SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: FOETAL TOXICITY

When pregnancy is detected, discontinue **VALSATRIL®** as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing foetus

1. NAME OF THE PRODUCT

VALSATRIL® 50 (Sacubitril/Valsartan) Film Coated Tablets

VALSATRIL® 100 (Sacubitril/Valsartan) Film Coated Tablets

VALSATRIL® 200 (Sacubitril/Valsartan) Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VALSATRIL® 50 Film Coated Tablets
Each film coated tablet contains:
Sacubitril.....24mg
Valsartan.....26mg
(as sacubitril valsartan sodium salt complex MS)

VALSATRIL® 100 Film Coated Tablets
Each film coated tablet contains:
Sacubitril.....49mg
Valsartan.....51mg
(as sacubitril valsartan sodium salt complex MS)

VALSATRIL® 200 Film Coated Tablets
Each film coated tablet contains:
Sacubitril.....97mg
Valsartan.....103mg
(as sacubitril valsartan sodium salt complex MS)

3. PHARMACEUTICAL FORM

Film-coated tablet

Appearance:

VALSATRIL® 50 Film Coated Tablets: White color, film coated tablet capsular shaped tablet, engraved SAMI on one side and plain on the other side.

VALSATRIL® 100 Film Coated Tablets: Light yellow to yellow color, film coated capsular shaped tablet, engraved SAMI on one side and plain on the other side.

VALSATRIL® 200 Film Coated Tablets: Light pink to pink color, film coated oblong shape tablet, plain from both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Adult heart failure: **VALSATRIL®** is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Paediatric heart failure: **VALSATRIL®** is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

General considerations: Sacubitril/valsartan 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. The valsartan contained within sacubitril/valsartan 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.

Adult heart failure: The recommended starting dose of **VALSATRIL®** 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] ≤95mmHg, symptomatic hypotension, hyperkalemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation is recommended. In the PARADIGM-HF study, sacubitril/valsartan was administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other 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 levels >5.4mmol/l or with SBP <100mmHg. A starting dose of 24mg/26mg twice daily should be considered for patients with SBP ≥100 to 110mmHg.

Paediatric heart failure: Table below shows the recommended dose for paediatric patients. The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient. Sacubitril/valsartan film-coated tablets are not suitable for children weighing less than 40kg. Sacubitril/valsartan granules are available for these patients.

Patient weight	To be given twice daily			
	Half the starting dose*	Starting dose	Intermediate dose	Target dose
Paediatric patients less than 40kg	0.8mg/kg#	1.6mg/kg#	2.3mg/kg#	3.1mg/kg#
Paediatric patients at least 40kg, less than 50kg	0.8mg/kg#	24mg/26mg	49mg/51mg	72mg/78mg
Paediatric patients at least 50kg	24mg/26mg	49mg/51mg	72mg/78mg	97mg/103mg

***** Half the starting dose is recommended in patients who have not been taking an ACE inhibitor or an ARB or have been taking low doses of these medicinal products, patients who have renal impairment (estimated glomerular filtration rate [eGFR] <60ml/min/1.73m^2) and patients who have moderate hepatic impairment.

0.8 mg/kg, 1.6mg/kg, 2.3mg/kg and 3.1mg/kg refer to the combined amount of sacubitril and valsartan and are to be given using granules.

In patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, half of the starting dose is recommended. For paediatric patients weighing 40kg to less than 50kg, a starting dose of 0.8mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased to the standard starting dose following the recommended dose titration in Table above and adjusted every 3-4 weeks. For example, a paediatric patient weighing 25kg who has not previously taken an ACE inhibitor should start with half the standard starting dose, which corresponds to 20mg (25kg × 0.8mg/kg) twice daily, given as granules. After rounding to the closest number of full capsules, this corresponds to 2 capsules of 6mg/6mg sacubitril/valsartan twice daily. Treatment should not be initiated in patients with serum potassium level >5.3mmol/l or with SBP <5th percentile for the age of the patient. If patients experience tolerability issues (SBP <5th percentile for the age of the patient, symptomatic hypotension, hyperkalemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation of sacubitril/valsartan is recommended.

