorption

Following oral administration, Sacubitril/Valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657 (sacubitrilat). 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 (sacubitrilat) and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 (sacubitrilat) 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 (sacubitrilat) and valsartan. Sacubitril/Valsartan can be administered with or without food.

Distribution

Sacubitril, LBQ657 (sacubitrilat) and valsartan are highly bound to plasma proteins (94-97%). Based on the comparison of plasma and CSF exposures, LBQ657 (sacubitrilat) 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 (sacubitrilat) by carboxylesterases 1b and 1c; LBQ657 (sacubitrilat) 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 (sacubitrilat)) and ~13% of valsartan and its metabolites are excreted in urine; 37-48% of sacubitril (primarily as LBQ657 (sacubitrilat)) and 86% of valsartan and its metabolites are excreted in faeces.

Sacubitril, LBQ657 (sacubitrilat) 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 (sacubitrilat) 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 (sacubitrilat) 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 (sacubitrilat) in patients with mild to severe renal impairment. The exposure of LBQ657 (sacubitrilat) 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 (sacubitrilat) 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 (sacubitrilat) 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 (sacubitrilat) 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 24mg/26mg twice daily is recommended in patients with heart failure and 49mg/51mg once daily in hypertensive patients.

Sacubitril/Valsartan has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis.

Effect of gender
The pharmacokinetics of Sacubitril/Valsartan [sacubitril, LBQ657 (sacubitrilat) 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

Tablet core:
Microcrystalline Cellulose, Hydroxypropyl Cellulose, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate, Talc

Film-coat:
Opadry AMB II High Performance Moisture Barrier Film Coating 88A180021 White (24mg/26mg), Opadry AMB II High Performance Moisture Barrier Film Coating 88A520126 Yellow (49mg/515mg), Opadry AMB II High Performance Moisture Barrier Film Coating 88A640044 Pink (97mg/103mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the expiry date on the product labels.

6.4 Special precautions for storage

Store below 30°C. Store in the original package. Protect from moisture.

6.5 Nature and contents of container

Alu/Alu blisters in carton of 1 x 10’s, 3 x 10’s, 6 x 10's, 10 x 10's, 50 x 10's and 100 x 10's. Not all packs sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MANUFACTURER

Manufactured by:
Novugen Pharma Sdn. Bhd.
No. 27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
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Product Registration Holder:
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8 DATE OF REVISION

30/09/2024

Package insert is drafted in Times New Roman with font size of 11, subject to change based on any other legible font and font size.