NOVARTIS

VYMADA®

50 mg, 100 mg, 200 mg film-coated tablets

sacubitril and valsartan

PROFESSIONAL INFORMATION

Document status: Final

Approval date: 17 November 2025

NOVARTIS

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

VYMADA 50 mg film-coated tablets

VYMADA 100 mg film-coated tablets

VYMADA 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VYMADA 50 mg film-coated tablets contain 24 mg sacubitril and 26 mg valsartan.

VYMADA 100 mg film-coated tablets contain 49 mg sacubitril and 51 mg valsartan.

VYMADA 200 mg film-coated tablets contain 97 mg sacubitril and 103 mg valsartan.

3. PHARMACEUTICAL FORM

VYMADA 50 mg

Violet white ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “LZ” on the other side.

VYMADA 100 mg

Pale yellow ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “L1” on the other side.

VYMADA 200 mg

Light pink ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “L11” on the other side.

VYMADA contains a salt complex of the anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5 respectively. The empirical formula of the complex (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3$ 2.5 H_2O. Its molecular mass is 957,99. Following oral administration, the complex dissociates into sacubitril (which is further metabolised to sacubitrilat) and valsartan.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Chronic heart failure with reduced ejection fraction (HFrEF)

VYMADA is indicated as a second-line therapy, replacing angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) for treatment of symptomatic heart failure (NYHA class II-IV) in patients with reduced ejection fraction.

VYMADA has been shown to reduce the rate of cardiovascular death and heart failure hospitalisation.

VYMADA is administered in combination with other heart failure therapies as appropriate.

Chronic heart failure with preserved ejection fraction (HFpEF)

VYMADA is indicated for the treatment of heart failure (NYHA class II-IV) in patients with preserved ejection fraction with left ventricular ejection fraction (LVEF) below normal. VYMADA has been shown to reduce the rate of cardiovascular death and heart failure hospitalisation in these patients.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The target dose of VYMADA is 200 mg twice daily.

To avoid hypotension the recommended starting dose of VYMADA in patients previously using high dose of ACE or ARB is 100 mg twice daily.

A starting dose of 50 mg twice daily is recommended for patients currently taking low doses of ACE or ARB. Dose up titration by resembling the dose every 3 – 4 weeks is recommended until a dose of 200 mg twice daily is achieved of tolerance. Each dose increment should be preceded by clinical observation for hypotension and laboratory evaluation of serum potassium and renal function.

VYMADA 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 VYMADA.

Special populations

Renal impairment

VYMADA is contraindicated in patients with severe impaired renal function.

Hepatic impairment

No dose adjustment is required when administering VYMADA 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 VYMADA in these patients is not recommended (see section 5).

Paediatric patients

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

Geriatric patients (older than 65 years)

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

Method of administration

VYMADA may be administered with or without food (see section 5.2*)*.

4.3 CONTRAINDICATIONS

- Sensitivity to the active substance, sacubitril, valsartan, or to any of the ingredients of VYMADA.
- Concomitant use with ACE inhibitors (see section 4.2; 4.4 and 4.5). VYMADA 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 VYMADA may lead to toxic blood concentrations of lithium (see section 4.5).
- Concomitant use of VYMADA with renin antagonists such as aliskiren (see section 4.4).
- Pregnancy and lactation (see section 4.6).
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- The concomitant use of VYMADA with aliskiren-containing products is contraindicated (see section 4.4)
- Concomitant use of fluoroquinolones with and Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance < 30 ml/min) and in elderly patients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Should a woman become pregnant while receiving VYMADA, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine

(see sections 4.3 and 4.6)

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

- VYMADA must not be administered with an ACE inhibitor or another ARB. VYMADA must not be initiated until 36 hours after taking the last dose of ACE inhibitor or ARB therapy. If treatment with VYMADA is stopped, ACE inhibitor or ARB therapy must not be initiated until 36 hours after the last dose of VYMADA (see 4.2, 4.3 and 4.5).
- VYMADA should not be used concomitantly with aliskiren (see section 4.3)

Hypotension

Cases of symptomatic hypotension have been reported commonly in patients treated with VYMADA during clinical trials. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive medicines, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. If hypotension persists despite such measures, the dosage of VYMADA 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 VYMADA.

