PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSACUBITRIL-VALSARTAN
sacubitril / valsartan film-coated tablets
(as sacubitril valsartan sodium hydrate complex)
24 mg sacubitril / 26 mg valsartan
49 mg sacubitril / 51 mg valsartan
97 mg sacubitril / 103 mg valsartan

neutral endopeptidase inhibitor/angiotensin II AT_1 receptor blocker

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[Pr]SACUBITRIL-VALSARTAN

sacubitril / valsartan film-coated tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Film coated tablets: 24 mg sacubitril / 26 mg valsartan 49 mg sacubitril / 51 mg valsartan 97 mg sacubitril / 103 mg valsartan	Colloidal silicon dioxide, crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate (vegetable origin), microcrystalline cellulose and talc. The film-coating contains hypromellose, iron oxide red (E 172), Macrogol 4000, talc and titanium dioxide (E 171). Sacubitril-Valsartan 24 mg sacubitril / 26 mg valsartan and Sacubitril-Valsartan 97 mg sacubitril / 103 mg valsartan film-coated tablets also contain iron oxide black (E 172), and Sacubitril-Valsartan 49 mg sacubitril / 51 mg valsartan film-coated tablets also contain iron oxide yellow (E 172).

INDICATIONS AND CLINICAL USE

Sacubitril-Valsartan (sacubitril/valsartan) is indicated for the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with NYHA Class II or III, to reduce the incidence of cardiovascular death and heart failure hospitalisation (see DOSAGE AND ADMINISTRATION).

Sacubitril-Valsartan should be administered in combination with other heart failure therapies, in place of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS).

Sacubitril-Valsartan should be initiated, and up-titration conducted, by a physician experienced with the treatment of heart failure.

Geriatrics:
No dosage adjustment is required in patients over 65 years. However, Sacubitril-Valsartan has been studied in a limited number of patients above the age of 80 years (see WARNINGS AND PRECAUTIONS, Geriatrics, and CLINICAL TRIALS). Caution is required in these patients (see

DOSAGE AND ADMINISTRATION).

Pediatrics (< 18 years of age):
Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Sacubitril-Valsartan in pediatric patients has not been established.

CONTRAINDICATIONS

- Recent symptomatic hypotension prior to initiation of treatment with Sacubitril-Valsartan (sacubitril/valsartan)
- Concomitant use with any drug formulation containing an angiotensin-converting enzyme inhibitor, due to potential enhanced risk of angioedema (see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION). **Sacubitril-Valsartan must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy**
- Known history of angioedema related to previous ACEi or ARB therapy
- History of hereditary or idiopathic angioedema
- As for any formulation containing an ACEi or ARB, use of Sacubitril-Valsartan together with aliskiren-containing drugs is contraindicated in patients with diabetes mellitus, whether Type 1 or 2, or in patients with moderate to severe renal impairment, i.e., eGFR < 60 mL/min/1.73m^2 (see WARNINGS AND PRECAUTIONS, General, and Renal, and DRUG INTERACTIONS)
- Pregnant and nursing women (see WARNINGS AND PRECAUTIONS, *Special Populations*, Women of child-bearing potential, Pregnant women, and Nursing women)
- Hypersensitivity to the active substances, sacubitril or valsartan, or to any of the excipients

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy **angiotensin receptor (AT_1) blockers (ARB)** can cause injury to or even death of the developing fetus. When pregnancy is detected, Sacubitril-Valsartan should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

- **Sacubitril-Valsartan (sacubitril/valsartan) must not be administered with an ACE**i **due to the risk of angioedema.** Sacubitril-Valsartan must not be initiated until at least 36 hours have elapsed following discontinuation of ACEi therapy. If treatment with Sacubitril-Valsartan is stopped, ACEi therapy must not be initiated until 36 hours after the last dose of Sacubitril-Valsartan (see CONTRAINDICATIONS, DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION).
- Sacubitril-Valsartan should not be administered with any other drug formulation containing an ARB, due to the angiotensin II receptor blocking activity of Sacubitril-Valsartan by its valsartan moiety (see DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION).
- Caution is required while co-administering Sacubitril-Valsartan with direct renin inhibitors such as aliskiren (see CONTRAINDICATIONS, and DRUG INTERACTIONS). In general, such use is not recommended, since this combination has not been adequately studied.

Sacubitril-Valsartan must not be administered with aliskiren in patients with Type 2 diabetes or having significantly impaired renal function (see CONTRAINDICATIONS).

- **While BNP is a neprilysin substrate, NT-proBNP is not. Due to the action of sacubitril, use of Sacubitril-Valsartan would be expected to raise BNP levels, without having a direct effect on NT-proBNP. Therefore, only NT-proBNP, and not BNP, may be a suitable biomarker for the monitoring of heart failure patients treated with Sacubitril-Valsartan.**

Angioedema

Angioedema has been reported in patients treated with Sacubitril-Valsartan (see ADVERSE REACTIONS, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). If angioedema occurs, Sacubitril-Valsartan should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Sacubitril-Valsartan 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., subcutaneous epinephrine 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 any angioedema have not been studied. As they may be at higher risk for angioedema, caution is recommended if Sacubitril-Valsartan is used in these patients. **Sacubitril-Valsartan must not be used in patients with a known history of angioedema related to previous ACE**i **or ARB therapy or in patients with a history of hereditary or idiopathic angioedema (see CONTRAINDICATIONS).**

Black patients treated with Sacubitril-Valsartan appear to have increased susceptibility to develop angioedema. In PARADIGM-HF, angioedema was confirmed in 2.4% of black patients treated with Sacubitril-Valsartan, compared to 0.5% of black patients treated with enalapril. In the same study, angioedema was confirmed in 0.4% of non-black patients treated with Sacubitril-Valsartan, compared to 0.2% of non-black patients treated with enalapril.

Hypotension

Sacubitril-Valsartan lowers blood pressure and may cause symptomatic hypotension (see ADVERSE REACTIONS). Patients with systolic blood pressure < 100 mmHg at the time of initiation of Sacubitril-Valsartan have not been studied. Use of Sacubitril-Valsartan in these patients is not recommended.

Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk of hypotension when treated with Sacubitril-Valsartan. In the double-blind period of PARADIGM-HF, 18% of patients treated with Sacubitril-Valsartan and 12% of patients treated with enalapril reported hypotension as an adverse event, with hypotension reported as a serious adverse event in approximately 1.5% of patients in both treatment arms.

If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and/or Sacubitril-Valsartan should be considered, along with treatment of any underlying cause, e.g., hypovolemia. Permanent discontinuation of Sacubitril-Valsartan is usually not required. Sodium and/or volume depletion should always be corrected before starting treatment with Sacubitril-Valsartan.

Hyperkalemia

As for any drug that acts on the renin-angiotensin-aldosterone system, use of Sacubitril-Valsartan is associated with an increased risk of hyperkalemia (see ADVERSE REACTIONS). Measure serum potassium before instituting Sacubitril-Valsartan, and during treatment, as appropriate, taking into account the patient's predisposition to develop hyperkalemia. Patients with serum potassium > 5.2 mmol/L prior to initiation of treatment with Sacubitril-Valsartan have not been studied.

In PARADIGM-HF, clinically-relevant hyperkalemia resulted in treatment discontinuation in 0.3% of Sacubitril-Valsartan treated patients, compared to 0.4% of enalapril-treated patients**. Medications known to raise serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution when co-administered with Sacubitril-Valsartan.** If clinically significant hyperkalemia occurs, or if such risk is high, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered. Dosage reduction or interruption of Sacubitril-Valsartan may be required. Careful monitoring of serum potassium is recommended especially in patients with risk factors, such as severe renal impairment, diabetes mellitus, hypoaldosteronism, or in those with a high potassium intake in their diet (see DOSAGE AND ADMINISTRATION).

Impaired renal function

As a consequence of inhibiting the renin-angiotensin system (RAS), decreases in renal function may be anticipated in susceptible individuals treated with Sacubitril-Valsartan. In patients whose renal function depends upon the activity of RAS, e.g., patients with more severe congestive heart failure, treatment with ACEi and ARB has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt Sacubitril-Valsartan in patients who develop a clinically significant decrease in renal function.

