SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

VYPORA 24 mg/26 mg (film-coated tablets)

VYPORA 49 mg/51 mg (film-coated tablets)

VYPORA 97 mg/103 mg (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VYPORA 24 mg/26 mg film-coated tablets contain 24 mg sacubitril and 26 mg valsartan.

VYPORA 49 mg/51 mg film-coated tablets contain 49 mg sacubitril and 51 mg valsartan.

VYPORA 97 mg/103 mg film-coated tablets contain 97 mg sacubitril and 103 mg valsartan.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

VYPORA 24 mg/26 mg: A white, film-coated, oval, biconvex, bevelled edge tablet debossed with V on one side of the tablet and SV0 on the other side.

VYPORA 49 mg/51 mg: A yellow, film-coated, oval, biconvex, bevelled edge tablet debossed with V on one side of the tablet and SV1 on the other side.

VYPORA 97 mg/103 mg: A pink, film-coated, oval, biconvex, bevelled edge tablet debossed with V on one side of the tablet and SV2 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The target dose of VYPORA is one tablet of 97 mg/103 mg twice daily.

To avoid hypotension, the recommended starting dose of VYPORA in patients previously using high dose of ACE or ARB is one tablet of 49 mg/51 mg twice daily.

A starting dose of one tablet of 24 mg/26 mg twice daily is recommended for patients currently taking low doses of ACE or ARB. Dose up-titration by doubling the dose every 3 – 4 weeks is recommended until a dose of one tablet of 97 mg/103 mg 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.

VYPORA must not be started until 36 hours after discontinuing ACE inhibitor therapy (see section 4.3).

If patients experience tolerability issues (symptomatic hypotension, hyperkalaemia, renal dysfunction), consideration should be given to adjustment of concomitant medications, or to down-titration or discontinuation of VYPORA.

Special populations

Elderly population

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

Renal impairment

VYPORA is contraindicated in patients with severe impaired renal function.

Hepatic impairment

No dose adjustment is required when administering VYPORA to 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 VYPORA in these patients is contraindicated (see sections 5.2 and 4.3).

Paediatric population

The safety and efficacy of VYPORA in paediatric patients aged below 18 years has not been established.

Method of administration

For oral use. VYPORA may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to sacubitril, valsartan or to any of the excipients of VYPORA (listed in section 6.1).
- Concomitant use with ACE inhibitors (see sections 4.2, 4.4 and section 4.5). VYPORA must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic valve stenosis.
- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with VYPORA may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and breastfeeding (see section 4.6).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- The concomitant use of VYPORA with aliskiren-containing medicines in patients with diabetes mellitus or in patients with renal impairment (eGFR < 60 mL/min/1,73 m^2) is contraindicated (see sections 4.4 and 4.5).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see sections 4.2, 4.4 and 5,2).
- Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin 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 receiving VYPORA, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and section 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

- The combination of sacubitril/valsartan as contained in VYPORA with an ACE inhibitor is contraindicated due to the increased risk of angioedema (see section 4.3). VYPORA must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with VYPORA is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of VYPORA (see sections 4.2, 4.3 and 4.5).
- The combination of sacubitril/valsartan as contained in VYPORA with direct renin inhibitors such as aliskiren is not recommended (see section 4.5). The combination of sacubitril/valsartan as contained in VYPORA 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 sections 4.3 and 4.5).
- VYPORA contains valsartan and therefore should not be co-administered with another ARB containing medicine (see section 4.5).

Hypotension

Treatment should not be initiated unless SBP is ≥ 100 mmHg for adult patients. Patients with SBP below these values were not studied. Cases of symptomatic hypotension have been reported in adult patients treated with the combination of sacubitril and valsartan as contained in VYPORA during clinical trials (see section 4.8), especially in patients ≥ 65 years old, patients with renal disease and patients with low SBP (< 112 mmHg). When initiating therapy or during dose titration with VYPORA, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of VYPORA is recommended (see section 4.2). Dose adjustment of diuretics, concomitant antihypertensive medicines, and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. If hypotension persists despite such measures, the dosage of VYPORA should be reduced or the product should be discontinued (see section 4.2). 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 VYPORA; 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 (see section 4.2). There is very limited clinical experience in patients with severe renal impairment (estimated creatinine clearance < 30 mL/min) and these patients may be at greatest risk of hypotension (see section 4.2). There is no experience in patients with end-stage renal disease and use of VYPORA is not recommended.