Impaired renal function

The use of VYMADA may be associated with decreased renal function. Down titration or discontinuation of VYMADA should be considered in patients who develop a clinically significant decrease in renal function (see section 4.3).

Hyperkalaemia

The use of VYMADA is associated with an increased risk of hyperkalaemia. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should not be used with VYMADA. 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 diabetes mellitus, hypoaldosteronism or receiving a high potassium diet (see section 4.2 and 4.3).

Angioedema

Angioedema has been reported in patients treated with VYMADA. If angioedema occurs, VYMADA should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. VYMADA 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., subcutaneous epinephrine/adrenaline solution 1:1000 (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).

Black patients may have increased susceptibility to develop angioedema.

Patients with renal artery stenosis

See section 4.3

Interactions with statins

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

Concomitant use of fluoroquinolones and Angiotensin receptor blockers may precipitate acute 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 Angiotensin receptor blockers.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Anticipated interactions resulting in a contraindication

ACE inhibitors: The concomitant use of VYMADA with ACE inhibitors and ARBs is contraindicated. VYMADA 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 VYMADA (see sections 4.2 and 4.3).

Fluoroquinolones: Concomitant use of fluoroquinolones and Angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3). The mechanism of the possible interaction between the different classes of medicines referred to, over and above different mechanism of kidney damage, is unknown (see sections 4.3 and 4.4)

Aliskiren: The concomitant use of VYMADA with aliskiren is contraindicated.

Observed interactions to be considered

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

Sildenafil: Addition of a single dose of sildenafil to VYMADA at steady state in patients with hypertension was associated with greater BP reduction compared to administration of VYMADA alone. Therefore, caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with VYMADA.

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 VYMADA is co-administered with these agents (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 VYMADA 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 VYMADA who are taking NSAIDs concomitantly.

Lithium: The potential for an interaction between VYMADA 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 VYMADA 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.

No significant interactions

No clinically meaningful drug-drug interaction was observed upon co-administration of VYMADA and furosemide, digoxin, warfarin, hydrochlorothiazide, amlodipine, metformin, omeprazole, carvedilol, intravenous nitroglycerin 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 VYMADA via the CYP450 enzymes. VYMADA does not induce or inhibit CYP450 enzymes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

VYMADA is contraindicated in pregnancy.

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

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

Breast feeding

VYMADA is contraindicated during breastfeeding.

Fertility

There are no available data on the effect of VYMADA 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 MACHINES

VYMADA may influence the ability to drive and use machines. Dizziness and fatigue have been reported in patients taking VYMADA and should be considered when assessing a patient's ability to drive or use machines.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

A total of 6 622 heart failure patients were treated with VYMADA in the PARADIGM-HF (vs. enalapril) and PARAGON-HF (vs. valsartan) clinical trials. Of these, 5 085 were exposed for at least 1 year.

PARADIGM-HF

The safety of VYMADA in patients with chronic heart failure with LVEF ≤40% (reduced ejection fraction) was evaluated in a study, in which patients treated twice daily with VYMADA 200 mg (n = 4 203). Patients treated with VYMADA 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 AE in the double-blind period of the PARADIGM-HF trial occurred in 450 (10,71 %) of patients treated with VYMADA. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalaemia and renal impairment.

Tabulated list of adverse reactions

Adverse drug reactions are ranked by System Organ Class and then by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1. 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
Nervous system disorders	Dizziness	Common
	Postural dizziness	Uncommon
	Headache	Common
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension*	Very common
	Syncope	Common
	Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
	Gastritis	Common
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Angioedema*	Uncommon
Renal and urinary disorders	Renal impairment*	Very common
	Renal failure (renal failure, acute renal failure)	Common

General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common

**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. 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 PARADIGM-HF, hyperkalaemia and serum potassium concentrations >5.4 mmol/l were reported in 11.6% and 19.7% of sacubitril/valsartan-treated patients and 14.0% and 21.1% of enalapril-treated patients, respectively.