Use of Sacubitril-Valsartan should include appropriate assessment of renal function, before initiation of therapy, and then during treatment, as appropriate.

Patients with renal artery stenosis

Similar to other drugs that affect the renin-angiotensin-aldosterone system, 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, if Sacubitril-Valsartan is to be used. Careful monitoring of renal function should be carried out.

Special Populations

Women of child-bearing potential

Women of childbearing potential should be advised about the consequences of exposure to

Sacubitril-Valsartan during pregnancy, and to use contraception during treatment with Sacubitril-Valsartan and for one (1) week after their last dose.

Pregnant women

As for other drugs that also act directly on the renin-angiotensin system (RAS), Sacubitril-Valsartan must not be used during pregnancy (see CONTRAINDICATIONS). Sacubitril-Valsartan exerts some of its effects through angiotensin II antagonism; therefore, a risk to the fetus cannot be excluded. There have been reports of injury to the developing fetus (e.g. spontaneous abortion, oligohydramnios and newborn renal dysfunction), when pregnant women have taken valsartan. If pregnancy is detected during therapy, Sacubitril-Valsartan should be discontinued as soon as possible.

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, valsartan should be discontinued as soon as possible.

The use of any drug formulation containing an ARB is not recommended during pregnancy. The use of an ARB during the second or third trimester of pregnancy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan.

Infants with histories of *in utero* exposure to an angiotensin II AT_1 receptor blocker should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit. Valsartan is not removed from plasma by dialysis.

Nursing women

It is not known whether Sacubitril-Valsartan is excreted in human milk. The components of Sacubitril-Valsartan, sacubitril and valsartan, have been observed to be excreted in the milk of lactating rats (see DETAILED PHARMACOLOGY). Because of the potential risk for adverse drug reactions in breastfed newborns, a decision should be made whether to abstain from breast-feeding or to discontinue Sacubitril-Valsartan while breast-feeding, taking into account the importance of Sacubitril-Valsartan to the mother (see CONTRAINDICATIONS).

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Sacubitril-Valsartan in pediatric patients has not been established.

Geriatrics: No dosage adjustment is required in patients over 65 years. However, Sacubitril-Valsartan has been studied in a limited number of patients above the age of 80 years (see CLINICAL TRIALS). Caution is required in these patients (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic Impairment: In patients with moderate hepatic impairment (Child-Pugh B classification), a starting dose of 24.3 mg sacubitril / 25.7 mg valsartan twice daily is recommended (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

In patients with severe hepatic impairment (Child-Pugh C classification), use of Sacubitril-Valsartan is not recommended (see ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics,* Hepatic Insufficiency).

Patients with Renal Impairment: Since patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) were excluded from the PARADIGM-HF trial, Sacubitril-Valsartan is not recommended in these patients (also, see ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics,* Renal Insufficiency).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of Sacubitril-Valsartan (sacubitril/valsartan) in patients with heart failure and reduced ejection fraction was evaluated in the pivotal Phase 3 study, PARADIGM-HF, which compared patients treated twice daily with Sacubitril-Valsartan at doses up to 97.2 mg sacubitril / 102.8 mg valsartan (n=4,203), or enalapril 10 mg (n=4,229) twice daily. Patients randomised to Sacubitril-Valsartan received treatment for a median duration of exposure of 24 months, with 3,271 patients treated for more than one year.

Discontinuation of therapy due to an adverse event in the double-blind period of the PARADIGM-HF trial occurred in 450 (10.7%) of Sacubitril-Valsartan-treated patients and 516 (12.2%) patients receiving enalapril. The adverse events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalemia and renal impairment.

In total, 4,138 patients aged 65 years or older were included in the PARADIGM-HF study, of which 2,083 were exposed to Sacubitril-Valsartan. Of these elderly patients, 1,563 were older than 75 years, of which 784 were treated with Sacubitril-Valsartan.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the PARADIGM-HF trial, patients were required to complete sequential single-blind enalapril and Sacubitril-Valsartan run-in periods of a median duration of 15 and 29 days, respectively, prior to entering the randomised double-blind period, comparing Sacubitril-Valsartan and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the Sacubitril-Valsartan run-in period, which followed the enalapril run-in phase, an additional 10.4% of patients permanently

discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below in the randomised double-blind period of the trial, see Table 2 below, may be lower than those expected to be seen in actual clinical practice.

In the double-blind period, safety was evaluated in 4,203 patients treated with Sacubitril-Valsartan and 4,229 treated with enalapril. In PARADIGM-HF, patients randomised to Sacubitril-Valsartan received treatment for up to 4.3 years, with a median duration of exposure of 24 months. 3,271 patients were treated with Sacubitril-Valsartan for more than one year in this trial. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of Sacubitril-Valsartan-treated patients and in 516 (12.2%) patients receiving enalapril.

Adverse events of interest observed in the PARADIGM-HF trial are presented in Tables 1 and 2, below.

Table 1 - Adverse events of interest in the single-blind run-in phases of PARADIGM-HF

	Sacubitril-Valsartan N=9,419 n (%)	**enalapril N= 10,513 n (%)**
General disorders and administration site conditions		
Edema peripheral	75 (0.8)	55 (0.5)
Fatigue	41 (0.4)	32 (0.3)
Asthenia	24 (0.2)	23 (0.2)
Metabolism and nutrition disorders		
Hyperkalemia	259 (2.8)	279 (2.7)
Nervous system disorders		
Dizziness	163 (1.7)	98 (0.9)
Renal and urinary disorders		
Renal impairment	212 (2.3)	229 (2.2)
Renal failure	32 (0.3)	23 (0.2)
Respiratory, thoracic and mediastinal disorders		
Cough	170 (1.8)	291 (2.8)
Skin and subcutaneous tissue disorders		
Angioedema	7 (0.1)	11 (0.1)
Rash	31 (0.3)	21 (0.2)
Pruritus	78 (0.8)	22 (0.2)
Vascular disorders		
Hypotension	291 (3.1)	214 (2.0)
Orthostatic hypotension	29 (0.3)	7 (0.1)

Table 2 - Adverse events of interest in the randomized, double-blind phase of PARADIGM-HF

	Sacubitril-Valsartan [+] N= 4,203 n (%)	**Enalapril[++] N= 4,229 n (%)**
Ear and labyrinth disorders		
Vertigo	61 (1.5)	59 (1.4)
Gastrointestinal disorders		
Diarrhea	194 (4.6)	189 (4.5)
Nausea	88 (2.1)	100 (2.4)
General disorders and administration site conditions		
Fatigue	125 (3.0)	129 (3.1)
Asthenia	88 (2.1)	78 (1.8)
Immune system disorders		
Drug hypersensitivity	10 (0.2)	11(0.3)
Hypersensitivity	7 (0.2)	8 (0.2)
Injury, poisoning and procedural complications		
Fall	80 (1.9)	54 (1.3)
Metabolism and nutrition disorders		
Hyperkalemia	488 (11.6)	592 (14.0)
Hypokalemia	139 (3.3)	107 (2.5)
Nervous system disorders		
Dizziness	266 (6.3)	206 (4.9)
Dizziness postural	24 (0.6)	12 (0.3)
Headache	103 (2.5)	106 (2.5)
Renal and urinary disorders		
Renal impairment	426 (10.1)	487 (11.5)
Renal failure, including acute	207 (4.9)	237 (5.6)
Respiratory, thoracic and mediastinal disorders		
Cough	369 (8. 8)	533 (12.6)
Skin and subcutaneous tissue disorders		
Angioedema	19 (0.5)	10 (0.2)

	Sacubitril-Valsartan [+] N= 4,203 n (%)	Enalapril[++] N= 4,229 n (%)
Rash	53 (1.3)	63 (1.5)
Pruritus	57 (1.4)	39 (0.9)
Vascular disorders		
Hypotension	740 (17.6)	506 (12.0)
Syncope	94 (2.2)	114 (2.7)
Orthostatic hypotension	64 (1.5)	34 (0.8)
Subdural hematoma	12 (0.3)	5 (0.1)

[+] Sacubitril-Valsartan dosed up to 97.2 mg sacubitril / 102.8 mg valsartan bid, equivalent to one Sacubitril-Valsartan-200 tablet taken twice daily

[++] enalapril dosed up to 10 mg bid

Sacubitril-Valsartan-treated patients who experienced a hypotensive event in the double-blind treatment phase were more commonly observed to have other associated hypotensive adverse events, compared to enalapril-treated patients, such as post-baseline systolic blood pressure (SBP) < 90 mmHg (5.2% vs 3.1%, respectively), a drop ≥ 30 mmHg in SBP from baseline (5.4% vs 3.2%), and simultaneous symptomatic hypotension and SBP < 90 mmHg (2.8% vs 1.5%).