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 60-90ml/min/1.73m^2) renal impairment. Half of the starting dose should be considered in patients with moderate renal impairment (eGFR 30-60ml/min/1.73m^2). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30ml/min/1.73m^2), sacubitril/valsartan should be used with caution and half of the starting dose is recommended. In paediatric patients weighing 40kg to less than 50kg, a starting dose of 0.8mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks. There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended. *Hepatic impairment:* No dose adjustment is required when administering Sacubitril/valsartan 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 aspartate transaminase (AST)/alanine transaminase (ALT) values more than twice the upper limit of the normal range. Sacubitril/valsartan should be used with caution in these patients and half of the starting dose is recommended. In paediatric patients weighing 40kg to less than 50kg, a starting dose of 0.8mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased following the recommended dose titration every 2- 4 week. Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification). *Paediatric population:* The safety and efficacy of sacubitril/valsartan in children aged below 1 year have not been established.

Method of administration: Oral use. **VALSATRIL®** may be administered with or without food. 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.
- 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 <60ml/min/1.73m^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 patients with renal impairment (eGFR <60ml/min/1.73m^2). ● **VALSATRIL®** contains valsartan, and therefore should not be co-administered with another ARB containing medicinal products.

Hypotension: Treatment should not be initiated unless SBP is ≥100mmHg for adult patients or ≥5th percentile SBP for the age of the paediatric patient. Patients with SBP below these values were not studied. Cases of symptomatic hypotension have been reported in adult patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112mmHg). 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.
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. There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30ml/min/1.73m^2) and these patients may be at greatest risk of hypotension. 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). Down-titration should be considered in patients who develop a clinically significant decrease in renal function.
Hyperkalemia: Treatment should not be initiated if the serum potassium level is >5.4mmol/l in adult patients and >5.3mmol/l in paediatric patients. Use of sacubitril/valsartan may be associated with an increased risk of hyperkalemia, although hypokalemia 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 antagonist. If patients experience clinically significant hyperkaliemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4mmol/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 1mg/1ml (0.3-0.5ml), 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 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.
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 the 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 medicinal product contains less than 1mmol sodium (23mg) per 97mg/103mg dose, that is to say essentially 'sodium free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:
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 patients with renal impairment (eGFR <60ml/min/1.73m^2). The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended. A combination of sacubitril/valsartan with aliskiren is potentially associated with a higher frequency of adverse reactions such as hypotension, hyperkalemia, 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 products.
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 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 5bpm 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:
Fertility: There are no available data on the effect of sacubitril/valsartan on human fertility. No impairment of fertility was demonstrated in studies.
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.
Breast-feeding: Because of the potential risk for adverse reactions in breastfed newborns/infants, it is not recommended during breast-feeding. A decision should be made whether to abstain from breast-feeding or to discontinue, taking into account the importance of sacubitril/valsartan to the mother.

4.7. EFFECTS ON THE 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:
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). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.
Blood and lymphatic system disorders: *Common:* Anaemia.
Immune system disorders: *Uncommon:* Hypersensitivity.
Metabolism and nutrition disorders: *Very common:* Hyperkalaemia. *Common:* Hypokalaemia, hypoglycaemia. *Uncommon:* Hyponatraemia.
Psychiatric disorders: *Rare:* Hallucinations**, sleep disorders. *Very rare:* Paranoia.
Nervous system disorders: *Common:* Dizziness, headache, syncope. *Uncommon:* Dizziness postural.
Ear and labyrinth disorders: *Common:* Vertigo.
Vascular disorders: *Very common:* Hypotension. *Common:* Orthostatic hypotension.
Respiratory, thoracic and mediastinal disorders: *Common:* Cough.
Gastrointestinal disorders: *Common:* Diarrhoea, nausea, gastritis.
Skin and subcutaneous tissue disorders: *Uncommon:* Pruritus, rash, angioedema.
Renal and urinary disorders: *Very common:* Renal impairment. *Common:* Renal failure (renal failure, acute renal failure).
General disorders and administration site conditions: *Common:* Fatigue, asthenia.
**Including auditory and visual hallucinations.

4.9. OVERDOSE:
Limited data are available with regard to overdose in humans. A single dose of 583mg sacubitril/617mg valsartan and multiple doses of 437mg sacubitril/463mg 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.

