SACUBITRIL-VALSARTAN

VYMADA™

50 mg Film-coated Tablet
100 mg Film-coated Tablet
200 mg Film-coated Tablet

Angiotensin Receptor-Neprilysin Inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Film-coated tablet.

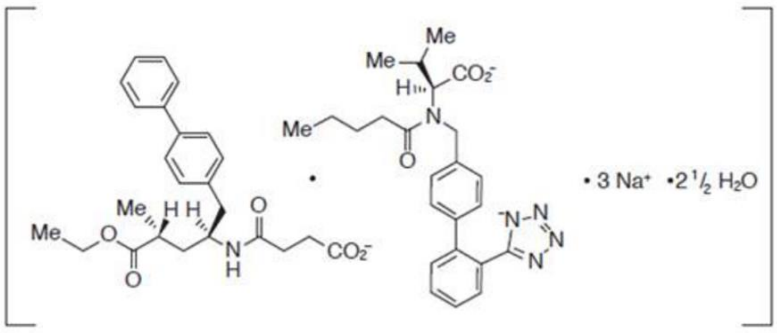
50 mg: Violet white ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with "NVR" on one side and "LZ" on the other side.

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.

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.

Active substance

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 and its schematic structural formula is:



Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan.

50 mg: Each film-coated tablet contains 50 mg sacubitril-valsartan, equivalent to 24.3 mg sacubitril and 25.7 mg valsartan as sodium salt complex.

100 mg: Each film-coated tablet contains 100 mg sacubitril-valsartan, equivalent to 48.6 mg sacubitril and 51.4 mg valsartan as sodium salt complex.

200 mg: Each film-coated tablet contains 200 mg sacubitril-valsartan, equivalent to 97.2 mg sacubitril and 102.8 mg valsartan as sodium salt complex.

Excipients

Tablet core: Microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone type A, magnesium stearate (vegetable origin), talc and colloidal anhydrous silica.

Film coat: Hypromellose substitution type 2910 (3 mPa-s), titanium dioxide (E 171), Macrogol 4000, talc, iron oxide red (E 172)

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

INDICATIONS

Sacubitril-valsartan (Vymada®) is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

Clinical judgement should be used in deciding whom to treat as LVEF is a variable measure.

Sacubitril-valsartan (Vymada®) is administered in place of an ACE inhibitor or ARB.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The recommended starting dose is 100 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of 200 mg twice daily, as tolerated by the patient (see section PHARMACODYNAMICS).

If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of treatment is recommended (see section WARNINGS AND PRECAUTIONS).

In PARADIGM-HF study, sacubitril-valsartan was administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other angiotensin II receptor blocker (ARB) (see section PHARMACODYNAMICS). There is limited experience in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, therefore a starting dose of 50 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended in these patients (see “Titration” in section PHARMACODYNAMICS).

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100

mmHg (see section 4.4). A starting dose of 50 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg.

Sacubitril-valsartan (Vymada™) should not be co-administered with an ACE inhibitor or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy (see sections CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and INTERACTIONS).

The valsartan contained within sacubitril-valsartan complex is more bioavailable than the valsartan in other marketed tablet formulations (see section PHARMACOKINETICS).

If a dose is missed, the patient should take the next dose at the scheduled time. Splitting or crushing of the tablets is not recommended.

Special populations

Geriatric patients (older than 65 years)
The dose should be in line with the renal function of the elderly patient.

Renal impairment
No dose adjustment is required in patients with mild (Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 m^2) renal impairment. A starting dose of 50 mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) (see section PHARMACODYNAMICS) sacubitril-valsartan (Vymada™) should be used with caution and a starting dose of 50 mg twice daily is recommended. There is no experience in patients with end-stage renal disease and treatment is not recommended.

Hepatic impairment
No dose adjustment is required when administering to patients with mild hepatic impairment (Child-Pugh A classification). There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Sacubitril-valsartan (Vymada™) should be used with caution in these patients and the recommended starting dose is 50 mg twice daily (see sections WARNINGS AND PRECAUTIONS and PHARMACOKINETICS). It is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section CONTRAINDICATIONS).

Pediatric patients
The safety and efficacy in children and adolescents aged below 18 years have not been established. No data are available.

Method of administration
Oral use.

May be administered with or without food (see section PHARMACOKINETICS). The tablets must be swallowed with a glass of water.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients listed in EXCIPIENTS section.
- Concomitant use with ACE inhibitors (see sections WARNINGS AND PRECAUTIONS and

INTERACTIONS). Sacubitril-valsartan (Vymada™) must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy (see section WARNINGS AND PRECAUTIONS).
- Hereditary or idiopathic angioedema (see section WARNINGS AND PRECAUTIONS).
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see section DOSAGE AND ADMINISTRATION).
- Second and third trimester of pregnancy (see section FEMALES OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).