Worsening renal function

The use of VYPORA may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) (see section 4.5). Down titration or discontinuation of VYPORA should be considered in patients who develop a clinically significant decrease in renal function (see section 4.3).

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is > 5,4 mmol/L in adult patients. The use of VYPORA is associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur (see section 4.8). Medicines known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should not be used with VYPORA. If clinically significant hyperkalaemia occurs, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered. Monitoring of serum potassium is recommended especially in patients with risk factors such as renal impairment, diabetes mellitus, hypoaldosteronism, who are on a high potassium diet or on mineralocorticoid antagonists (see section 4.2 and section 4.3). If patients experience clinically significant hyperkalaemia, adjustment of concomitant medicines, temporary down-titration or discontinuation is recommended. If serum potassium level is > 5,4 mmol/L, discontinuation should be considered.

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan as in VYPORA. If angioedema occurs, VYPORA should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. VYPORA 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. subcutaneous epinephrine/adrenaline solution 1:1 000 (0,3 mL to 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 (see section 4.3). As they may be at higher risk for angioedema, caution is recommended if VYPORA is used in these patients.

VYPORA 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 may have an increased susceptibility to develop angioedema (see section 4.8).

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, VYPORA should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Patients with renal artery stenosis

VYPORA may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. VYPORA is contraindicated in renal artery stenosis (see section 4.3).

Patients with New York Heart Association (NYHA) functional classification IV

Caution should be exercised when initiating VYPORA 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 (see section 4.2 and 5.2). VYPORA is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section

4.3).

Fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/renin-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/renin-angiotensin receptor blockers.

Psychiatric disorders

Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with VYPORA use. If a patient experiences such events, discontinuation of VYPORA treatment should be considered.

Interactions with statins

In vitro data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. VYPORA may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of VYPORA 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 upon co-administration of VYPORA with statins as the adverse effects of statins are dose/exposure related.

VYPORA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Anticipated interactions resulting in a contraindication

ACE inhibitors

The concomitant use of VYPORA with ACE inhibitors and ARBs is contraindicated. VYPORA 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 VYPORA (see section 4.2 and section 4.3).

Aliskiren

The concomitant use of sacubitril/valsartan as contained in VYPORA 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). The combination of sacubitril/valsartan as contained in VYPORA with direct renin inhibitors such as aliskiren is not recommended (see section 4.4). Combination of sacubitril/valsartan as contained in VYPORA with aliskiren is potentially associated with a higher frequency of adverse reactions such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) (see sections 4.3 and 4.4).

Observed interactions to be considered

Statins

In vitro data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. VYPORA may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of VYPORA 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 upon co-administration of VYPORA with statins as the adverse effects of statins are dose/exposure related.

Sildenafil

Addition of a single dose of sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with greater blood pressure reduction compared to administration of sacubitril/valsartan as in VYPORA alone. Therefore, caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with VYPORA.

Anticipated interactions to be considered

Potassium

Concomitant use of potassium-sparing diuretics (e.g. triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if VYPORA is co-administered with these medicines (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors)

In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of VYPORA 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 the treatment in patients on VYPORA who are taking

NSAIDs concomitantly.

Lithium

The potential for an interaction between VYPORA and lithium has not been investigated. 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).

Transporters

The active metabolite of sacubitril (LBQ657) and valsartan are OATP1B1, OATP1B3 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of VYPORA with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin) or MPR2 (e.g. ritonavir) may increase the systemic exposure to LBQ657 or valsartan, respectively. Exercise appropriate care when initiating or ending concomitant treatment with such medicines.

Fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers

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

No significant interactions

No clinically meaningful drug-drug interaction was observed upon co-administration of sacubitril/valsartan as in VYPORA and furosemide, digoxin, warfarin, hydrochlorothiazide, amlodipine, metformin, omeprazole, carvedilol, intravenous nitroglycerine 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 limited metabolism of VYPORA via the CYP450 enzymes. VYPORA does not induce or inhibit CYP450 enzymes.

4.6 Fertility, pregnancy and lactation

Pregnancy

VYPORA is contraindicated in pregnancy.

Safety in pregnancy has not been established (see section 4.3).

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

Breastfeeding

VYPORA is contraindicated in breastfeeding.

Safety in breastfeeding has not been established (see section 4.3).

Fertility

There are no available data on the effect of sacubitril/valsartan on human fertility.