Table 3 – Hypotension-related adverse events during the randomised double-blind phase of PARADIGM-HF

	Sacubitril-Valsartan N=4203		enalapril N=4229	
Number of patients with at least one AE of hypotension	1027		786	
SBP at screening (mmHg)	m	n (%)	m	n (%)
100-109	377	138 (36.6)	432	127 (29.4)
110-119	800	252 (31.5)	766	202 (26.4)
120-129	988	263 (26.6)	950	172 (18.1)
130-139	905	193 (21.3)	944	154 (16.3)
≥ 140	1131	180 (15.9)	1135	130 (11.4)

Table 4 shows the estimated cumulative rate of selected adverse events at Day 180 following randomisation for the double blind period, and at Day 180 following start of study drug, accounting for exposure during both the run-in and double blind treatment periods. As expected, the rates of adverse events in both the Sacubitril-Valsartan and enalapril treatment arms increase when run-in adverse events are added to the double-blind adverse events. This summary presents adverse events reported for 4,203 Sacubitril-Valsartan-treated patients and 4,229 enalapril-treated patients in the double-blind treatment period, and 9,419 and 10,514 patients, respectively, in the run-in + double blind treatment phases.

Table 4: Estimated Cumulative Rates of Selected Adverse Events at Day 180 in PARADIGM-HF

		Sacubitril-Valsartan	enalapril
Selected AE of interest	**Estimation scope**	**Estimate (%) (95% CI)**	**Estimate (%) (95% CI)**
Angioedema (adjudicated)	DB period	0.29 (0.16, 0.51)	0.10 (0.04, 0.25)
	Run-in + DB	0.40 (0.25, 0.61)	0.24 (0.14, 0.38)
Hyperkalemia	DB period	5.4 (4.7, 6.1)	6.4 (5.7, 7.2)
	Run-in + DB	7.9 (7.2, 8.7)	9.2 (8.5, 10.1)
Hypersensitivity	DB period	0.02 (0.00, 0.17)	0.10 (0.04, 0.26)
	Run-in + DB	0.07 (0.02, 0.20)	0.10 (0.04, 0.25)
Hypotension	DB period	8.8 (8.0, 9.7)	5.1 (4.5, 5.8)
	Run-in + DB	10.8 (10.0, 11.7)	6.7 (6.1, 7.5)
Orthostatic hypotension	DB period	0.94 (0.69, 1.28)	0.43 (0.27, 0.68)
	Run-in + DB	1.2 (0.9, 1.5)	0.47 (0.31, 0.70)
Pruritus	DB period	0.41 (0.25, 0.66)	0.26 (0.15, 0.47)
	Run-in + DB	0.82 (0.63, 1.07)	0.36 (0.23, 0.56)
Renal failure (renal failure, acute renal failure)	DB period	1.3 (1.0, 1.7)	1.5 (1.1, 1.9)
	Run-in + DB	1.6 (1.3, 2.0)	1.6 (1.3, 2.0)
Renal impairment	DB period	3.3 (2.8, 3.9)	3.9 (3.4, 4.5)
	Run-in + DB	5.7 (5.1, 6.3)	6.4 (5.8, 7.1)

DB = double blind

TITRATION was a 12 week safety and tolerability study in 538 patients with chronic heart failure (NYHA Class II – IV) and reduced ejection fraction (left ventricular ejection fraction ≤35%), whether naïve to ACEi or ARB therapy (6.6%) or on varying doses of ACEi or ARB prior to study entry. All patients initiated Sacubitril-Valsartan at 24.3 mg sacubitril / 25.7 mg valsartan bid, were then up-titrated to 48.6 mg sacubitril / 51.4 mg valsartan bid, as tolerated, and then to the target dose of 97.2 mg sacubitril / 102.8 mg valsartan bid, with either a 3-week (condensed) or 6-week (conservative) up-titration regimen. Overall, 76% of patients achieved and maintained the target dose of one tablet of Sacubitril-Valsartan (97.2 mg sacubitril / 102.8 mg valsartan) taken twice daily without any dose interruption or down-titration over 12-weeks. Adverse events leading to study drug discontinuation are shown in Table 5 below.

Table 5 - Adverse events leading to study drug discontinuation in TITRATION

	Sacubitril-Valsartan Condensed titration regimen N=246 n (%)	**Sacubitril-Valsartan Conservative titration regimen N=251 n (%)**
Discontinuation in post-randomization period		
Any Adverse Event(s)	20 (8.1)	14 (5.6)
Hypotension	5 (2.0)	3 (1.2)
Renal failure/impairment	6 (2.4)	1 (0.4)
Hyperkalemia	3 (1.2)	1 (0.4)
Cardiogenic shock	2 (0.8)	0 (0.0)
Angioedema	0	1 (0.4)

In the run-in phase of the TITRATION study, a dose of 24.3 mg sacubitril / 25.7 mg valsartan given twice daily was used for (1) one week. The incidence of patients with an adverse event leading to treatment discontinuation in this phase of the trial was 5.6%, including, hypotension/orthostatic hypotension 1.7%, hyperkalemia 1.5%, renal failure/impairment 0.8%, drug hypersensitivity 0.2%, and angioedema 0.2%.

Abnormal Hematologic and Clinical Chemistry Findings

Hemoglobin and Hematocrit

Decreases in hemoglobin of > 20% were observed in 5% of Sacubitril-Valsartan patients, compared with 6% in enalapril-treated patients in the double-blind treatment period.

BUN and Creatinine

Increases in BUN and creatinine of > 50% were observed in 37% and 14%, respectively, of Sacubitril-Valsartan-treated patients, compared with 41% and 16% in enalapril-treated patients in the double-blind treatment period. Increases in serum creatinine of > 50% were observed in 2.2%

of patients in the Sacubitril-Valsartan run-in period and in 1.4% of those in the enalapril run-in period.

Serum Potassium
In patients treated with either Sacubitril-Valsartan or enalapril in the double-blind period, approximately 16% had potassium increases > 5.5 mmol/L. Increases of potassium were observed in approximately 4% of both Sacubitril-Valsartan- and enalapril-treated patients in the run-in phases of PARADIGM-HF.

Post-Market Adverse Drug Reactions

Sacubitril-Valsartan
The following adverse drug reactions have been derived from post-marketing experience with Sacubitril-Valsartan via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known.

Immune system disorders: Hypersensitivity (including rash, pruritus, and anaphylaxis).

Valsartan
Other adverse reactions reported for valsartan in post-marketing use include: anaphylaxis (very rare), angioedema (involving swelling of the face, lips and/or tongue), dermatitis bullous (unknown frequency), renal impairment (very rare), photosensitivity, increase in blood pressure and taste disorders.

The following serious adverse events, irrespective of causality and with unknown frequency, have been reported from clinical studies or post-marketing experiences: Toxic epidermal necrolysis (TEN), Stevens-Johnsons syndrome (SJS), erythema multiforme (EM), toxic skin eruption, skin necrosis, exfoliative rash, pemphigus and pemphigoid.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

The following other adverse drug reactions with unknown frequency have been reported from clinical studies or post-marketing experiences: Hypersensitivity including serum sickness, vasculitis, insomnia and libido decrease.

Hepato-biliary disorder: hepatic enzymes increased, including blood bilirubin increased.

