PROFESSIONAL INFORMATION FOR

SACUBITRIL VALSARTAN 24/26 mg CIPLA

SACUBITRIL VALSARTAN 49/51 mg CIPLA

SACUBITRIL VALSARTAN 97/103 mg CIPLA

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SACUBITRIL VALSARTAN 24/26 mg CIPLA film-coated tablets.

SACUBITRIL VALSARTAN 49/51 mg CIPLA film-coated tablets.

SACUBITRIL VALSARTAN 97/103 mg CIPLA film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SACUBITRIL VALSARTAN 24/26 mg CIPLA: Each film-coated tablet contains 24,3 mg of sacubitril and 25,7 mg of valsartan.

SACUBITRIL VALSARTAN 49/51 mg CIPLA: Each film-coated tablet contains 48,6 mg of sacubitril and 51,4 mg of valsartan.

SACUBITRIL VALSARTAN 97/103 mg CIPLA: Each film-coated tablet contains 97,2 mg of sacubitril and 102,8 mg of valsartan.

Sugar free.

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets.

SACUBITRIL VALSARTAN 24/26 mg CIPLA: White to off white, modified capsule shaped, biconvex film-coated tablets debossed with “725” on one side and “L” on the other side.

SACUBITRIL VALSARTAN 49/51 mg CIPLA: Light yellow to yellow, modified capsule shaped, biconvex film-coated tablets debossed with “726” on one side and “L” on the other side.

SACUBITRIL VALSARTAN 97/103 mg CIPLA: Light pink to pink, modified capsule shaped, biconvex film-coated tablets debossed with “L727” on one side and “plain” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SACUBITRIL VALSARTAN CIPLA is indicated in adult patients as second line treatment, replacing ACE inhibitors or ARB’s for treatment of symptomatic heart failure (NYHA class II - IV) in patients with systolic dysfunction. SACUBITRIL VALSARTAN CIPLA is administered as combination therapy with other appropriate heart failure therapies.

4.2 Posology and method of administration

Posology

The target dose is one (1) tablet of SACUBITRIL VALSARTAN 97/103 mg CIPLA twice daily.

The recommended starting dose is one (1) tablet of SACUBITRIL VALSARTAN 24/26 mg CIPLA twice daily for patients currently taking low doses of ACE inhibitors or ARB's.

Dose up titration by doubling the dose every 3 - 4 weeks is recommended until the target dose of one (1) tablet of SACUBITRIL VALSARTAN 97/103 mg CIPLA twice daily is achieved as tolerated by the patient. Each dose increment should be preceded by clinical observation for hypotension and laboratory evaluation of serum potassium and renal function.

To avoid hypotension, the recommended starting dose in patients previously using a high dose of ACE inhibitor or ARB is one (1) tablet of SACUBITRIL VALSARTAN 49/51 mg CIPLA twice daily.

SACUBITRIL VALSARTAN CIPLA must not be started for at least 36 hours after discontinuing ACE inhibitor therapy due to the potential risk of angioedema when used concomitantly with an ACE inhibitor (see **sections 4.3**, **4.4**, and **4.5**).

If patients experience tolerability issues (systolic blood pressure [SBP] ≤ 95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicines, down-titration or discontinuation of SACUBITRIL VALSARTAN CIPLA is recommended (see **section 4.4**).

Special populations

Elderly

Patients over the age of 65 years may have impaired renal function, therefore a lower starting dose in line with the renal function is recommended.

Renal impairment

SACUBITRIL VALSARTAN CIPLA is contraindicated in patients with severe renal function impairment (see **section 4.3**).

Hepatic impairment

No dose adjustment of SACUBITRIL VALSARTAN CIPLA is required in patients with mild to moderate hepatic impairment (Child-Pugh A and B classification).

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification). Therefore, use of SACUBITRIL VALSARTAN CIPLA in these patients is contraindicated (see **section 4.3**).

Paediatric patients

The safety and efficacy of SACUBITRIL VALSARTAN CIPLA in children and adolescents below 18 years have not been established. No data are available.

Method of administration

SACUBITRIL VALSARTAN CIPLA is administered orally. SACUBITRIL VALSARTAN CIPLA may be administered with or without food (see **section 5.2**). The tablets must be swallowed with a glass of water.

