NOVARTIS

VYMADA® (sacubitril / valsartan)

50 mg, 100 mg, 200 mg Film-coated tablet

Professional Information

Document status: Final

Approval date: 29 September 2017

SCHEDULING STATUS: S3

PROPRIETARY NAME and Dosage Form:

VYMADA 50 mg film-coated tablets

VYMADA 100 mg film-coated tablets

VYMADA 200 mg film-coated tablets

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.

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).

PHARMACOLOGICAL CLASSIFICATION:

A7.6 Vascular medicines Others

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

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.

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.

Pharmacokinetics

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 dosage and directions for use).

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 Contraindications).

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.

INDICATIONS

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

CONTRAINDICATIONS

- Sensitivity to the active substance, sacubitril, valsartan, or to any of the ingredients of VYMADA.
- Concomitant use with ACE inhibitors (see *Warnings and Special precautions*; *Dosage and Directions for use* and *Interactions*). 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 recepter 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 *Interactions*)
- Porphyria
- Lithium therapy: Concomitant administration with VYMADA may lead to toxic blood concentrations of lithium (see *Interactions*).
- Concomitant use of VYMADA with renin antagonists such as aliskiren (see Warnings and Special precautions and Interactions).
- Pregnancy and lactation (see Pregnancy and Lactation).
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- The concomitant use of VYMADA with aliskiren-containing products is contraindicated (see *Warnings and special preciations and Interactions*)

WARNINGS and SPECIAL PRECAUTIONS

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

(see *Contraindications and Pregnancy and lactation*)

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 *Contraindications, Dosage and Directions for use* and *Interactions*).
- VYMADA should not be used concomitantly with aliskiren (see *Contraindications*)

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 *Dosage and Directions for use*). 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 *Contraindications*).

Hyperkalaemia

The use of VYMADA is associated with an increased risk of hyperkalemia. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should not be used with VYMADA. If clinically significant hyperkalemia 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 *Dosage and Directions for use* and *Contraindications*).

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 *Contraindications*).

Black patients may have increased susceptibility to develop angioedema.

Patients with renal artery stenosis

See *Contraindications*

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.

INTERACTIONS

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 *Contraindications* and *Dosage and Directions for use*).

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 *Warnings and Special Precautions*).

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 *Contraindications*).

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.

PREGNANCY AND LACTATION

Pregnancy:

VYMADA is contraindicated in pregnancy and lactation.

Safety in pregnancy and lactation has not been established (see *Contraindications*).

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.

DOSAGE AND DIRECTIONS FOR USE

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 *Contraindications*).

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

Special populations

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 *Pharmacological Action – Special Populations*).

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 *Pharmacokinetics – absorption)*.

SIDE EFFECTS

Summary of the safety profile

The safety of VYMADA in patients with chronic heart failure 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 VYMADA treated. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalemia and renal impairment.

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 2

Adverse Drug Reactions

Adverse drug reactions	**VYMADA** 200 mg twice daily (%)*	**Frequency category**
Blood and lymphatic system disorders		
Anaemia	4,00	Common
Immune system disorders		
Hypersensitivity	0,17	Uncommon
Metabolism and nutrition disorders		
Hyperkalemia	11,61	Very common
Hypokalemia	3,31	Common
Hypoglycaemia	1,36	Common
Nervous system disorders		
Dizziness	6,33	Common
Postural dizziness	0,57	Uncommon
Headache	2,45	Common
Ear and labyrinth disorders		
Vertigo	1,45	Common
Vascular disorders		
Hypotension	17,61	Very common
Syncope	2,24	Common
Orthostatic hypotension	1,52	Common
Respiratory, thoracic and mediastinal disorders		
Cough	8,78	Common
Gastrointestinal disorders		
Diarrhoea	4,62	Common
Nausea	2,09	Common
Gastritis	1,48	Common
Skin and subcutaneous tissue disorders		

Pruritus	0,86	Uncommon
Rash	0,81	Uncommon
Angioedema	0,45	Uncommon
Renal and urinary disorders		
Renal impairment	10,14	Very Common
Renal failure (renal failure, acute renal failure)	4,76	Common
General disorders and administration site conditions		
Fatigue	2,97	Common
Asthenia	2,09	Common

* *Safety analysis set*

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

VYMADA 50 mg

Violet white ovaloid biconvex film-coated tablet with beveled 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 beveled 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 beveled edges, unscored, debossed with "NVR" on one side and "L11" on the other side.

PRESENTATION:

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 package insert.

STORAGE INSTRUCTIONS:

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

Store in the original package.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

VYMADA 50 mg: 50/7.6/1019

VYMADA 100 mg: 50/7.6/1020

VYMADA 200 mg: 50/7.6/1021

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION:

Novartis SA (Pty) Ltd

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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