WARNINGS AND PRECAUTIONS

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
- Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema (see section CONTRAINDICATIONS). It must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of the drug (see sections DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS and WARNINGS AND PRECAUTION).
- Combination with direct renin inhibitors such as aliskiren is not recommended (see section INTERACTIONS). The combination with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections CONTRAINDICATIONS and INTERACTIONS).
- Sacubitril-valsartan (Vymada™) contains valsartan, and therefore should not be co-administered with another ARB-containing product (see sections DOSAGE AND ADMINISTRATION and INTERACTIONS).

Hypotension

Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied (see section PHARMACODYNAMICS). Cases of symptomatic hypotension have been reported in patients in clinical studies (see section ADVERSE DRUG REACTIONS), especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). When initiating therapy or during dose titration, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of the drug is recommended (see section DOSAGE AND ADMINISTRATION). Dose adjustment of diuretics, concomitant antihypertensives 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, diarrhea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment, however, such corrective action must be carefully weighed against the risk of volume overload.

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 very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2) and these patients may be at greatest risk of hypotension (see section DOSAGE AND ADMINISTRATION). There is no experience in patients with end-stage renal disease and use of sacubitril-valsartan (Vymada™) is not recommended.

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

Hyperkalemia
Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Use may be associated with an increased risk of hyperkalemia, although hypokalemia may also occur (see section ADVERSE DRUG REACTIONS). Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists (see section DOSAGE AND ADMINISTRATION). If patients experience clinically significant hyperkalemia, adjustment of concomitant medicinal products, or temporary down–titration or discontinuation of treatment 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. If angioedema occurs, treatment should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. It must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal edema 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 history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if used in these patients. Sacubitril-valsartan (Vymada^{TM}) 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 CONTRAINDICATIONS).

Black patients have an increased susceptibility to develop angioedema (see section ADVERSE DRUG REACTIONS).

Patients with renal artery stenosis
Sacubitril-valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. Caution is required in patients with renal artery stenosis and monitoring of renal function is recommended.

Patients with NYHA functional classification IV
Caution should be exercised when initiating treatment 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 (see section PHARMACODYNAMICS).

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 DOSAGE AND ADMINISTRATION and PHARMACOKINETICS). Sacubitril-valsartan (Vymada™) is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section CONTRAINDICATIONS).

Psychiatric disorders

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

ADVERSE DRUG REACTIONS

Summary of the safety profile

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

The most commonly reported adverse reactions during treatment were hypotension, hyperkalemia and renal impairment (see section WARNINGS AND PRECAUTIONS). Angioedema was reported in patients (see description of selected adverse reactions).

PARADIGM-HF

The safety in patients with chronic heart failure with LVEF ≤40% (reduced ejection fraction) was evaluated in the pivotal phase 3 study PARADIGM-HF, which compared patients treated twice daily with sacubitril-valsartan 200 mg (n=4,203) or enalapril 10 mg (n=4,229). Patients randomized to the sacubitril-valsartan group received treatment for a median duration of exposure of 24 months; 3,271 patients were treated for more than one year.

In the PARADIGM-HF study, subjects were previously treated with ACE inhibitors and/or ARBs and also had to successfully complete sequential enalapril and sacubitril-valsartan run-in periods (median drug exposure of 15 and 29 days, respectively) prior to the randomised double-blind period. During the enalapril run-in period, 1,102 patients (10.5%) permanently discontinued from the study, 5.6% because of an adverse reaction, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the sacubitril-valsartan run-in period, 10.4% of patients permanently discontinued, 5.9% because of an adverse reaction, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Due to discontinuations during the run-in period, the adverse reaction rates as presented in table below may be lower than the adverse reaction rates expected in clinical practice.

Discontinuation of therapy due to an adverse reaction in the double-blind period of the PARADIGM-HF study occurred in 450 sacubitril-valsartan-treated patients (10.7%) and 516 enalapril-treated patients (12.2%).

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 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). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 List of adverse reactions in the PARADIGM-HF

System Organ Class	Preferred term	Frequency category
Blood and lymphatic system disorders	Anemia	Common
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalemia*	Very common
	Hypokalemia	Common
	Hypoglycemia	Common
Nervous system disorders	Dizziness	Common
	Headache	Common
	Syncope	Common
	Dizziness postural	Uncommon
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension*	Very common
	Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Diarrhea	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
Psychiatric disorders	Hallucinations**	Rare
	Sleep disorders	Rare
	Paranoia	Very rare

*See description of selected adverse reactions.

**Including auditory and visual hallucinations

PARAGON-HF

The safety of sacubitril-valsartan 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 sacubitril-valsartan 200 mg (n=2,419) or valsartan 160 mg (n=2,402). The safety profile of sacubitril-valsartan was consistent with the safety profile in patients with heart failure with reduced ejection fraction

Description of selected adverse reactions

Angioedema

Angioedema has been reported in patients. 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 WARNINGS AND PRECAUTIONS).

Hyperkalemia and serum potassium

In PARADIGM-HF, hyperkalemia 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **www.fda.gov.ph**.