4.3 Contraindications

SACUBITRIL VALSARTAN CIPLA is contraindicated:

- In patients who are hypersensitive to sacubitril, valsartan or any other ingredient of SACUBITRIL VALSARTAN CIPLA (see **section 6.1**).
- In concomitant use with ACE inhibitors (see **section 4.4** and **4.5**). SACUBITRIL VALSARTAN CIPLA must not be administered for at least 36 hours after discontinuing ACE inhibitor therapy.
- In patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy (see **section 4.4**). These patients must never be given these medicines again.
- In patients with hereditary or idiopathic angioedema (see **section 4.4**).
- In patients with hypertrophic obstructive cardiomyopathy (HOCM).
- In patients with bilateral renal artery stenosis.
- In patients with renal artery stenosis in patients with a single kidney.
- In patients with aortic valve stenosis.
- In concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **section 4.5**).
- In patients with porphyria.
- In patients on lithium therapy. Concomitant administration of SACUBITRIL VALSARTAN CIPLA may lead to toxic blood concentrations of lithium (see **section 4.5**).
- In concomitant use with renin antagonists such as aliskiren-containing medicines in patients with diabetes mellitus or in patients with renal impairment (eGFR < 60 mL/min/1,73 m^2) (see **section 4.4** and **4.5**).
- In pregnancy and lactation (see **section 4.6**).
- In patients with severe renal function impairment (creatinine clearance less than 30 mL/min).

- In patients with severe hepatic impairment, biliary cirrhosis and cholestasis (see **section 4.2**).
- Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatine clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

Should a woman become pregnant while taking SACUBITRIL VALSARTAN CIPLA, the treatment should be stopped promptly and switched to a different antihypertensive medicine, see sections 4.3 and 4.8.

Dual blockage of the Renin-Angiotensin Aldosterone System (RAAS)

SACUBITRIL VALSARTAN CIPLA must not be administered with an ACE inhibitor or another ARB due to an increased risk of angioedema (see **section 4.3**). SACUBITRIL VALSARTAN CIPLA must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with SACUBITRIL VALSARTAN CIPLA is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of SACUBITRIL VALSARTAN CIPLA (see **section 4.2**, **4.3** and **4.5**).

SACUBITRIL VALSARTAN CIPLA should not be used concomitantly with direct renin inhibitors such as aliskiren (see **section 4.5**). SACUBITRIL VALSARTAN CIPLA with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR < 60 mL/min/1,73 m^2) (see **section 4.3** and **4.5**).

Hypotension

Cases of symptomatic hypotension have been reported commonly in patients treated with SACUBITRIL VALSARTAN CIPLA. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive medicines and treatment of other causes of hypotension (e.g. hypovolemia) 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 CIPLA.

If hypotension persists despite the measures taken, the dosage of SACUBITRIL VALSARTAN CIPLA should be reduced or the product should be discontinued (see **section 4.2**).

Treatment should not be initiated unless SBP ≥ 100 mmHg.

Impaired renal function

Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension (see **section 4.2**). There is limited experience in patients with severe renal impairment (estimated GFR < 30 mL/min/1,73 m^2) and these patients may be at greater risk of hypotension (see **section 4.3**) (Ref 6). The use of SACUBITRIL VALSARTAN CIPLA may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal inflammatory medicines (NSAIDs) (see **section 4.5**). Down titration or discontinuation of SACUBITRIL VALSARTAN CIPLA should be considered in patients who develop a clinically significant decrease in renal function. **(1A15, 2C3)** There is no experience in patients with end-stage renal disease and use of SACUBITRIL VALSARTAN CIPLA is not recommended.

Hyperkalaemia

The use of SACUBITRIL VALSARTAN CIPLA is associated with an increased risk of hyperkalaemia although hypokalaemia may also occur (see **section 4.8**). If clinically significant hyperkalaemia occurs, measures such as reducing dietary potassium or adjusting the dose of concomitant medications should be considered or temporary down-titration or discontinuation is recommended.

Monitoring of serum potassium is recommended especially in patients with risk factors such as diabetes mellitus, hypoaldosteronism or receiving a high potassium diet or on mineralocorticoid antagonists (see **section 4.2**).

Treatment should not be initiated if the serum potassium level is > 5,4 mmol/L.