4.7 Effects on ability to drive and use machines

VYPORA 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

Summary of the safety profile

The safety of sacubitril/valsartan in patients with chronic heart failure was evaluated in a study in which patients were treated twice daily with sacubitril/valsartan 97 mg/103 mg. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalaemia and renal impairment.

Tabulated list of adverse reactions

Adverse reactions are ranked by System Organ Class and then by frequency with the most frequent first, using the following conventions: Frequent, less frequent, frequency unknown.

MedDRA System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Frequent	Anaemia
Immune system disorders	Less frequent	Hypersensitivity
Metabolism and nutrition disorders	Frequent	Hyperkalaemia*, hypokalaemia, hypoglycaemia
	Less frequent	Hyponatraemia
Psychiatric disorders	Less frequent	Hallucinations**, sleep disorders,

		paranoia
Nervous system disorders	Frequent	Dizziness, headache
	Less frequent	Postural dizziness
Ear and labyrinth disorders	Frequent	Vertigo
Vascular disorders	Frequent	Hypotension*, syncope, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Cough
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, gastritis
	Less frequent	Intestinal angioedema
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash, angioedema*
Renal and urinary disorders	Frequent	Renal impairment*, renal failure (renal failure, acute renal failure)
General disorders and administration site conditions	Frequent	Fatigue, asthenia

* See description of selected adverse reactions.

** Including auditory and visual hallucinations.

Other adverse events that were commonly reported with sacubitril/valsartan as in VYPORA in patients during the double-blind period of a study include gynaecomastia, fall, back pain, influenza, nasopharyngitis. These events were reported more frequently with sacubitril/valsartan as in VYPORA but the causal relationship to VYPORA cannot be determined.

Description of selected adverse reactions

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan. In a study, angioedema was reported in 0,5 % of patients treated with sacubitril/valsartan, compared with 0,2 % of patients treated with enalapril. A higher incidence of angioedema was observed in Black patients treated with sacubitril/valsartan (2,4 %) and enalapril (0,5 %) (see section 4.4).

Hyperkalaemia and serum potassium

In a study, 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 a study, hypotension and clinically relevant low systolic blood pressure (< 90 mmHg and decrease from baseline of > 20 mmHg) were reported in 17,6 % and 4,76 % of sacubitril/valsartan treated patients compared with 11,9 % and 2,67 % of enalapril-treated patients, respectively.

Renal impairment

In a study, renal impairment was reported in 10,1 % of sacubitril/valsartan-treated patients and 11,5 % of enalapril-treated patients.

Paediatric population

In a study, the safety of sacubitril/valsartan was assessed in a randomised, active-controlled, 52-week study of 375 paediatric heart failure (HF) patients aged 1 month to < 18 years compared to enalapril. The safety profile observed in paediatric patients aged 1 month to < 18 years who received treatment with sacubitril/valsartan was similar to that observed in adult patients. Safety data in patients aged 1 month to < 1 year was limited.

Limited safety data are available in paediatric patients with moderate hepatic impairment or moderate to severe renal impairment.

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 providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Hypotension is the most likely symptom of overdosage due to the blood pressure lowering effects of VYPORA. Symptomatic treatment should be provided.

VYPORA is unlikely to be removed by haemodialysis due to high protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.6 Vascular medicines – Others

Pharmacotherapeutic group and ATC code: Agents acting on the renin-angiotensin system; angiotensin II receptor blockers (ARBs), other combinations; ATC code: C09DX04

Mechanism of action

Sacubitril/valsartan sodium hydrate combines an angiotensin receptor and neprilysin inhibitor (ARNI) 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 cardiovascular and renal effects of sacubitril/valsartan sodium hydrate 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 deleterious effects of angiotensin II by valsartan.

Pharmacodynamic effects

The pharmacodynamic effects of sacubitril/valsartan sodium hydrate are consistent with simultaneous neprilysin inhibition and RAAS blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of sacubitril/valsartan sodium hydrate resulted in a significant non-sustained increase in natriuresis, increased urine cyclic guanosine monophosphate (cGMP), and decreased plasma midregional pro-atrial natriuretic peptide (MR-proANP) and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP). In a 21-day study in HFrEF patients, sacubitril/valsartan sodium hydrate significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. Sacubitril/valsartan sodium hydrate 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 1 200 mg had no effect on cardiac repolarisation.