INTERACTIONS

Interactions resulting in a contraindication

ACE inhibitors: The concomitant use with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. Treatment must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of sacubitril-valsartan (Vymada^{TM}) (see sections DOSAGE AND ADMINISTRATION and CONTRAINDICATIONS).

Aliskiren: The concomitant use with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see section CONTRAINDICATIONS). The combination with direct renin inhibitors such as aliskiren is not recommended (see section WARNINGS AND PRECAUTIONS). Combination with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Interactions resulting in concomitant use not being recommended

Sacubitril-valsartan (Vymada^{TM}) contains valsartan, and therefore should not be co-administered with another ARB containing product (see section WARNINGS AND PRECAUTIONS).

Interactions requiring precautions

***OATP1B1 and OATP1B3 substrates, e.g. statins*:** *In vitro* data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. Sacubitril-valsartan may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins.

Co-administration increased the C_{max} of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Caution should be exercised when co-administering with statins. No clinically relevant drug-drug interaction was observed when simvastatin was co-administered.

PDE5 inhibitors including sildenafil: Addition of a single dose of sildenafil to sacubitril-valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril-valsartan alone. Therefore, caution should be exercised when sildenafil or another PDE5 inhibitor is initiated in patients.

Potassium: Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if co-administered with these agents (see section WARNINGS AND PRECAUTIONS).

Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) Inhibitors: In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use with NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in patients who are taking NSAIDs concomitantly (see section WARNINGS AND PRECAUTIONS).

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. Interactions with lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Furosemide: Co-administration with furosemide had no effect on the pharmacokinetics of sacubitril-valsartan but reduced C_{max} and AUC of furosemide by 50% and 28%, respectively. While there was no relevant change in urine volume, the urinary excretion of sodium was reduced within 4 hours and 24 hours after co-administration. The average daily dose of furosemide was unchanged from baseline until the end of the PARADIGM-HF study in patients.

Nitrates, e.g. nitroglycerine: There was no drug-drug interaction with intravenously administered nitroglycerin with regard to blood pressure reduction. Co-administration with nitroglycerine 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 co-administered with sublingual, oral or transdermal nitrates. In general no dose adjustment is required.

OATP and MRP2 transporters: The active metabolite of sacubitril (LBQ657) and valsartan are OATP1B1, OATP1B3, OAT1 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised when initiating or ending concomitant treatment with such medicinal products.

Metformin: Co-administration with metformin reduced both C_{max} and AUC of metformin by 23%. The clinical relevance of these findings is unknown. Therefore, when initiating therapy in patients receiving metformin, the clinical status of the patient should be evaluated.

No significant interaction

No clinically meaningful drug-drug interaction was observed when co-administered with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol.

CYP 450 interactions: *In vitro* metabolism studies indicate that potential for CYP 450-based drug interactions is low since there is limited metabolism of sacubitril-valsartan via CYP450 enzymes. Sacubitril-valsartan does not induce or inhibit CYP450 enzymes.

FEMALES OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING, AND FERTILITY

Pregnancy

Use is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy (see section CONTRAINDICATIONS).

Valsartan

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with ARBs, similar risks may exist for this class of medicinal product. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ARBs should be stopped immediately and, if appropriate, alternative therapy should be started. Exposure to ARBs therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

Should exposure to ARBs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension (see section CONTRAINDICATIONS).

Sacubitril

There are no data from the use of sacubitril in pregnant women. Studies in animals have shown reproductive toxicity (see section NON-CLINICAL SAFETY DATA).

Sacubitril-valsartan

There are no data on use in pregnant women. Animal studies have shown reproductive toxicity (see section NON-CLINICAL SAFETY DATA).

Breast-feeding

It is not known whether the drug is excreted in human milk. The components of Vymada™, sacubitril and valsartan, were excreted in the milk of lactating rats (see section NON-CLINICAL SAFETY DATA). Because of the potential risk for adverse reactions in breast-fed newborns/infants, it is not recommended during breast-feeding. A decision should be made whether to abstain from breast-feeding or to discontinue treatment while breast-feeding, taking into account the drug's importance to the mother.

Fertility

There are no available data on the drug's effect on human fertility. No impairment of fertility was demonstrated in studies with it in male and female rats (see section NON-CLINICAL SAFETY DATA).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Sacubitril-valsartan (Vymada™) 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.

OVERDOSAGE

Limited data are available with regard to overdose in humans. A single dose of 1200 mg and multiple doses of 900 mg (14 days) were studied in healthy volunteers and were well tolerated.

Hypotension is the most likely symptom of overdose due to the blood pressure lowering effects of sacubitril-valsartan (Vymada^{TM}). Symptomatic treatment should be provided.

The medicinal product is unlikely to be removed by hemodialysis due to high protein binding.

CLINICAL PHARMACOLOGY

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 complementary cardiovascular benefits 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.