Medications known to raise potassium levels (e.g. potassium sparing diuretics, potassium supplements) should not be used with SACUBITRIL VALSARTAN CIPLA.

Angioedema

Angioedema has been reported in patients treated with SACUBITRIL VALSARTAN CIPLA. If angioedema occurs, SACUBITRIL VALSARTAN CIPLA should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. SACUBITRIL VALSARTAN CIPLA must not be re-administered.

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 prior angioedema were not studied (see **section 4.3**). As they may be at high risk for angioedema, caution is recommended if SACUBITRIL VALSARTAN CIPLA is used in these patients. SACUBITRIL VALSARTAN CIPLA is contraindicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema (see **section 4.3**).
Black patients have an increased susceptibility to develop angioedema (see **section 4.8**).

Patients with renal artery stenosis
SACUBITRIL VALSARTAN CIPLA is contraindicated in patients with renal artery stenosis with one kidney (see **section 4.3**).

Patients with NYHA functional classification IV
Caution should be exercised when initiating SACUBITRIL VALSARTAN CIPLA 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 CIPLA because it is a neprilysin substrate (see **section 5.1**).

Patients with hepatic impairment

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

Fluoroquinolones and ACE inhibitors/angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **section 4.3**). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/angiotensin receptor blockers, whether used separately and/or concomitantly.

4.5 Interaction with other medicines and other forms of interaction

Interactions resulting in contraindications

ACE inhibitors

The concomitant use of SACUBITRIL VALSARTAN CIPLA with ACE inhibitors and ARBs is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. SACUBITRIL VALSARTAN CIPLA must not be started until 36 hours after taking the last dose of ACE inhibitor or ARB therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of SACUBITRIL VALSARTAN CIPLA (see **section 4.2** and **4.3**).

Aliskiren

The concomitant use of SACUBITRIL VALSARTAN CIPLA with aliskiren is contraindicated (see **section 4.3**).

Interactions resulting in concomitant use not being recommended

SACUBITRIL VALSARTAN CIPLA contains valsartan, and therefore should not be co-administered with another ARB-containing medicine (see **section 4.4**).

Interactions requiring precautions

Statins

In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. SACUBITRIL VALSARTAN CIPLA may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of SACUBITRIL VALSARTAN CIPLA increased the C_{max} of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1,3-fold. Therefore, caution should be exercised when co-administering SACUBITRIL VALSARTAN CIPLA with statins as the adverse effects of statins are dose/exposure related.

Sildenafil

Addition of a single dose of sildenafil to SACUBITRIL VALSARTAN CIPLA at steady state in patients with hypertension was associated with greater blood pressure reduction compared to administration of SACUBITRIL VALSARTAN CIPLA alone. Therefore, caution should be exercised when sildenafil or another PDE5 inhibitor is initiated in patients treated with SACUBITRIL VALSARTAN CIPLA.

Potassium

Concomitant use of potassium-sparing diuretics (e.g. triamterene, amiloride), mineralocorticoid, antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium may lead to increases in serum potassium, and to increased serum creatinine. Other medicines (such as heparin) may also lead to increases in serum creatinine. Monitoring of serum potassium is recommended if SACUBITRIL VALSARTAN CIPLA is co-administered with these medicines (see **section 4.4**).

Non-steroidal Anti-inflammatory drugs (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 CIPLA and NSAIDs may lead to an increased risk of worsening of renal function and increase in blood pressure. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in patients on SACUBITRIL VALSARTAN CIPLA who are taking NSAIDs concomitantly (see **section 4.4**).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists (see **section 4.3**). Therefore, this combination is contraindicated (see **section 4.3**). If diuretic is also used, the risk of lithium toxicity maybe increased further.

Furosemide

Co-administration of SACUBITRIL VALSARTAN CIPLA and furosemide had no effect on the pharmacokinetics of SACUBITRIL VALSARTAN CIPLA 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.

Nitrates

There was no interaction between SACUBITRIL VALSARTAN CIPLA and intravenously administered nitroglycerin with regards to blood pressure reduction. Co-administration of nitroglycerin and SACUBITRIL VALSARTAN CIPLA 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 CIPLA is co-administered with sublingual, oral or transdermal nitrates. In general, no dose adjustment is required.