DRUG INTERACTIONS

Overview

In vitro drug metabolism and transporter data suggest that clinically relevant drug-drug interactions may be expected with Sacubitril-Valsartan (sacubitril/valsartan), also known as

LCZ696, due to inhibition of OATP1B1 and OATP1B3 by sacubitril, and inhibition of OAT3 by sacubitril, sacubitrilat, and valsartan. Drug-drug interactions due to inhibition of other transporters are unlikely.

Both sacubitrilat, the active metabolite of sacubitril, and valsartan are OATP1B1, OATP1B3 and OAT3 substrates. Valsartan is also a MRP2 substrate. Therefore, co-administration of Sacubitril-Valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) or MRP2 (e.g. ritonavir) may increase the systemic exposure of sacubitrilat, or valsartan, respectively.

Although sacubitril is a substrate of P-gp, there is a low likelihood for a clinically-relevant drug interaction of Sacubitril-Valsartan when co-administered with a P-gp inhibitor because of its high estimated bioavailability of ≥ 60%.

In vitro studies indicate that the potential for CYP 450-based drug interactions is low since there is limited metabolism of Sacubitril-Valsartan by the cytochrome P450 system. Sacubitril-Valsartan does not induce or inhibit CYP isozymes itself.

No clinically meaningful drug-drug interaction was observed with co-administration of Sacubitril-Valsartan with digoxin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol, or intravenous nitroglycerin in dedicated interaction studies.

Warfarin: Following administration of the target dose of Sacubitril-Valsartan (97.2 mg sacubitril / 102.8 mg valsartan bid), taken twice daily for five days, a single oral dose of warfarin 25 mg or placebo was administered in healthy subjects. No pharmacokinetic or pharmacodynamic interactions were detected, in respect of plasma concentrations of both enantiomers of warfarin, LCZ696 moieties, or INR values. Evaluation under warfarin steady-state conditions was not conducted.

Furosemide: When the target dose of Sacubitril-Valsartan (97.2 mg sacubitril / 102.8 mg valsartan bid,) was administered for four days, a single dose of furosemide 40 mg was then administered. Although no clinically-relevant changes in plasma levels of sacubitril, sacubitrilat or valsartan were noted, the Cmax and AUC of furosemide decreased significantly by 50% and 26%, respectively, compared to furosemide administration alone. However, in PARADIGM-HF, there was no evidence of a need for increased dosing of loop diuretic in patients treated with Sacubitril-Valsartan, compared to enalapril.

Metformin: When metformin 1,000 mg OD for four days was added to LCZ696 (194.3 mg sacubitril / 205.7 mg valsartan given once daily) at steady-state in healthy Japanese subjects, both the Cmax and AUC of metformin were decreased by 23%. Sacubitril-Valsartan steady-state pharmacokinetics were not affected.

Oral contraceptive pill: When a single dose of levonorgesterel 150 µg and ethinyl estradiol 30 µg was co-administered with LCZ696 (194.3 mg sacubitril / 205.7 mg valsartan given once daily) at steady-state, although the AUC of levonorgesterel was unchanged, its Cmax decreased by 15%. Pharmacokinetics of ethinyl estradiol did not change. Also, the pharmacokinetics of sacubitrilat and valsartan were not changed in a clinically-relevant manner.

Drug-Drug Interactions

Table 6 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
ACE inhibitors	T	The concomitant use of Sacubitril-Valsartan with ACEi is contraindicated, as the concomitant inhibition of neprilysin and ACE inhibitor therapy may increase the risk of angioedema.	Sacubitril-Valsartan must not be started until 36 hours after taking the last dose of ACEi therapy. ACEi therapy must not be started until 36 hours after the last dose of Sacubitril-Valsartan (see CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).
Aliskiren	CT	The concomitant use of aliskiren with other agents acting on the RAS, such as ARB, is associated with an increased risk of hypotension, hyperkalemia, and deterioration of renal function (including acute renal failure) compared to monotherapy.	Concomitant use with aliskiren is contraindicated in patients with diabetes mellitus or with significant renal impairment (eGFR <60 mL/min/1.73 m^2) (see CONTRAINDICATIONS)
ARB	T	Sacubitril-Valsartan should not be co-administered with any drug formulation containing an ARB, due to the angiotensin II receptor blocking activity of Sacubitril-Valsartan (see WARNINGS AND PRECAUTIONS)	Sacubitril-Valsartan should be used in place of an angiotensin II receptor blocker (see INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION)

Proper name	Ref	Effect	Clinical comment
Statins	T	*In vitro* data indicates 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 of Sacubitril-Valsartan increased the Cmax of atorvastatin and its metabolites by up to 2-fold, and AUC by up to 1.3-fold.	Caution should be exercised upon co-administration of Sacubitril-Valsartan with statins, especially simvastatin, a sensitive OATP1B1/1B3 substrate. Downward dose adjustment of simvastatin and atorvastatin may be considered with such co-administration.
Sildenafil	CT	Administration of a single dose of 50 mg sildenafil to Sacubitril-Valsartan at steady-state (194.4 mg sacubitril / 205.6 mg valsartan OD for 5 days) was associated with additional blood pressure reduction (~5/4 mmHg).	Caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with Sacubitril-Valsartan.
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 required, if Sacubitril-Valsartan is co-administered with these agents (see WARNINGS AND PRECAUTIONS).

Proper name	Ref	Effect	Clinical comment
Non-Steroidal Anti-Inflammatory Agents (NSAID), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors)		Especially in elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of Sacubitril-Valsartan and NSAID may lead to an increased risk of worsening of renal function.	Monitoring of renal function is mandatory when initiating or modifying the treatment in patients on Sacubitril-Valsartan who are taking NSAID concomitantly. In general, avoid such combined use.
Lithium	T	The potential for a drug interaction between Sacubitril-Valsartan 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.	Careful monitoring of serum lithium levels is recommended during concomitant use with Sacubitril-Valsartan. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions
Sacubitril-Valsartan may be administered with or without food.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Sacubitril-Valsartan (sacubitril/valsartan) should normally be used in clinically stable patients in conjunction with other medical treatment for heart failure with reduced ejection fraction (HFrEF), including diuretics, beta-blockers, and mineralocorticoid receptor antagonists (MRA), as appropriate and as tolerated. Sacubitril-Valsartan should be used in place of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (see INDICATIONS AND CLINICAL USE, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS). Sacubitril-Valsartan should not be initiated in patients with acutely decompensated heart failure, or clinically-relevant ischemic events, such as acute myocardial or cerebral infarction.

In stable patients whose baseline systolic blood pressure, serum potassium and renal function are at acceptable levels (see WARNINGS AND PRECAUTIONS, and CLINICAL TRIALS), Sacubitril-Valsartan may be initiated.

The usual recommended starting dose is one tablet of 49 mg sacubitril / 51 mg valsartan taken twice daily. The target dose is one tablet of 97 mg sacubitril / 103 mg valsartan taken twice daily.

A starting dose of one tablet of 24 mg sacubitril / 26 mg valsartan taken twice daily should be considered in certain patients:

- Patients on less than guideline-recommended doses of ACEi or ARB prior to initiation of Sacubitril-Valsartan
- Patients who have risk factors for hypotension, including patients ≥ 75 years old and patients with low systolic blood pressure (see WARNINGS AND PRECAUTIONS, Hypotension)

The dose of Sacubitril-Valsartan should be increased every 2-4 weeks, as tolerated by the patient, to the target dose of one tablet of 97 mg sacubitril/ 103 mg valsartan taken twice daily. If patients experience tolerability issues, e.g. symptomatic hypotension or hyperkalemia, consideration should be given to temporary down–titration or treatment interruption of Sacubitril-Valsartan.

Due to the potential risk of angioedema when used concomitantly with an ACEi, Sacubitril-Valsartan must not be started until 36 hours has passed following discontinuation of ACEi therapy (see CONTRAINDICATIONS).

Sacubitril-Valsartan should not be co-administered with any other medication containing an ARB due to the angiotensin II receptor blocking activity of Sacubitril-Valsartan (see WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS).

Note that the oral bioavailability of valsartan, when Sacubitril-Valsartan is administered, is greater than that of valsartan in other marketed tablet formulations (see ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics,* Absorption). Administer Sacubitril-Valsartan as directed above, based on patient tolerability, and not on a mg-to-mg substitution basis with valsartan.