Pharmacodynamics (PD)

The pharmacodynamic effects were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure, and 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 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 21-day 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. The AT1-receptor was also blocked as evidenced by increased plasma renin activity and plasma renin concentrations. In the PARADIGM-HF study, sacubitril-valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. In PARAGON-HF, sacubitril-valsartan decreased NT-proBNP, troponin and soluble ST2 (sST2) and increased urine cGMP compared to valsartan. BNP is not a suitable biomarker of heart failure in patients because BNP is a neprilysin substrate (see section 4.4). NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

In a thorough QTc clinical study in healthy male subjects, single doses of sacubitril-valsartan 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 400 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 this finding is not known (see section

NON-CLINICAL SAFETY DATA).

Pharmokinetics (PK)
The valsartan contained within the sacubitril-valsartan complex is more bioavailable than the valsartan in other marketed tablet formulations; 25.7 mg, 51.4 mg, and 102.8 mg of valsartan in sacubitril-valsartan is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.

Absorption
Following oral administration, the drug 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, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1.6-fold. Administration with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. Sacubitril-valsartan (Vymada™) 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 and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volume of distribution of valsartan and sacubitril were 75 litres to 103 litres, respectively.

Biotransformation
Sacubitril is readily converted to LBQ657 by carboxylesterases 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 medicinal products 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 feces.

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 9.90 hours, respectively.

Linearity/non-linearity
The pharmacokinetics of sacubitril, LBQ657 and valsartan were approximately linear over a sacubitril-valsartan dose range of 50 mg to 100 mg.

Special populations

Elderly patients (aged over 65 years)
LBQ657 and valsartan exposure are increased in subjects over 65 years of age by 42% and 30%, respectively, compared to younger subjects.

Pediatric patients (aged below 18 years)
Sacubitril-valsartan (Vymada™) has not been studied in pediatric patients.

Impaired renal function
A correlation was observed between renal function and systemic exposure to LBQ657 in patients with mild to severe renal impairment. The exposure of LBQ657 in patients with moderate (30 ml/min/1.73 m^2 ≤ eGFR <60 ml/min/1.73 m^2) and severe renal impairment (15 ml/min/1.73 m^2 ≤ eGFR <30 ml/min/1.73 m^2) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60 ml/min/1.73 m^2 ≤ eGFR <90 ml/min/1.73 m^2), the largest group of patients enrolled in PARADIGM-HF). 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 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. However, in patients with mild to moderate hepatic impairment, the exposures of free concentrations of LBQ657 increased by 1.47- and 3.08-fold, respectively, and the exposures of free concentrations of valsartan increased by 1.09-fold and 2.20-fold, respectively, compared to matching healthy subjects. Sacubitril-valsartan (Vymada™) has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Effect of gender
The pharmacokinetics of the drug (sacubitril, LBQ657 and valsartan) are similar between male and female subjects.

Race/Ethnicity

The pharmacokinetics of Vymada™ (sacubitril, sacubitrilat and valsartan) are comparable across different race and ethnic groups (Caucasians, Blacks, Asians, Japanese and others).

CLINICAL STUDIES

The 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg strengths are in some publications referred to as 50, 100 or 200 mg.

PARADIGM-HF
PARADIGM-HF was a multinational, randomized, double-blind study of 8,442 patients comparing sacubitril-valsartan to enalapril, both given to adult patients with chronic heart failure, NYHA class II-IV and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤40%, amended later to ≤35%) in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF). Patients with SBP <100 mmHg, severe renal impairment (eGFR <30 ml/min/1.73 m^2) and severe hepatic impairment were excluded at screening and therefore not prospectively studied.

Prior to study participation, patients were well treated with standard of care therapy which included ACE inhibitors/ARBs (>99%), beta blockers (94%), mineralocorticoid antagonists (58%) and diuretics (82%). The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and enter a

sequential single-blind run-in period during which they received treatment with enalapril 10 mg twice daily, followed by single-blind treatment with sacubitril-valsartan 100 mg twice daily, increasing to 200 mg twice daily (see section 4.8 for discontinuations during this period). They were then randomized to the double-blind period of the study, during which they received either sacubitril-valsartan 200 mg or enalapril 10 mg twice daily [sacubitril-valsartan (n=4,209); enalapril (n=4,233)].

The mean age of the population studied was 64 years of age and 19% were 75 years of age or older. At randomization, 70% of patients were NYHA class II, 24% were class III and 0.7% were class IV. The mean LVEF was 29% and there were 963 (11.4%) patients with a baseline LVEF >35% and ≤40%.

In the sacubitril-valsartan group, 76% of patients remained on the target dose of 200 mg twice daily at the end of the study (mean daily dose of 375 mg). In the enalapril group, 75% of patients remained on the target dose of 10 mg twice daily at the end of the study (mean daily dose of 18.9 mg).

Sacubitril-valsartan was superior to enalapril, reducing the risk of cardiovascular death or heart failure hospitalizations to 21.8% compared to 26.5% for enalapril treated patients. The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalization, 3.1% for CV death alone, and 2.8% for first HF hospitalization alone. The relative risk reduction was 20% versus enalapril (see Table 2). This effect was observed early and was sustained throughout the duration of the study (see Figure 1). Both components contributed to the risk reduction. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in sacubitril-valsartan-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 sacubitril-valsartan-treated patients compared to enalapril-treated patients (HR 0.79, p=0.0338).

