SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medical Product
Sacuzac 200 (Sacubitril/Valsartan Tablets 97/103 mg)

2. Qualitative & Quantitative Composition:

Sacuzac 200 (Sacubitril/Valsartan Tablets 97/103 mg)
Each film coated tablet contains:
97 mg Sacubitril and 103 mg Valsartan

(As Sodium Salt Complex)
Excipients q.s.
Colour: Titanium Dioxide

For a full list of excipients, see section 6.1 of SmPC

3.0 PHARMACEUTICAL FORM

White to off-white coloured, ovaloid, film coated tablets, plain on both sides.

CLINICAL PARTICULARS

4.1: Therapeutic Indications:

Adult Heart Failure
Sacubitril/Valsartan tablet is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Paediatric Heart Failure
Sacubitril/Valsartan tablet 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

General Considerations

Sacubitril/Valsartan tablet 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 mustnot be started for at least 36 hours after discontinuing ACE inhibitor therapy.
The valsartan contained within Sacubitril/Valsartan tablet 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 Sacubitril/Valsartan tablet is one tablet of 49 mg/51 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 97 mg/103 mg 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 Sacubitril/Valsartan tablet is recommended.
In PARADIGM-HF study, Sacubitril/Valsartan tablet 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 24 mg/26 mg 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 24 mg/26 mg twice daily should be considered for patients with SBP ≥ 100 to 110 mmHg.

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

Renal impairment
No dose adjustment is required in patients with mild (eGFR 60-90 ml/min/1.73 m2) renal impairment. Half of the starting dose should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m2). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2), Sacubitril/Valsartan tablet should be used with caution and half of the starting dose is recommended. In paediatric patients weighing 40kg to less than 50 kg, a starting dose of 0.8 mg/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 tablet is not recommended.

Hepatic impairment
No dose adjustment is required when administering Sacubitril/Valsartan tablet 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 tablet should be used with caution in these patients and half of the starting dose is recommended. In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks.
Sacubitril/Valsartan tablet is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh classification).

Paediatric population
The safety and efficacy of Sacubitril/Valsartan tablet in children aged below 1 year have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration
Oral use.
Sacubitril/Valsartan tablet 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 listed.
- Concomitant use with ACE inhibitors. Sacubitril/Valsartan tablet 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 warning 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 36hours 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 m2).
- Sacubitril/Valsartan tablet 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 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 symptom atichypotension 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 (<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 shouldbe corrected before starting treatment with sacubitril/valsartan, however, such corrective action must be carefullyweighed against the risk of volume overload.

Renal impairment

Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild andmoderate 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 atgreatest risk of hypotension. There is no experience in patients with end-stage renal disease and useof 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 bydehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs). Down-titrationshould be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is >5.4 mmol/l in adult patients and >5.3 mmol/l inpaediatric patients. 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 patientswho have risk factors such as renal impairment, diabetes mellitus or hypo aldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If patients experience clinically significant hyperkalaemiaadjustment of concomitant medicinal products, or temporary down– titration or discontinuation is recommended. Ifserum 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 isrecommended if sacubitril/valsartan is used in these patients. Sacubitril/valsartan is contraindicated in patients with aknown history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathicangioedema.
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 isrecommended.

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 tolimited 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 neprilysinsubstrate.

Patients with hepatic impairment
There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or withAST/ALT values more than twice the upper limit of the normal range. In these patients, exposure may be increased andsafety 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 beenassociated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartantreatment should be considered.

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

Interactions with other medicinal products and other forms of Interactions :

Interactions resulting in a contraindication

ACE inhibitors

The concomitant use of sacubitril/valsartan with ACE inhibitors is contraindicated, as the concomitant inhibition ofneprilysin (NEP) and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hoursafter taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the lastdose of sacubitril/valsartan

Aliskiren

The concomitant use of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patientswith diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2).
Thecombination 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 reactionssuch as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors).

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 tablet may therefore increase thesystemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of sacubitril/valsartanincreased the Cmax of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Caution should beexercised when co-administering sacubitril/valsartan with statins. No clinically relevant interaction was observed whensimvastatin and Sacubitril/Valsartan tablet 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 renalf unction, 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 treatedwith sacubitril/valsartan.