Sacubitril-Valsartan can be administered with or without food.

Special populations

Renal impairment

No dose adjustment is required in patients with mild (eGFR 60-90 mL/min/1.73 m^2) or moderate (eGFR 30-60 mL/min/1.73 m^2) renal impairment. Since there are no adequate data in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), Sacubitril-Valsartan use is not recommended in these patients (also, see ACTION AND CLINICAL PHARMACOLOGY, *Pharmacokinetics,* Renal Insufficiency).

Hepatic impairment

No dose adjustment is required when administering Sacubitril-Valsartan to patients with mild hepatic impairment (Child-Pugh A classification). In patients with moderate hepatic impairment (Child-Pugh B classification), a starting dose of one tablet of 24 mg sacubitril / 26 mg valsartan taken twice daily is recommended.

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification). Therefore, use of Sacubitril-Valsartan in these patients is not recommended.

Pediatrics (< 18 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Sacubitril-Valsartan in pediatric patients has not been established.

Geriatrics

No dosage adjustment is required in patients over 65 years (see ACTION AND CLINICAL PHARMACOLOGY, Geriatrics). However, Sacubitril-Valsartan has been studied in a limited number of patients above the age of 80 years (see CLINICAL TRIALS). In patients ≥ 75 years old, a starting dose of one tablet of 24 mg sacubitril / 26 mg valsartan taken twice daily should be considered (see Recommended Dose and Dosage Adjustment, above).

Administration

Sacubitril-Valsartan may be administered with or without food (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Monitor serum potassium in all patients treated with Sacubitril-Valsartan. If hyperkalemia occurs, dose adjustment or interruption of drugs that increase serum potassium may be required, e.g., mineralocorticoid receptor antagonists, or Sacubitril-Valsartan.

Missed Dose

If a dose is missed, patients should be advised to take it as soon as they remember and then take the next tablet at the usual time. Doses should not be doubled to make up for the missed dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Limited clinical data are available with regards to overdosage with Sacubitril-Valsartan (sacubitril/valsartan). In healthy volunteers, a single dose of 583 mg sacubitril/617 mg valsartan, equivalent to about six (6) tablets of 97.2 mg sacubitril/ 102.8 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan, equivalent to about nine (9) tablets of 48.6 mg sacubitril / 51.4 mg valsartan, taken daily over 14 days have been studied and were well tolerated.

Hypotension is the most likely sign of overdosage due to the blood pressure lowering effects of Sacubitril-Valsartan. Dizziness, syncope, or orthostatic changes may occur. Symptomatic treatment should be provided.

Sacubitril-Valsartan is unlikely to be removed by hemodialysis due to high protein binding.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Sacubitril-Valsartan (sacubitril/valsartan) contains sacubitril, a prodrug that results in neprilysin inhibition via its active metabolite, sacubitrilat, and the angiotensin II Type-1 (AT_1) receptor blocker, valsartan. Neprilysin is also known as neutral endopeptidase.

The cardiovascular and renal effects of Sacubitril-Valsartan in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, including natriuretic peptides such as BNP and ANP, and the simultaneous inhibition of the effects of angiotensin II by valsartan through blockade of the AT_1 receptor. Natriuretic peptides exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger, cyclic guanosine monophosphate (cGMP), which may lead to physiologically relevant effects, including vasodilation, natriuresis and diuresis, and inhibition of renin and aldosterone release.

Pharmacodynamics

The pharmacodynamic effects of Sacubitril-Valsartan 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 renin-angiotensin system blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction, administration of Sacubitril-Valsartan resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and 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. Sacubitril-Valsartan also blocked the AT_1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, Sacubitril-Valsartan decreased plasma NT-proBNP, and increased plasma BNP, along with urine cGMP, compared with enalapril (see CLINICAL TRIALS). While BNP is a neprilysin substrate, NT-proBNP is not (see WARNINGS AND PRECAUTIONS).

In a thorough QTc clinical study in healthy male subjects, single doses of 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan] had no effect on cardiac repolarisation.

Bradykinin is a substrate of both ACE and neprilysin. Thus, inhibition of these enzymes would be expected to lead to increased levels of circulating bradykinin. This phenomenon is likely the basis for the observed increases in the incidence of angioedema with use of each of these treatments.

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of 194 mg sacubitril/206 mg valsartan once daily for 2 weeks to healthy subjects was associated with an increase in CSF Aβ 1-38 compared to placebo, however, there were no changes in concentrations of CSF Aβ 1-40 and 1-42. The clinical relevance of this finding is unknown (also, see DETAILED PHARMACOLOGY).

Pharmacokinetics

Table 7 - Mean plasma pharmacokinetic parameters of Sacubitril-Valsartan analytes following single dose administration of 97.2 mg sacubitril / 102.8 mg valsartan in healthy subjects

	C_{max} (ng/mL)	$t_{½}$ (h)	AUC_{0-12} (ng*h/mL)	Cl/F (L/h)	Vz/F (L)
Sacubitril	1919.7 ± 967.83	1.43 ± 0.64	2450.7 ± 642.53	51.07 ± 14.65	103.41 ± 46.96
Sacubitrilat	8086.2 ± 1617.94	11.48 ± 2.55	58339.7 ± 8224.7	-	-
Valsartan	3969.8 ± 1427.66	9.9 ± 5.14	22160.3 ± 6502.9	5.44 ± 2.68	75.44 ± 50
Data is presented as arithmetic mean ± SD					

The pharmacokinetics of sacubitril, sacubitrilat, and valsartan appear to be linear when Sacubitril-Valsartan was administered orally at doses from 50 to 400 mg.

Absorption: Following oral administration, Sacubitril-Valsartan dissociates into sacubitril, which is then further metabolised to sacubitrilat, 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.

Oral bioavailability of valsartan, following administration of Sacubitril-Valsartan, is greater than that of valsartan in other marketed tablet formulations. For example, 26 mg, 51 mg, and 103 mg of valsartan in Sacubitril-Valsartan are equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively (also, see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Following twice daily dosing of Sacubitril-Valsartan, steady-state levels of sacubitril, sacubitrilat, and valsartan, are reached in 3 days. At steady-state, sacubitril and valsartan do not accumulate significantly, while sacubitrilat accumulates by 1.6-fold.

Sacubitril-Valsartan administration with food has no clinically significant impact on the systemic exposures of sacubitril, sacubitrilat, or valsartan.

Distribution: Sacubitril, sacubitrilat, and valsartan are highly bound to plasma proteins (94% - 97%). Based on the comparison of plasma and CSF exposures, sacubitrilat does cross the blood brain barrier to a very limited extent, i.e., 0.3%. The average apparent volume of distribution of sacubitril and valsartan were 103 and 75 liters, respectively.

Metabolism: Sacubitril is readily converted to sacubitrilat by esterases, with sacubitrilat 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%).

Elimination: Following oral administration, 52% to 68% of sacubitril (primarily as sacubitrilat) and ~13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as sacubitrilat), and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, sacubitrilat, and valsartan are eliminated from plasma with a mean elimination half-life ($t_{1/2}$) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.

Special Populations and Conditions

Pediatrics:
Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Sacubitril-Valsartan in pediatric patients has not been established.

Pediatric study
An analysis from a multinational, randomized, double-blind trial evaluating Sacubitril-Valsartan versus enalapril in 90 pediatric patients 6 to < 18 years old with heart failure (NYHA/Ross class II-IV) due to systemic left ventricular systolic dysfunction (LVEF ≤ 40%) was performed. The target maintenance dose of Sacubitril-Valsartan in pediatric patients was 3.1 mg/kg twice daily.

The endpoint in the analysis was the between-group difference in the change in plasma NT-proBNP from baseline to 12 weeks. The reduction from baseline in NT-proBNP was 41% and 26% in the Sacubitril-Valsartan and enalapril groups, respectively. While the between-group difference was not statistically significant, the reductions of NT-proBNP for Sacubitril-Valsartan and enalapril in pediatric patients from 6 to < 18 years old were similar to what was seen in adults (See CLINICAL TRIALS).