Blood pressure

In PARADIGM-HF, hypotension and clinically relevant low systolic blood pressure (<90 mmHg and decrease from baseline of >20 mmHg) were reported in 17.6% and 4.76% of sacubitril/valsartan-treated patients compared with 11.9% and 2.67% of enalapril-treated patients, respectively.

Renal impairment

In PARADIGM-HF, renal impairment was reported in 10.1% of sacubitril/valsartan-treated patients and 11.5% of enalapril-treated patients.

PARAGON-HF

The safety of VYMADA in patients with chronic heart failure and LVEF ≥ 45% (preserved ejection fraction) was evaluated in the pivotal phase 3 study PARAGON-HF, which compared patients treated twice daily with VYMADA 200 mg (n = 2 419) or valsartan 160 mg (n = 2 402). The safety profile of VYMADA was consistent with the safety profile in patients with heart failure with reduced ejection fraction.

Other AEs that were commonly reported with VYMADA in >1 % of patients during the double-blind period of PARADIGM-HF include: gynaecomastia, fall, back pain, influenza, nasopharyngitis. These events were reported more frequently with VYMADA but the causal relationship to VYMADA cannot be determined.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of VYMADA is important. It allows continued monitoring of the benefit / risk balance of VYMADA. Health care providers 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

4.9 OVERDOSE

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

A7.6 Vascular medicines Others

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 1200 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.

Clinical efficacy and safety

Dosing in clinical trials was based on the total amount of both components of VYMADA, i.e., 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.

Heart Failure

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind study of 8,442 patients comparing VYMADA to enalapril, both given to adult patients with chronic heart failure, NYHA class II – IV, and systolic dysfunction (left ventricular ejection fraction ≤ 40%), in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF).

The median follow-up duration was 27 months and patients were treated for up to 4.3 years. The mean age of the population studied was 64 years of age and 19% were 75 years or older. At randomization, 70% of patients were NYHA Class II and 25% were Class III/IV.

VYMADA demonstrated clinically relevant and statistically significant superiority to enalapril, reducing the risk of cardiovascular death or heart failure hospitalizations by 20% (hazard ratio (HR): 0.80, 95% CI [0.73; 0.87], 1-sided p =0.0000002) versus enalapril. This effect was observed early and was sustained throughout the duration of the trial. The absolute risk reduction was 4.69%. A statistically significant reduction for CV death and first HF hospitalization was observed (CV death, RRR 20%, HR 0.80; 95% CI [0.71, 0.89], 1-sided p= 0.00004; and hospitalization for heart failure RRR 21%; HR 0.79; 95% CI 0.71, 0.89], 1-sided p= 0.00004). Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in VYMADA treated patients compared to enalapril treated patients (HR 0.80, p= 0.0082). Pump

failure accounted for 26% of cardiovascular deaths and was reduced by 21% in VYMADA treated patients compared to enalapril treated patients (HR 0.79, p = 0.0338).

This risk reduction was consistently observed across subgroups including: age, gender, race, geography, NYHA class, ejection fraction, renal function, history of diabetes or hypertension, prior heart failure therapy, and atrial fibrillation.

VYMADA also significantly reduced all-cause mortality by 16% compared with enalapril (RRR 16%, HR 0.84; 95% CI [0.76 to 0.93], 1-sided p=0.0005). The absolute risk reduction was 2.84%.

Overall, there were fewer all cause hospital admissions in patients treated with VYMADA compared to enalapril, including a 12% relative risk reduction for the first hospitalization (HR 0.88 [95% CI: 0.82, 0.94], P<0.001), and a 16% relative rate reduction for total number of hospitalizations (RR 0.84 [95% CI: 0.78, 0.91], P<0.001).