Nitrates, e.g. nitro-glycerine
There was no interaction between sacubitril/valsartan and intravenously administered nitro-glycerine with regard to blood pressure reduction. Co-administration of nitro-glycerine and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitro-glycerine 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 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 firsttrimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there isno 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 alternativeantihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy isdiagnosed, treatment with ARBs should be stopped immediately and, if appropriate, alternative therapy should bestarted. 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.

Breast-feeding
It is not known whether sacubitril/valsartan is excreted in human milk. The components of Sacubitril/Valsartan tablet, 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 Sacubitril/Valsartan tablet 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 machine:**
Sacubitril/valsartan has a minor influence on the ability to drive and use machines. When driving vehicles or operatingmachines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable Effects:
Summary of the safety profile
The most commonly reported adverse reactions in adults during treatment with sacubitril/valsartan were hypotension(17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%). Angioedema was reported in patientstreated with sacubitril/valsartan (0.5%).

Tabulated list of adverse reactions
Adverse reactions are ranked by System organ class and then by frequency with the most frequent first, using thefollowing convention: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1 000 to <1/100); rare (≥ 1/10000 to <1/1 000); very rare (<1/10 000). Within each frequency grouping, adverse reactions are ranked in order ofdecreasing seriousness.

Table 2: List of adverse reactions

System Organ Class	**Preferred Term**	**Frequency Category**
Blood and lymphatic system disorders	Anaemia	Common
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalaemia*	Very common
	Hypokalaemia	Common
	Hypoglycaemia	Common
	Hyponatraemia	Uncommon
Psychiatric disorders	Hallucinations**	Rare
	Sleep disorders	Rare
	Paranoia	Very rare
Nervous system disorders	Dizziness	Common
	Headache	Common
	Syncope	Common
	Dizziness postural	Uncommon
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 (acute renal failure)	Common
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common

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

Description of selected adverse reactions

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan. In PARADIGM-HF, angioedema was reported in 0.5% of patients treated with sacubitril/valsartan, compared
with 0.2% of patients treated with enalapril. Ahigher 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 frombaseline 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% ofenalapril-treated patients.

Note for Tanzania: Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Paper based reporting: TMDA yellow card; Online reportinghttps/Isort.tmda.go.t/USSO; reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152ᵒ00# and follow the instructions.
Note For Kenya: Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

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

5.0 PHARMACOLOGICAL PROPERTIES
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 simultaneouslyinhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and byblocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits ofsacubitril/valsartan in heart failure patients are attributed to the enhancement of peptides that are degraded byneprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin IIby valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting inincreased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result invasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin andaldosterone 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 ofcellular growth and proliferation, and subsequent maladaptive cardiovasculair re-modelling.

5.2 Pharmacokinetics Properties

Absorption

Following oral administration, Sacubitril / Valsartan dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be ≥ 60%. The valsartan in 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.

Following twice-daily dosing of Sacubitril / Valsartan, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, whereas LBQ657 accumulates by 1.6-fold. Sacubitril / Valsartan administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Although there is a decrease in exposure to valsartan when Sacubitril / Valsartan is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. Sacubitril / Valsartan can therefore be administered with or without food.

Distribution

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 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 volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively.

Biotransformation

Sacubitril is readily converted to LBQ657 by esterase; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (< 10%).

Elimination

Following oral administration, 52% to 68% of sacubitril (primarily as LBQ657) and ~ 13% of valsartan and its metabolites are excreted in urine; 37% to 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 (T1/2) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.

5.3 Preclinical Safety data:

Non-clinical data (including studies with sacubitril and valsartan components and/or sacubitril/valsartan) reveal nospecial hazard for humans based on

conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity,carcinogenic potential and fertility.