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of sacubitril/valsartan sodium hydrate 400 mg once daily for 2 weeks to healthy subjects was associated with an increase in CSF Aβ 1-38 compared to placebo; there were no changes in concentrations of CSF Aβ 1-40 and 1-42. The clinical relevance of this finding is unknown.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, sacubitril/valsartan sodium hydrate dissociates into sacubitril, which is further metabolized to LBQ657, and valsartan, which reach peak plasma concentrations in 0,5 hours, 3 hours, and 1,5 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be ≥ 60 % and 23 %, respectively.

Following twice daily dosing of sacubitril/valsartan sodium hydrate, steady state levels of sacubitril, LBQ657 and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates by 1,6-fold. Sacubitril/valsartan sodium hydrate administration with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. Although there is a decrease in exposure to valsartan when sacubitril/valsartan sodium hydrate is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. Sacubitril/valsartan sodium hydrate can therefore be administered with or without food.

Distribution

Sacubitril/valsartan sodium hydrate is highly bound to plasma proteins (94 – 97 %). Based on the comparison of plasma and CSF exposures, LBQ657 does cross the blood brain barrier to a limited extent (0,28 %). Sacubitril/valsartan sodium hydrate has an apparent volume of distribution ranging from 107,8 L to 157,4 L.

Biotransformation

Sacubitril is readily converted to LBQ657 by esterases; 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 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 the pharmacokinetics.

Elimination

Following oral administration, 52 – 68 % of sacubitril (primarily as LBQ657) and ~13 % of valsartan and its metabolites are excreted in urine; 37 – 48 % of sacubitril (primarily as LBQ657), and 86 % of valsartan and its metabolites are excreted in faeces.

Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life ($t_{1/2}$) of approximately 1,43 hours, 11,48 hours, and 9,90 hours, respectively.

Linearity/non-linearity

The pharmacokinetics of sacubitril, LBQ657 and valsartan are linear in the dose range tested (50 – 400 mg of sacubitril/valsartan sodium hydrate).

Special populations

Elderly population (aged over 65 years)

The exposures of LBQ657 and valsartan are increased in elderly subjects by 42 % and 30 %, respectively, compared to younger subjects (see section 4.2).

Renal impairment

A correlation was observed between renal function and systemic exposure to LBQ657, but not to valsartan. 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 < 30 mL/min/1,73 m^2). No dosage adjustment is required in patients with mild or moderate renal impairment. There are only limited data in patients with severe renal impairment (see section 4.3).

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. No dosage adjustments are recommended when administering sacubitril valsartan sodium hydrate to patients with mild to moderate hepatic impairment (Child-Pugh A and B classification) including patients with biliary obstructive disorders. Sacubitril/valsartan sodium hydrate has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (see sections 4.3 and 4.4). Therefore, it is contraindicated in patients with severe hepatic impairment.

Paediatric population (aged below 18 years)

Sacubitril/valsartan sodium hydrate has not been studied in paediatric patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose microcrystalline

Crospovidone

Low-substituted hydroxypropylcellulose

Magnesium stearate

Silica colloidal anhydrous

Talc

Film-coat

VYPORA 24 mg/26 mg: Opadry II White coating contains: Hypromellose, macrogol, polydextrose, titanium dioxide (E171).

VYPORA 49 mg/51 mg: Opadry II Yellow coating contains: Hypromellose, iron oxide yellow (E172), macrogol, polydextrose, quinoline yellow aluminium lake (E104), titanium dioxide (E171).

VYPORA 97 mg/103 mg: Opadry II Pink coating contains: Hypromellose, iron oxide red (E172), macrogol, polydextrose, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicine does not require any special temperature storage conditions.

Store at or below 25 °C. Store in original package.

6.5 Nature and contents of container

VYPORA is packed in cold form blister pack composed of aluminium foil laminated to oriented polyamide on one side and laminated to PVC on the other side, and hard tempered aluminium foil coated with heat seal lacquer. Pack sizes: 14, 28, 30, 56 or 60 tablets per pack enclosed in a cardboard box with a package insert.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

Tel.: +27(0)11 451 1300

8 REGISTRATION NUMBERS

VYPORA 24 mg/26 mg: 59/7.6/0545.0542

VYPORA 49 mg/51 mg: 59/7.6/0546.0543

VYPORA 97 mg/103 mg: 59/7.6/0547.0544

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 May 2026

10 DATE OF REVISION OF THE TEXT

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