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

Sacubitril-valsartan improved survival with a significant reduction in all-cause mortality of 2.8% (sacubitril-valsartan, 17%, enalapril, 19.8%). The relative risk reduction was 16% compared with enalapril (see Table 2).

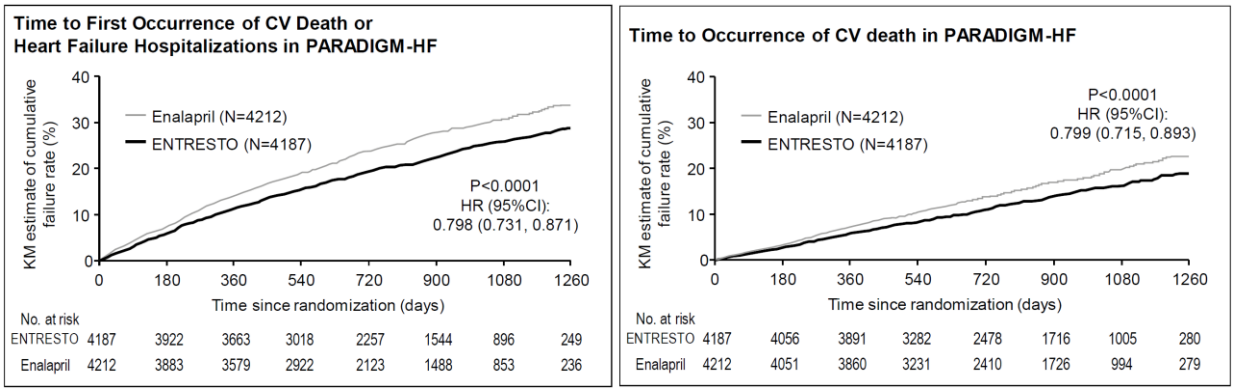
Table 2 Treatment effect for the primary composite endpoint, its components and all-cause mortality over a median follow-up of 27 months - PARADIGM-HF

	Sacubitril-valsartan N=4187[#] n (%)	**Enalapril N=4212[#] n (%)**	**Hazard ratio (95% CI)**	**Relative risk reduction**	**p-value *****
Primary composite endpoint of CV death and heart failure hospitalizations*	914 (21.83)	1117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual components of the primary composite endpoint					
CV death**	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	0.00004

First heart failure hospitalization	537 (12.83)	658 (15.62)	0.79 (0.71, 0.89)	21%	0.00004
Secondary endpoint					
All-cause mortality	711 (16.98)	835 (19.82)	0.84 (0.76, 0.93)	16%	0.0005

*The primary endpoint was defined as the time to first event of CV death or hospitalization for HF.
**CV death includes all patients who died up to the cut-off date irrespective of previous hospitalization.
***One-sided p-value
[#]Full analysis set

Figure 1 Kaplan-Meier curves for the primary composite endpoint and the CV death component - PARADIGM-HF



PARAGON-HF

PARAGON-HF, was a multicenter, randomized, double-blind trial comparing sacubitril-valsartan 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.

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received valsartan 80 mg twice-daily, followed by sacubitril-valsartan 100 mg twice-daily. Patients on prior low doses of an ACEi or ARB began the run-in period receiving valsartan 40 mg twice-daily for 1-2 weeks. Patients who successfully completed the sequential run-in periods were randomized to receive either sacubitril-valsartan 200 mg (N=2,419) twice-daily or valsartan 160 mg (N=2,403) twice-daily. The median follow-up duration was 35 months and patients were treated for up to 4.7 years.