The population pharmacokinetic analysis including 54 pediatric patients from 6 to < 18 years old indicated comparable exposures in those patients to adults with heart failure, the estimated mean differences at steady state for AUC were less than 15% and for Cmax less than 40%.

The long-term effects of Sacubitril-Valsartan on development, growth, and/or maturation of organ/system function, as well as the long-term efficacy of treatment with Sacubitril-Valsartan in pediatric patients to reduce cardiovascular morbidity and mortality, are yet to be demonstrated. Exposure to sacubitril and valsartan in juvenile animals has been associated with bone and kidney effects, respectively (see TOXICOLOGY: Juvenile animal data).

Geriatrics: The exposures of sacubitrilat and valsartan are increased in elderly subjects by 42% and 30%, respectively, compared to younger subjects.

Gender: The pharmacokinetics of Sacubitril-Valsartan (sacubitril, sacubitrilat, and valsartan) are similar for male and female subjects.

Race: The pharmacokinetics of Sacubitril-Valsartan (sacubitril, sacubitrilat, and valsartan) are comparable across different race and ethnic groups (Caucasians, Blacks, Asians, Japanese and others).

Hepatic Insufficiency: In patients with mild to moderate hepatic impairment, the exposure of sacubitril increased by 1.5- and 3.4- fold, that of sacubitrilat increased by 1.5- and 1.9-fold, and

that of valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects (see DOSAGE AND ADMINISTRATION). Sacubitril-Valsartan has not been studied in patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS, Patients with Hepatic Impairment).

Renal Insufficiency: A correlation has been observed between renal function and systemic exposure to sacubitrilat, but not to valsartan. In patients with mild to moderate renal impairment (30-90 mL/min/1.73 m^2), the AUC for sacubitrilat was up to 2-fold higher. A 2.7-fold higher AUC for sacubitrilat was observed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) (see WARNINGS AND PRECAUTIONS, Patients with Renal Impairment).

No studies have been performed in patients undergoing dialysis. However, sacubitrilat and valsartan are highly bound to plasma protein and, therefore, unlikely to be effectively removed by dialysis.

STORAGE AND STABILITY

Do not store above 30°C and protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sacubitril-Valsartan 24 mg sacubitril / 26 mg valsartan, Sacubitril-Valsartan 49 mg sacubitril / 51 mg valsartan, Sacubitril-Valsartan 97 mg sacubitril / 103 mg valsartan

Sacubitril-Valsartan 24 mg sacubitril / 26 mg valsartan: Violet white ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “LZ” on the other side. Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium hydrate complex).

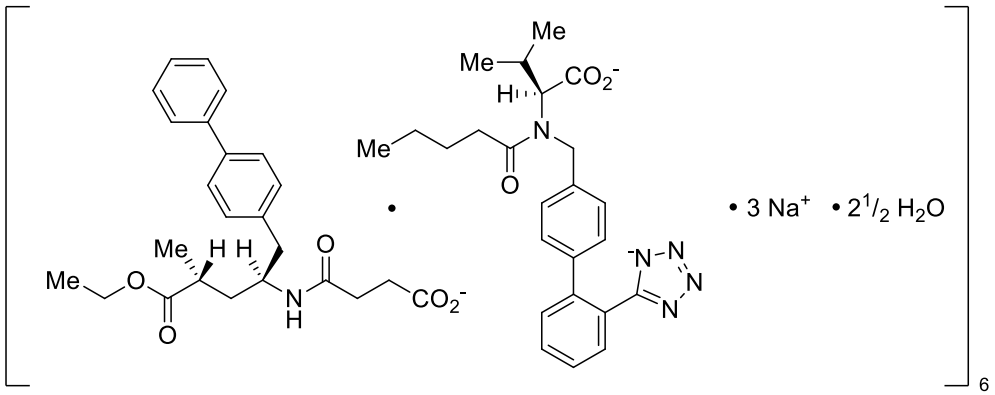
Sacubitril-Valsartan 49 mg sacubitril / 51 mg valsartan: Pale yellow ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L1” on the other side. Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium hydrate complex).

Sacubitril-Valsartan 97 mg sacubitril / 103 mg valsartan: Light pink ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L11” on the other side. Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium hydrate complex).

Composition

Sacubitril-Valsartan is a fixed-dose combination. Sacubitril-Valsartan 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. Following oral administration, Sacubitril-Valsartan dissociates into sacubitril (which is further metabolised to sacubitrilat) and valsartan.

Schematic 2-D structure of sacubitril valsartan sodium hydrate complex



Sacubitril-Valsartan is available in 3 strengths:
24 mg sacubitril / 26 mg valsartan
49 mg sacubitril / 51 mg valsartan
97 mg sacubitril / 103 mg valsartan

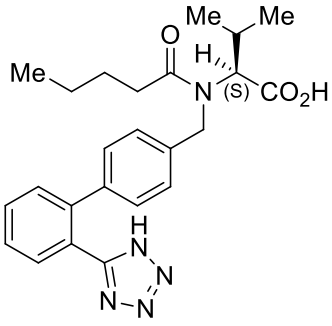
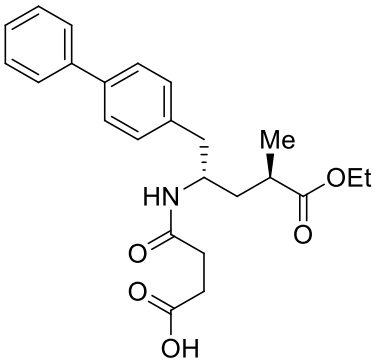
Sacubitril-Valsartan film-coated tablets also contain the following excipients: Colloidal silicon dioxide, crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate (vegetable origin), microcrystalline cellulose and talc. The film-coating contains hypromellose, iron oxide red (E 172), Macrogol 4000, talc and titanium dioxide (E 171). 24 mg sacubitril / 26 mg valsartan and 97 mg sacubitril / 103 mg valsartan film-coated tablets also contain iron oxide black (E 172), and 49 mg sacubitril / 51 mg valsartan film-coated tablets also contain iron oxide yellow (E 172).

Packaging
Sacubitril-Valsartan (24 mg sacubitril / 26 mg valsartan) film-coated tablets are available in cartons of 30 tablets (3 blister cards of 10 tablets). Sacubitril-Valsartan (49 mg sacubitril /51 mg valsartan) and Sacubitril-Valsartan (97 mg sacubitril / 103 mg valsartan) film-coated tablets are available in cartons of 60 tablets (6 blister cards of 10 tablets).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substances

Proper names:	
Valsartan	Sacubitril
Chemical names:	
CAS L-Valine, *N*-(1-oxopentyl)-*N*-[[2'-(2*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- IUPAC *N*-Pentanoyl-*N*-{[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl}-L-valine	CAS [1,1'-Biphenyl]-4-pentanoic acid, γ-[(3-carboxy-1- oxopropyl)amino]-α-methyl-, α-ethyl ester, (α*R*, γ*S*) IUPAC 4-{[(1*S*,3*R*)-1-([1,1'-Biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoic acid
Molecular formulae:	
$C_{24}H_{29}N_5O_3$	$C_{24}H_{29}NO_5$
Molecular weights:	
435.52	411.49
Structural formulae:	
	
Description:	

Fine white to practically white, practically odourless powder. It is soluble in ethanol, methanol and slightly soluble in water.	Not isolated
Dissociation constants: 1. pKa 3.9 for carboxylic acid group 2. pKa 4.7 for tetrazole-NH group	pKa 4.6

CLINICAL TRIALS

The PARADIGM-HF trial was a multinational, randomised, double-blind trial comparing Sacubitril-Valsartan (sacubitril/valsartan) to enalapril in 8,442 adult patients with symptomatic chronic heart failure and reduced ejection, i.e., left ventricular ejection fraction ≤ 40% in NYHA Class II-IV. Prior to study enrolment, patients were required to have a plasma B-type natriuretic peptide (BNP) ≥ 150 pg/mL or N-terminal pro-BNP (NT-proBNP) ≥ 600 pg/mL, or, if they had been hospitalised for heart failure in the last 12 months, a BNP ≥ 100 pg/mL or a NT-proBNP ≥ 400 pg/mL. Patients had to have been on an ACEi or ARB at a dose equivalent to at least 10 mg of enalapril daily for at least four weeks prior to screening, and on maximally tolerated doses of beta-blockers.