OATP and MRP2 transporters

The active metabolites of sacubitril (LBQ657) and valsartan are OATP1B1, OATP1B3, OAT1 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of SACUBITRIL VALSARTAN CIPLA 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 LBQ657 or valsartan. Appropriate care should be exercised when initiating or ending concomitant treatment with such medicines.

Metformin

Co-administration of SACUBITRIL VALSARTAN CIPLA 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 CIPLA in patients receiving metformin, the clinical status of the patient should be evaluated.

Fluoroquinolones and ACE inhibitors/angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is the unknown (see **section 4.3**).

No significant interaction

No clinically meaningful interaction was observed when SACUBITRIL VALSARTAN CIPLA was co-administered with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol. No interaction is expected with atenolol, indomethacin, glyburide or cimetidine.

CYP450 interactions

In vitro metabolism studies indicate that the potential for CYP450 based interactions is low since there is a limited metabolism of SACUBITRIL VALSARTAN CIPLA via the CYP450 enzymes. SACUBITRIL VALSARTAN CIPLA does not induce or inhibit CYP450 enzymes.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

Women of childbearing potential should ensure effective contraception.

Pregnancy

SACUBITRIL VALSARTAN CIPLA is contraindicated in pregnancy (see **section 4.3**).

There are no data from the use of SACUBITRIL VALSARTAN CIPLA in pregnant women.

When pregnancy is planned or confirmed, SACUBITRIL VALSARTAN CIPLA should be discontinued. Medicines affecting the renin angiotensin system, such as SACUBITRIL VALSARTAN CIPLA, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Breastfeeding

It is not known whether SACUBITRIL VALSARTAN CIPLA is excreted in human milk. Because of the potential risk for adverse reactions in breastfed new-borns/infants, it is contraindicated during breastfeeding (see **section 4.3**).

Fertility

There are no available data on the effect of SACUBITRIL VALSARTAN CIPLA on human fertility.

4.7 Effects on ability to drive and use machines

SACUBITRIL VALSARTAN CIPLA 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

a) Summary of safety profile

The safety of sacubitril / valsartan in patients with chronic heart failure was evaluated in a reported study, in which patients were treated twice daily with sacubitril 97 mg / valsartan 103 mg. Patients received treatment for up to 4,3 years, with a median duration of exposure of 24 months; 3 271 patients were treated for more than one year.

Discontinuation of therapy due to an adverse event occurred in 450 (10,71 %) of sacubitril / valsartan treated patients. The events most frequently associated with dosage adjustment or treatment interruption were hypotension, hyperkalaemia and renal impairment.

b) Tabulated summary of adverse reactions

Table 1 List of adverse reactions

MedDRA system organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequent	Anaemia.
Immune system disorders	Less frequent	Hypersensitivity, angioedema.
Metabolism and nutrition disorders	Frequent	Hyperkalaemia, hypokalaemia, hypoglycaemia.
Nervous system disorders	Frequent	Dizziness, headache, syncope.
	Less frequent	Postural dizziness.
Ear and labyrinth	Frequent	Vertigo.
Vascular disorders	Frequent	Hypotension, orthostatic hypotension, syncope.

MedDRA system organ Class	Frequency	Side effects
Respiratory, thoracic and mediastinal disorders	Frequent	Cough.
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, gastritis.
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash
Renal and urinary disorders	Frequent	Renal impairment, renal failure (renal failure, acute renal failure).
General disorders and administration site conditions	Frequent	Fatigue, asthenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Hypotension is the most likely symptom of overdose due to the blood pressure lowering effects of SACUBITRIL VALSARTAN CIPLA. Symptomatic treatment should be provided.

SACUBITRIL VALSARTAN CIPLA is unlikely to be removed by haemodialysis due to high protein binding (see **section 5.2**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 7.6 Vascular medicines, others

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

ATC code: C09DX04

Mechanism of action

Sacubitril/valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase, NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complimentary cardiovascular benefits of sacubitril/valsartan in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan.

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

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

Pharmacodynamic effects

The pharmacodynamic effects of sacubitril/valsartan are consistent with simultaneous neprilysin inhibition and RAAS blockade. In a 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 longer 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. Sacubitril/valsartan also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations.