Fertility, reproduction and development

Sacubitril/valsartan treatment during organogenesis resulted in increased embryofoetal lethality in rats at doses ≥ 49 mgsacubitril/51 mg valsartan/kg/day (≤ 0.72-fold the maximum recommended human dose [MRHD] on the basis of AUC)and rabbits at doses ≥ 4.9 mg sacubitril/5.1 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis ofvalsartan and LBQ657 AUC, respectively). It is teratogenic based on a low incidence of foetal hydrocephaly, associatedwith maternally toxic doses, which was observed in rabbits at a sacubitril/valsartan dose of ≥ 4.9 mg sacubitril/5.1 mgvalsartan/kg/day. Cardiovascular abnormalities (mainly cardiomegaly) were observed in rabbit foetuses at a maternallynon-toxic dose (1.46 mg sacubitril/1.54 mg valsartan/kg/day). A slight increase in two foetal skeletal variations(misshapen sternebra, sternebra bipartite ossification) was observed in rabbits at a sacubitril/valsartan dose of 4.9 mgsacubitril/5.1 mg valsartan/kg/day. The adverse embryofoetal effects of sacubitril/valsartan are attributed to theangiotensin receptor antagonist activity.

Sacubitril treatment during organogenesis resulted in embryo-foetal lethality and embryo-foetal toxicity (decreasedfoetal body weights and skeletal malformations) in rabbits at doses associated with maternal toxicity (500 mg/kg/day;5.7-fold the MRHD on the basis of LBQ657 AUC). A slight generalised delay in ossification was observed at doses of>50 mg/kg/day. This finding is not considered adverse. No evidence of embryo-foetal toxicity or teratogenicity wasobserved in rats treated with sacubitril. The embryo-foetal no-observed adverse effect level (NOAEL) for sacubitril wasat least 750 mg/kg/day in rats and 200 mg/kg/day in rabbits (2.2-fold the MRHD on the basis of LBQ657 AUC).

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

Other preclinical findings

Sacubitril/valsartan

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

Sacubitril

In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone massdevelopment and bone elongation at approximately 2-fold the AUC exposure to the active metabolite of sacubitril,LBQ657, based on sacubitril/valsartan paediatric clinical dose of 3.1 mg/kg twice daily. The mechanism for thesefindings in juvenile rats, and consequently the relevance to the human paediatric population, is unknown. A study inadult rats showed only a minimal transient inhibitory effect on bone mineral density but not on any other parametersrelevant for bone growth, suggesting no relevant effect of sacubitril on bone in adult patient populations under normalconditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults cannotbe excluded. Clinical data in paediatric patients (PANORAMA-HF study) did not show evidence that sacubitril/valsartanhas an impact on body weight, height, head circumference and fracture rate. Bone density was not measured in thestudy. However, long-term paediatric data on (bone)growth and fracture rates are not available.

Valsartan

In juvenile rats treated with valsartan (postnatal days 7 to 70), doses as low as 1 mg/kg/day produced persistentirreversible kidney changes consisting of tubular nephropathy (sometimes accompanied by tubular epithelial necrosis)and pelvic dilatation. These kidney changes represent an expected exaggerated pharmacological effect of angiotensinconverting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during thefirst 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to44 weeks after conception in humans. Functional renal maturation is an ongoing process within the first year of life inhumans. Consequently, a clinical relevance in paediatric patients less than 1 year of age cannot be excluded, whilepreclinical data do not indicate a safety concern for paediatric patients older than 1 year.

6.0 Pharmaceutical particulars

6.1 List of Excipients
Microcrystalline Cellulose
Low-substituted Hydroxypropyl Cellulose (LH-21)
Crospovidone
Isopropyl Alcohol BP
Colloidal Silicon Dioxide
Magnesium Stearate
Insta Moist shield
Aqua II A22R00896
White (Polyvinyl Alcohol
Triacetin
Talc
Titanium Dioxide
Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special Precautions for Storage
Keep out of reach of children.

6.5 Nature and Contents of Container.
10 tablets in Alu-Alu Blister pack, 3 such blisters in a printed carton along with pack Insert.

6.6 Special precautions for disposal:
Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 Storage Condition
Do not store above 30°C. Protect from moisture.

7.0 MARKETING AUTHORIZATION HOLDER

Ajanta Pharma Limited,
Ajanta House, Charkop, Kandivli (West),
Mumbai- 400 067, India

8.0 MARKETTING AUTHORIZATION NUMBER
CTD12009/25409

9.0 DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION
08-12-2025

10. DATE OF REVISION OF TEXT
08-12-2025