Patients with symptomatic hypotension, or having a systolic blood pressure of < 100 mmHg at screening were excluded. Patients with eGFR < 30 mL/min/1.73m^2 or serum potassium ≥ 5.2 mmol/L at baseline, or those with any history of angioedema, were also excluded.

The primary objective of PARADIGM-HF was to determine whether Sacubitril-Valsartan, a combination of sacubitril and valsartan, was superior to enalapril alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalisation for heart failure (HF).

After discontinuing their existing ACEi or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice daily for a median duration of 15 days, followed by one tablet of Sacubitril-Valsartan containing 48.6 mg sacubitril / 51.4 mg valsartan (referred to as 100 mg in the Clinical Trial) taken twice daily, for a median duration of 29 days. Patients who successfully completed the sequential run-in periods were randomised to receive either one tablet of Sacubitril-Valsartan containing 97.2 mg sacubitril / 102.8 mg valsartan (referred to as 200 mg in the Clinical Trial) (N=4,209) twice-daily or enalapril 10 mg (N=4,233) twice daily in a double-blind manner. The primary endpoint was the first event in the composite of CV death or hospitalisation for HF. The median follow-up duration of double-blind treatment was 27 months, with some patients treated for up to 4.3 years.

In PARADIGM-HF, 18,071 patients with HFrEF were initially screened for enrolment into the trial. Of these, 7,534 did not meet study entry criteria at screening, with 62% of these patients not meeting minimum levels of elevated NT-proBNP as described above, 19% having serum potassium ≥ 5.2 mmol/L, and 5.5% having eGFR < 30 mL/min/1.73m^2.

The population enrolled in the trial was 66% Caucasian, 18% Asian, and 5% Black, with a mean age of 64 years, of which 19% were ≥ 75 years, 7% were ≥ 80 years, and <1.5% were ≥ 85 years. In this trial, 78% of patients were male. At randomisation, 70% were NYHA Class II, 24% NYHA Class III, and 0.7% NYHA Class IV. The mean left ventricular ejection fraction was about 29% at baseline. The underlying cause of heart failure was coronary artery disease in 60% of patients. Baseline characteristics revealed that 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR 30-60 mL/min/1.73m^2, and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Essentially all patients were taking ACEi or ARB at baseline. Some patients had an

implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) (15%).

In the Sacubitril-Valsartan group, 76% of patients remained on the target dose of one tablet of 97.2 mg sacubitril / 102.8 mg valsartan taken twice daily at the end of the study, with a reported mean daily dose of 182.2 mg sacubitril and 192.8 mg valsartan. In the enalapril group, 75% of patients remained on the target dose of 10 mg twice daily at the end of the study, with a reported mean daily dose of 18.9 mg.

Sacubitril-Valsartan demonstrated clinically relevant and statistically significant superiority to enalapril in the randomised data set, reducing the risk of cardiovascular death or heart failure hospitalisations by 20% (hazard ratio (HR): 0.80, 95% CI [0.73; 0.87], 1-sided p =0.0000002) versus enalapril, see Table 8, below. This effect was observed early and was sustained throughout the duration of the trial, see Figure 1, below. 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= 0.008). 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 = 0.03).

This risk reduction was generally observed consistently across subgroups including: age, gender, race, geography, ejection fraction, renal function, history of diabetes or hypertension, and presence of atrial fibrillation.

The mean change in systolic blood pressure (SBP) from baseline to Month 28 during this study was 0.7 mmHg (from 122.1 mmHg to 122.9 mmHg) in Sacubitril-Valsartan -treated patients, compared to 3.1 mmHg (from 121.9 mmHg to 125.0 mmHg) Hg) in enalapril-treated patients, a difference of 2.3 mmHg.

Table 8 - Treatment effect in PARADIGM-HF

	Sacubitril-Valsartan N = 4187 n (%)	**enalapril N = 4212 n (%)**	**Hazard Ratio (95% CI)**	**p-value *****
Primary Composite Endpoint of CV Death or First Heart Failure Hospitalisation*	914 (21.8)	1117 (26.5)	0.80 (0.73,0.87)	0.0000002
CV Death **	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	0.00004
First Heart Failure Hospitalisation	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	0.00004
Total HF hospitalisations[♯]	851	1079	0.77 (0.67, 0.89)	0.0004
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76, 0.93)	0.0005

**The primary endpoint was defined as the time-to-first-event.*

*** CV death includes all patients who died up to the cut-off date irrespective of previous hospitalisation.*
**** Two-sided p-value for Total HF hospitalizations, all others p-values one sided as pre-specified*
 # Total HF hospitalisations are provided as number of events and therefore the ratio given is a relative rate

Time-to-first-occurrence of the primary composite endpoint of CV death or heart failure hospitalisation, and CV death alone, over the duration of the study are shown below in Figure 1.

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

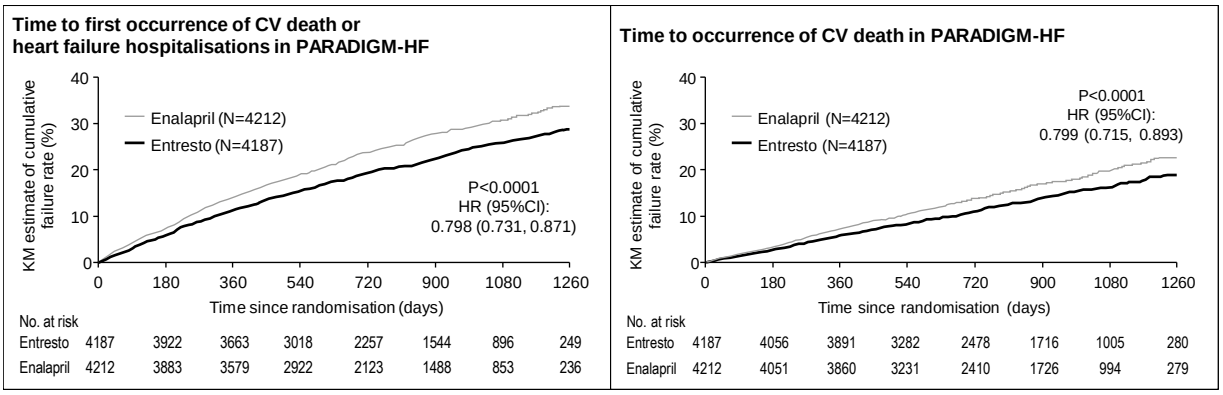


Table 9 below presents results for the primary pre-specified endpoint of CV death and HF hospitalisation by NT-proBNP values at screening.

Table 9 - Between-treatment comparison of primary endpoint results by NT-proBNP quartiles at screening in PARADIGM-HF

NT-proBNP (pg/mL) quartile at screening	Sacubitril-Valsartan			enalapril			Sacubitril-Valsartan vs. enalapril HR (95% CI)		P-value
	m	n	(%)	m	n	(%)			
<886.0	1035	118	11.4	1048	175	16.7	0.66	(0.52, 0.83)	0.3442
886.0 to 1610.5	1030	180	17.5	1061	226	21.3	0.78	(0.64, 0.95)	
1610.5 to 3228.0	1071	248	23.2	1016	267	26.3	0.87	(0.73, 1.03)	
≥3228.0	1028	363	35.3	1059	442	41.7	0.81	(0.71, 0.93)	

m: number of patients at risk
n: number of events

Hazard ratio (95% CI) is from a Cox model with treatment and region fixed factors within each subgroup. The interaction p-value (2-sided) is from the Cox model with additional terms of subgroup by treatment. A hazard ratio < 1 favours Sacubitril-Valsartan.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) values were obtained in PARADIGM-HF at baseline and during the post-randomisation treatment phase of the trial. Median NT-proBNP level at study enrolment was 1,629 pg/mL for Sacubitril-Valsartan-treated patients, and 1,593 pg/mL for enalapril-treated patients.