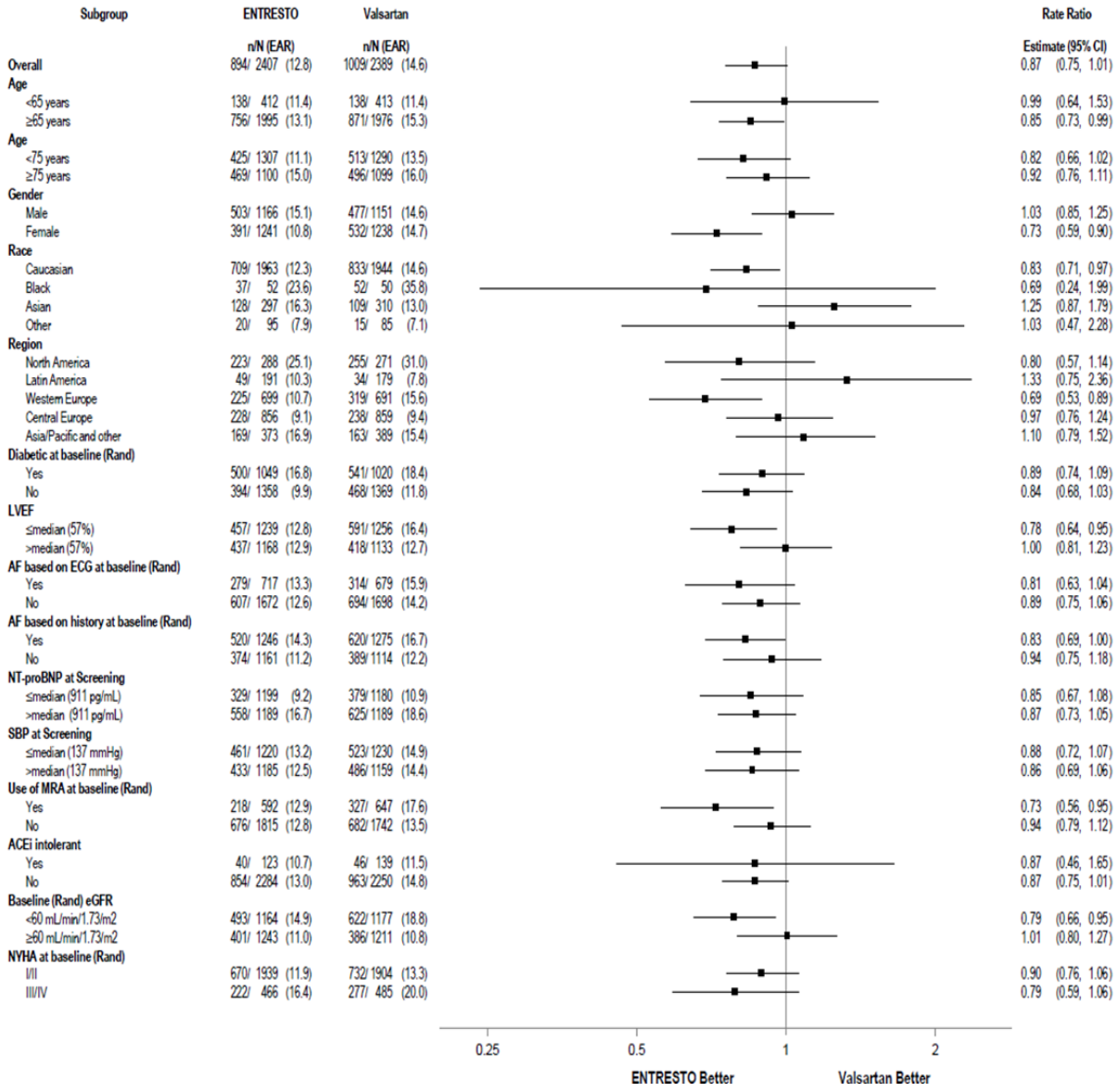
The mean age of the population studied was 73 years and 52% were female. At randomization, 77% of patients were NYHA Class II, 19% were NYHA Class III, and 0.4% were NYHA Class IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic etiology in 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, sacubitril-valsartan 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 sacubitril-valsartan of 15% (RR 0.85; 95% CI [0.72, 1.00]).

Sacubitril-valsartan 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]).

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes (Figure 2).

Figure 2 **Primary Composite Endpoint of Total HF Hospitalizations and CV Death – Subgroup Analysis - PARAGON-HF**



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors.

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 sacubitril-valsartan experienced greater risk reduction (Table 4 and Figure 3, and Figure 4). 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 sacubitril-valsartan was demonstrated early and sustained throughout the duration of the trials (Figure 1 and 4).

Table 4 Treatment Effect for Composite Endpoints (Primary and Expanded) and Components for LVEF ≤ 60% - PARAGON-HF

	Sacubitril-valsartan N = 1,688		Valsartan N = 1,683		Effect Size (95% CI)
Efficacy Endpoints	**n**	**Event Rate[a]**	**n**	**Event Rate[a]**	
Composite endpoint of total (first and recurrent) HF hospitalizations and CV death	619	12.7	761	15.9	RR = 0.79 (0.67, 0.94)
Composite endpoint of total worsening HF[b] and CV death	653	13.3	798	16.7	RR = 0.80 (0.67, 0.94)
Individual components of the composite endpoints					
Total HF Hospitalizations	469	9.6	594	12.4	RR = 0.76 (0.62, 0.92)
CV Death	150	3.1	167	3.5	HR = 0.88 (0.71, 1.10)
Total worsening HF[b]	503	10.3	631	13.2	RR = 0.75 (0.62, 0.91)
Secondary Endpoints	**n/N**	**Change From Baseline (SE)**	**n/N**	**Change From Baseline (SE)**	**Treatment difference (95% CI)**
KCCQ Clinical Summary Score (CSS) change at 8 months	1578/1677	-1.67 (0.42)	1571/1671	-2.71 (0.42)	LSM = 1.03 (-0.13, 2.20)
	n/N	**Event Rate**	**n/N**	**Event Rate**	**Treatment difference (95% CI)**
NYHA class favorable change at 8 months	1481/1625	N/A	1452/1618	N/A	OR = 1.42 (1.08, 1.88)[c]
Renal composite endpoint[d]	22/1688	0.45	47/1683	0.99	HR = 0.45 (0.27, 0.75)
All-cause death	256/1688	5.23	267/1683	5.57	HR = 0.94 (0.79, 1.11)

Abbreviations: RR = rate ratio, HR = hazard ratio, OR = odds ratio, SE = standard error

[a] Event rate per 100 patient-years

[b] The composite of worsening HF included total (first and recurrent) urgent HF visits and HF hospitalizations. An urgent HF visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring intravenous treatment.