In a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1200 mg had no effect on cardiac repolarisation.

In another the study, sacubitril/valsartan decreased the plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because BNP is a neprilysin substrate (see **section 4.4**). NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

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 sacubitril 194 mg / valsartan 206 mg 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 these findings is not known.

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 formulation, respectively.

Absorption

Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657. These reach peak plasma concentrations in 2 hours, 1 hour and 2 hours respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60 % and 23 %, respectively.

Following twice daily dosing of sacubitril/valsartan, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three (3) days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates by 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 CSF exposures, LBQ657 crosses blood brain barrier to a limited extent (0,28 %). The average apparent volume of distribution of sacubitril/valsartan is ranging from 107,8 L to 157,4 L.

Biotransformation

Sacubitril is readily converted to LBQ657 by carboxylesterase 1b and 1c; LBQ657 is not further metabolised to a significant extent. Valsartan is minimally metabolised, as only about 20 % of the dose is recovered as metabolites. A hydroxyl metabolite of valsartan has been identified in plasma at low concentrations (< 10 %).

Since CYP450-enzyme mediated metabolism of sacubitril and valsartan is minimal, co-administration with medicines that impact CYP450 enzymes is not expected to impact pharmacokinetics.

In vitro metabolism studies indicate that potential for CYP450 based 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 LBQ657) and 13 % of valsartan and its metabolites are excreted in urine; 37 – 48 % of sacubitril (primarily as LBQ657) and 86 % of valsartan and its metabolites are excreted in faeces.

Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life ($T_{½}$) of approximately 1,-43 hours, 11,-48 hours and 9,-9 hours, respectively.

Linearity/non-linearity

The pharmacokinetics of sacubitril, LBQ657 and valsartan are linear over a sacubitril/valsartan dose range of sacubitril 24 mg/valsartan 26 mg to sacubitril 96 mg/valsartan 103 mg.

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.

Impaired renal function

A correlation was observed between renal function and systemic exposure to LBQ657 patients in patients with mild to severe renal impairment. In patients with mild to moderate renal impairment (30 mL/min/1,73 m^2 ≤ eGFR < 60 mL/ min/1,73 m^2), the AUC for LBQ657 was up to 2-fold higher. A 2,7-fold higher AUC for LBQ657 was observed in patients with severe renal impairment (eGFR). The results of the studies showed that 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 removed effectively by dialysis.

Impaired hepatic function

In patients with mild to moderate hepatic impairment, the exposure 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. No dosage adjustments are recommended when administering sacubitril/valsartan to patients with mild to moderate hepatic impairment (Child-Pugh A and B classification) including patients with biliary obstructive disorders.Sacubitril/valsartan has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (see **section 4.3** and **4.4**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SACUBITRIL VALSARTAN 24/26 mg CIPLA:

Tablet core

Colloidal silicon dioxide

Crospovidone

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Talc

Film coating: Opadry 02F540024 Pink

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol/PEG (E1521)

Talc (E553b)

Iron oxide red (E172)

Ferrosoferric oxide/black iron oxide (E172)

SACUBITRIL VALSARTAN 49/51 mg CIPLA:

Tablet core

Colloidal silicon dioxide

Crospovidone

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Talc

Film coating: Opadry 02F520038 Yellow

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol/PEG (E1521)

Talc (E553b)

Iron oxide yellow (E172)

Iron oxide red (E172)

SACUBITRIL VALSARTAN 97/103 mg CIPLA:

Tablet core

Colloidal silicon dioxide

Crospovidone

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Talc

Film coating: Opadry 02F540028 Pink

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol/PEG (E1521)

Talc (E553b)

Iron oxide red (E172)

Ferrosoferric oxide/black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

6.5 Nature and contents of container

SACUBITRIL VALSARTAN CIPLA is supplied in pack sizes of 14, 28 and 56 film-coated tablets packed in blister packs (aluminium foil and cold form blister foil), enclosed in a carton with a leaflet. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

SACUBITRIL VALSARTAN 24/26 mg CIPLA: 56/7.6/0349

SACUBITRIL VALSARTAN 49/51 mg CIPLA: 56/7.6/0350

SACUBITRIL VALSARTAN 97/103 mg CIPLA: 56/7.6/0351

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 19 September 2023

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

19 September 2023