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.

SUMMARY OF PRODUCT CHARACTERISTICS

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 remodeling.

5.2. PHARMACOKINETICS:
The valsartan contained within sacubitril/valsartan is more bioavailable than the valsartan in other marketed tablet formulations; 26mg, 51mg, and 103mg of valsartan in sacubitril/valsartan is equivalent to 40mg, 80mg and 160mg of valsartan in other marketed tablet formulations, respectively.
Paediatric population: The pharmacokinetics of sacubitril/valsartan were evaluated in paediatric heart failure patients aged 1 month to <1 year and 1 year to <18 years and indicated that the pharmacokinetic profile of sacubitril/valsartan in pediatric and adult patients is similar.
Adult population: *Absorption:* Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolized 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 a 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 was 75 liters to 103 liters, respectively. *Biotransformation:* Sacubitril is readily converted to LBQ657 by carboxylesterases 1b and 1c; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized, 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%). *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 feces. 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 24mg sacubitril/26mg valsartan to 97mg sacubitril/103mg 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 (30ml/min/1.73m^2 ≤ eGFR <60ml/min/1.73m^2) and severe renal impairment (15ml/min/1.73m^2 ≤ eGFR <30ml/min/1.73m^2) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60ml/min/1.73m^2 ≤ eGFR <90ml/min/1.73m^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. *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.
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 (24mg sacubitril/26mg valsartan/kg/day) for two weeks. In this study CSF Aβ clearance in cynomolgus monkeyswas 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. Additionally, in a toxicology study in cynomolgus monkeys treated with sacubitril/valsartan at 146mg sacubitril/154mg 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:
VALSATRIL® 50 Film Coated Tablets:
Core: ● Microcrystalline cellulose ● Hydroxypropyl cellulose ● Crospovidone ● Talcum ● Silicon dioxide ● Magnesium stearate
Coating: ● Hydroxypropyl methyl cellulose ● Simethicone ● Talcum Powder ● Titanium dioxide ● Polyethylene glycol ● Poly vinyl pyrrolidone
VALSATRIL® 100 Film Coated Tablets:
Core: ● Microcrystalline cellulose ● Hydroxypropyl cellulose ● Crospovidone ● Talcum ● Silicon dioxide ● Magnesium stearate
Coating: ● Hydroxypropyl methyl cellulose ● Simethicone ● Talcum Powder ● Titanium dioxide ● Polyethylene glycol ● Poly vinyl pyrrolidone ● Yellow iron oxide color
VALSATRIL® 200 Film Coated Tablets:
Core: ● Microcrystalline cellulose ● Hydroxypropyl cellulose ● Crospovidone ● Talcum ● Silicon dioxide ● Magnesium stearate
Coating: ● Hydroxypropyl methyl cellulose ● Simethicone ● Talcum Powder ● Titanium dioxide ● Polyethylene glycol ● Poly vinyl pyrrolidone ● Red iron oxide color

6.2. INCOMPATIBILITIES:
Not applicable

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Do not store over 30°C, and protect from heat and moisture. Improper storage may deteriorate the medicine. Keep out of reach of chlildren.

6.5. NATURE AND CONTENTS OF CONTAINER:
VALSATRIL® 50 Film Coated Tablets: Alu/Alu blister, pack size is 14 tablets.
VALSATRIL® 100 Film Coated Tablets: Alu/Alu blister, pack size is 14 tablets.
VALSATRIL® 200 Film Coated Tablets: Alu/Alu blister, pack size is 14 tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
Innovator's Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)

VALSATRIL® 50 Film Coated Tablets: 093098
VALSATRIL® 100 Film Coated Tablets: 093083
VALSATRIL® 200 Film Coated Tablets: 093082

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

VALSATRIL® 50 Film Coated Tablets: 16th January, 2019
VALSATRIL® 100 Film Coated Tablets: 16th January, 2019
VALSATRIL® 200 Film Coated Tablets: 16th January, 2019

10. DATE OF REVISION OF THE TEXT

ویل ساٹرل® ٹیبلٹ

(سیکیوبیٹرل/والسارٹن)

ہدایات:

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