[c] The odds ratio for the NYHA class change represents the model-based common odds ratio of improvement and non-worsening, with OR >1 reflecting favorable changes in the sacubitril-valsartan group.

[d] Defined as renal death, reaching end stage renal disease, or ≥50% decline in estimated glomerular filtration rate (eGFR) relative to baseline.

Figure 3 **Mean Number of Events Over Time for the Primary Composite Endpoint of Total HF Hospitalizations and CV Death in patients with LVEF ≤ 60% - PARAGON-HF**

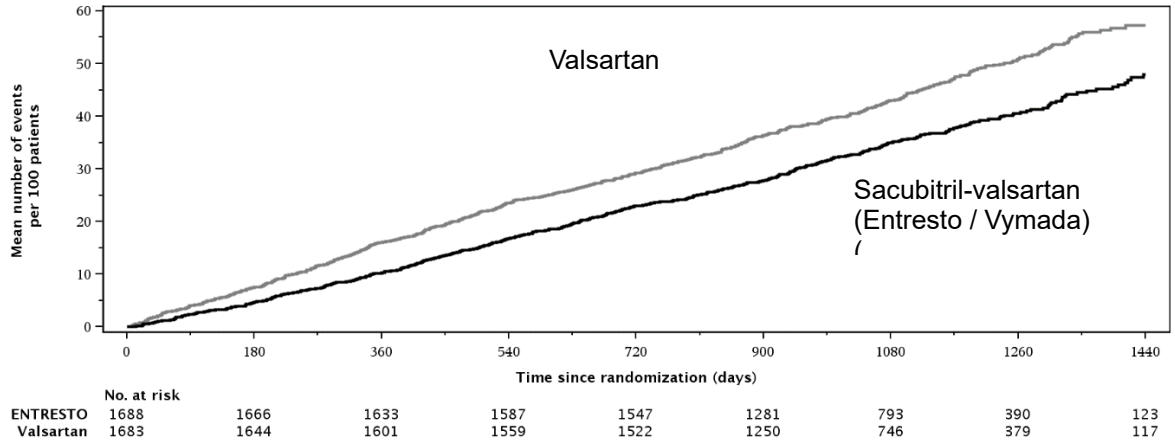
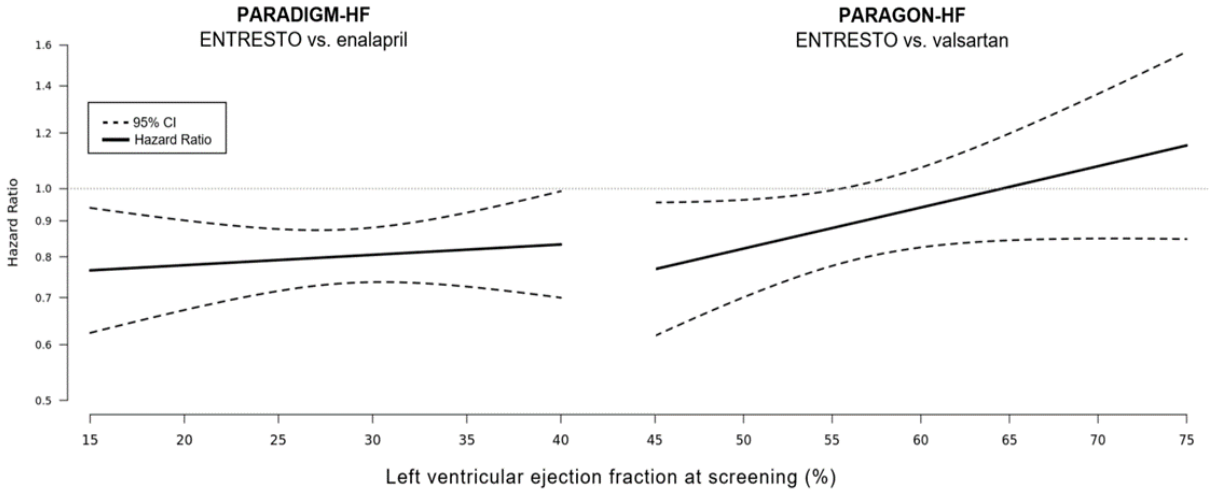


Figure 4 **Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by LVEF in PARADIGM-HF and PARAGON-HF**



TITRATION

TITRATION was a 12-week safety and tolerability study in 538 patients with chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤35%) naïve to ACE inhibitor or ARB therapy or on varying doses of ACE inhibitors or ARBs prior to study entry. Patients received a starting dose of 50 mg twice daily and were up-titrated to 100 mg twice daily, then to the target dose of 200 mg twice daily, with either a 3-week or a 6-week regimen.