VYMADA demonstrated a significantly better clinical summary score for the domains related to HF symptoms and physical limitations as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), a self- administered questionnaire. More patients had improved NYHA functional class from baseline to Month 8 on VYMADA (16%) compared to enalapril (14%), and fewer patients had worsened NYHA functional class (10% vs 13%, respectively).

PARAGON-HF

PARAGON-HF, was a multicentre, randomized, double-blind trial comparing VYMADA and valsartan in 4,796 adult patients with symptomatic heart failure with preserved ejection fraction (left ventricular ejection fraction ≥45%), and structural heart disease [either left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)]. Patients with a systolic blood pressure of < 110 mmHg and patients with any prior echocardiographic LVEF < 40% at screening were excluded.

The primary endpoint of PARAGON-HF was the composite of total (first and recurrent) heart failure (HF) hospitalizations and cardiovascular (CV) death.

The mean age of the population studied was 73 years and 52% were female. At randomization, 77% of patients were NYHA Class II, 19% were NYHA Class III, and 0.4% were NYHA Class IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic aetiology in 36% of patients. Furthermore, 96% had a history of hypertension, 23% had a history of myocardial infarction, 46% had an eGFR < 60 mL/min/1.73 m^2, and 43% had diabetes mellitus. Most patients were taking beta-blockers (80%) and diuretics (95%).

In PARAGON-HF, VYMADA reduced the rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death, based on an analysis using a proportional rates model, by 13% compared to valsartan (rate ratio [RR]; 0.87; 95% CI [0.75, 1.01], p = 0.059). The treatment effect was primarily driven by the reduction in total HF hospitalizations in patients randomized to VYMADA of 15% (RR 0.85; 95% CI [0.72, 1.00]).

VYMADA reduced by 14% the rate of the composite endpoint of total worsening heart failure (HF hospitalizations and urgent HF visits) and CV death (RR 0.86; 95% CI [0.75, 0.99]).

In an analysis of the relationship between LVEF and outcome in PARADIGM-HF and PARAGON-HF, patients with LVEF below normal (up to approximately 60%) treated with VYMADA experienced greater risk reduction. LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment; prescribers should use clinical judgment in deciding whom to treat. In both studies the treatment effect with VYMADA was demonstrated early and sustained throughout the duration of the trials.

5.2 PHARMACOKINETICS 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/metabolism

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 (T1/2) of approximately 1,43 hours, 11,48 hours, and 9,90 hours, respectively.

Dose 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 patients (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).

Paediatric patients (aged below 18 years)

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

Impaired renal function

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.

Impaired hepatic function

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. Therefore, its use is not recommended in patients with severe hepatic impairment.

6. LIST OF PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS:

Colloidal silicon dioxide, crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate (vegetable origin), microcrystalline cellulose and talc.

Excipients of film-coating: Hypromellose, iron oxide red (E 172), Macrogol 4000, talc, titanium dioxide (E 171)

For 50 and 200 mg: iron oxide black (E 172). For 100 mg: iron oxide yellow (E 172).

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF-LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 30 °C, protect from moisture.

Store in the original package.

6.5 NATURE AND CONTENTS OF THE CONTAINER

VYMADA 50/100/200 mg tablets are packed in PVC/PVDC blister packs with transparent colourless PVC/PVDC film as the forming component and aluminium foil with heat seal lacquer as the backing components. Pack sizes: 14, 28 or 56 tablets per pack enclosed in a cardboard box with a professional information.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

+27 10 347 6600

8. REGISTRATION NUMBERS:

VYMADA 50 mg: 50/7.6/1019

VYMADA 100 mg: 50/7.6/1020

VYMADA 200 mg: 50/7.6/1021

9. DATE OF FIRST AUTHORISATION

29 September 2017

10. DATE OF REVISION OF THE TEXT

17 November 2025