More patients who were naïve to previous ACE inhibitor or ARB therapy or on low-dose therapy (equivalent to <10 mg enalapril/day) were able to achieve and maintain 200 mg when up-titrated over 6 weeks (84.8%) versus 3 weeks (73.6%). Overall, 76% of patients achieved and maintained the target dose of 200 mg twice daily without any dose interruption or down-titration over 12 weeks.

PARAMOUNT

PARAMOUNT, a randomized, double-blind trial in patients with left ventricular ejection fraction ≥ 45% comparing 200 mg of sacubitril-valsartan (n=149) to 160 mg of valsartan (n=152) twice daily, demonstrated statistically greater reduction (p= 0.0050) in NT pro-BNP from baseline to Week 12. The reduction from baseline in NT-proBNP was similar at Weeks 12 and 36 in patients treated with sacubitril-valsartan, while NT-proBNP decreased from Week 12 to 36 in patients treated with valsartan. Significant reductions in left atrial size, both left atrial volume index (p=0.0069) and left atrial dimension (p=0.0337) were observed at Week 36. A statistically significant improvement in NYHA class was noted at Week 36 (p=0.0488).

NON-CLINICAL SAFETY DATA

Non-clinical data (including studies with sacubitril and valsartan components and/or sacubitril-valsartan) reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility.

Fertility, reproduction and development

Treatment during organogenesis resulted in increased embryofetal lethality in rats at doses ≥49 mg sacubitril/51 mg valsartan/kg/day (≤0.72-fold the maximum recommended human dose [MRHD] on the basis of AUC) and rabbits at doses ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). It is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a dose of ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day. Cardiovascular abnormalities (mainly cardiomegaly) were observed in rabbit fetuses at a maternally non-toxic dose (1.46 mg sacubitril/1.54 mg valsartan/kg/day). A slight increase in two fetal skeletal variations (misshapen sternebra, sternebra bipartite ossification) was observed in rabbits at a dose of 4.9 mg sacubitril/5.1 mg valsartan/kg/day. The adverse embryofetal effects are attributed to the angiotensin receptor antagonist activity (see section FEMALES OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).

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

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

Other preclinical findings

Sacubitril-Valsartan

The effects on amyloid-β concentrations in CSF and brain tissue were assessed in young (2-4 years old) cynomolgus monkeys (24 mg sacubitril/26 mg valsartan/kg/day) for two weeks. In this study CSF Aβ clearance in cynomolgus monkeys was reduced, increasing CSF Aβ1-40, 1-42 and 1-38 levels; there was no corresponding increase in Aβ levels in the brain. Increases in CSF Aβ1-40 and 1-42 were not observed in a two-week healthy volunteer study in humans (see section 5.1). Additionally, in a toxicology study in cynomolgus monkeys at a dose 146 mg sacubitril/154 mg valsartan/kg/day for 39 weeks, there was no evidence for the presence of amyloid plaques in the brain. Amyloid content was not, however, measured quantitatively in this study.

Sacubitril
In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation. A study in adult rats showed only a minimal transient inhibitory effect on bone mineral density but not on any other parameters relevant for bone growth, suggesting no relevant effect of sacubitril on bone in adult patient populations under normal conditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults cannot be excluded.

Valsartan
In juvenile rats treated with valsartan (postnatal days 7 to 70), doses as low as 1 mg/kg/day produced persistent irreversible kidney changes consisting of tubular nephropathy (sometimes accompanied by tubular epithelial necrosis) and pelvic dilatation. These kidney changes represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans.

INCOMPATIBILITIES

Not applicable.

STORAGE

Do not use after the date marked “EXP” on the pack.
Do not store above 30°C. Store in the original package to protect from moisture.
Drugs must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Not applicable.

AVAILABILITY

50 mg and 100 mg Film-coated Tablet: 2 PA/Al/PVC (Alu-Alu) blister pack x 14’s (Box of 28’s)
200 mg Film-coated Tablet: 4 PA/Al/PVC (Alu-Alu) blister pack x 7’s (Box of 28’s)

CAUTION: Foods, Drugs, Devices, And Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reactions, report to the FDA: **www.fda.gov.ph**

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Manufactured by
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Via Provinciale Schito 131-80058 Torre Annunziata, Napoli, Italy

Imported by
Sandoz Philippines Corporation
5th and 6th Floors Ayala North Exchange Building, Tower 1 (HQ),
Ayala Avenue corner Salcedo & Amorsolo Sts. Brgy. San Lorenzo, Makati, Metro Manila

Date of First Authrorization: 02 May 2018

FDA Registration Number:
50 mg: DR-XY46317, 100 mg: DR-XY46318, 200 mg: DR-XY46319

Information issued: June 2021