For patients having NT-proBNP measurements both at baseline and at 4 weeks following randomisation, median NT-proBNP level was 938 pg/mL at 4 weeks following randomisation, compared to 1,304 pg/mL at baseline, for Sacubitril-Valsartan-treated patients, a decrease of 28%. For similar enalapril-treated patients, median NT-proBNP level was 1,203 pg/mL at 4 weeks, compared to 1,268 pg/mL at baseline, a decrease of 5%. Similarly, for patients with NT-proBNP measurement at 34 weeks post-randomisation, median NT-proBNP level was 859 pg/mL for Sacubitril-Valsartan-treated patients, compared to 1,226 pg/mL at baseline, a decrease of 30%. For these enalapril-treated patients, median NT-proBNP was 1,103 pg/mL at 34 weeks, compared to 1,222 pg/mL at baseline, a decrease of 10%. **In patients treated with Sacubitril-Valsartan, only NT-proBNP, but not BNP, is a suitable biomarker for myocardial wall stress and disease status in heart failure patients (see WARNINGS AND PRECAUTIONS).**

Comparative Bioavailability Study

A randomized, single-dose, two-treatment, semi-replicate, three-period crossover study to measure the comparative bioavailability of the commercial Sacubitril-Valsartan (24.3 mg sacubitril/ 25.7 mg valsartan) versus the clinical service form (CSF) (24.3 mg sacubitril/ 25.7 mg valsartan) was conducted under fasted conditions in 81 male and female healthy volunteers. The data from this study meets the applicable standards for comparative bioavailability from the Sacubitril-Valsartan (24.3 mg sacubitril/ 25.7 mg valsartan) and the CSF (24.3 mg sacubitril/ 25.7 mg valsartan).

Sacubitrilat (1 x 24.3 mg sacubitril, administered as the 24.3 mg sacubitril/ 25.7 mg valsartan tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Sacubitril-Valsartan Tablet	CSF Tablet	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng*hr/mL)	22000 22800 (26.7)	22800 23600 (29.3)	98.85%	97.63% - 100.08%
AUC_I (ng*hr/mL)	22600 23300 (26.6)	23400 24200 (29.5)	98.79%	97.61% - 99.99%

Sacubitrilat (1 x 24.3 mg sacubitril, administered as the 24.3 mg sacubitril/ 25.7 mg valsartan tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Sacubitril-Valsartan Tablet	CSF Tablet	% Ratio of Geometric Means	Confidence Interval (90%)
C_{max} (ng/mL)	2120 2180 (22.1)	2160 2220 (22.8)	99.71%	97.35% - 102.14%
T_{max}[§] (hr)	2.32 (44.5)	2.24 (40.1)		
$T_{½}$[§] (hr)	10.1 (22.7)	10.2 (25.3)		

[§] Expressed as the arithmetic mean (CV %)

Valsartan (1 x 25.7 mg, administered as the 50 mg tablet (24.3 mg sacubitril/ 25.7 mg valsartan) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Sacubitril-Valsartan Tablet	CSF Tablet	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng*hr/mL)	6430 6890 (36.0)	6630 7130 (38.2)	95.70%	90.05% - 101.45%
AUC_I (ng*hr/mL)	6580 7030 (35.3)	6810 7300 (37.6)	95.62%	90.13% - 101.45%
C_{max} (ng/ml)	1080 1160 (39.1)	1100 1190 (39.0)	95.76%	89.46% - 102.50%
T_{max}[§] (hr)	1.59 (37.9)	1.55 (38.9)		
$T_{½}$[§] (hr)	5.76 (31.7)	6.11 (69.9)		

[§] Expressed as the arithmetic mean (CV %)

DETAILED PHARMACOLOGY

The effects of Sacubitril-Valsartan (sacubitril/valsartan) on amyloid-β (Aβ) concentrations in cerebrospinal fluid (CSF) and brain tissue were assessed in young (2-4 year old) cynomolgus monkeys treated with 24 mg sacubitril/26 mg valsartan/kg/dayfor 2 weeks. In this study, sacubitril/valsartan affected CSF Aβ clearance, increasing CSF Aβ 1-40, 1-42, and 1-38 levels, with no corresponding increase in Aβ levels in the brain.

Additionally, in a toxicology study in cynomolgus monkeys treated with 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no Aβ accumulation in the brain.

TOXICOLOGY

Non-clinical safety studies conducted with sacubitril/valsartan included assessment of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and reproductive and development toxicity.

Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of AT_1 receptor blockade.

Carcinogenicity, mutagenesis and genetic toxicity

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for Sacubitril-Valsartan (sacubitril/valsartan). The sacubitrilat C_{max} at 1,200 mg sacubitril/kg/day in male and female mice was, 14 and 16 times that of the maximum recommended human dose (MRHD), respectively. The sacubitrilat C_{max} in male and female rats at 400 mg sacubitril/kg/day was 1.7 and 3.5 times that of the MRHD, respectively. The doses of valsartan studied (high dose of 160 and 200 mg/kg/day in mice and rats, respectively) were about 4 and 10 times, respectively, the MRHD on a mg/m^2 basis.

Mutagenicity and clastogenicity studies conducted with sacubitril/valsartan did not reveal any effects at either the gene or chromosome level.

Fertility, reproduction and development

A dose of 73 mg sacubitril/77 mg valsartan/kg/day did not show any effects on fertility or early embryonic development in rats (≤ 0.6-fold the MRHD on the basis of valsartan and ≤0.1-fold the MRHD on the basis of sacubitrilat AUC).

Sacubitril/valsartan administration during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥ 49 mg sacubitril/51 mg valsartan (0.06-fold the MRHD for sacubitrilat, and 0.72-fold for valsartan, based on AUC) and in rabbits at doses ≥ 5 mg sacubitril/5 mg valsartan (0.03-fold the MRHD for sacubitrilat, and 2.0-fold for valsartan, based on AUC). Sacubitril-Valsartan is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a dose of ≥ 5 mg sacubitril/5 mg valsartan/kg/day.

Pre- and postnatal development studies in rats conducted with sacubitril at doses up to 750 mg/kg/day (1.0-fold the MRHD on the basis of sacubitrilat AUC) and valsartan at doses up to 600 mg/kg/day (≤0.9-fold the MRHD on the basis of its AUC) indicate that treatment with Sacubitril-Valsartan during organogenesis, gestation and lactation may affect pup development (lower pup weights) and survival.

Following an oral dose of [^{14}C] 15 mg sacubitril/15 mg valsartan/kg to lactating rats, transfer of sacubitrilat into milk was observed. After a single oral administration of 3 mg/kg [^{14}C] valsartan to lactating rats, transfer of valsartan into milk was observed.

Juvenile animal data

Sacubitril given orally to juvenile rats from postnatal day (PND) 7 to PND 35 or PND 70 (an age approximately equivalent to neonatal through pre-pubertal development or adulthood in humans) at doses ≥ 400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, at a Sacubitril-Valsartan pediatric clinical dose of 3.1 mg/kg twice daily) resulted in decreases in body weight, bone length, and bone mass. The decrease in body weight was transient from PND 10 to PND 20 and the effects for most bone parameters were reversible after treatment stopped. Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657 at the 3.1 mg/kg twice daily dose of Sacubitril-Valsartan. The mechanism underlying bone effects in rats and the translatability to pediatric patients are unknown.

Valsartan given orally to juvenile rats from PND 7 to PND 70 (an age approximately equivalent to neonatal through adulthood in humans) produced persistent, irreversible kidney damage at all dose levels. Exposure at the lowest tested dose of 1 mg/kg/day was approximately 0.2-fold the exposure at 3.1 mg/kg twice daily dose of Sacubitril-Valsartan based on AUC. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr]Sacubitril-Valsartan
sacubitril / valsartan film-coated tablets

Read this carefully before you start taking **Sacubitril-Valsartan** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sacubitril-Valsartan**.

Serious Warnings and Precautions
Valsartan should not be used during pregnancy. If you discover that you are pregnant while taking Sacubitril-Valsartan stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

What is Sacubitril-Valsartan used for?

Sacubitril-Valsartan is used to treat heart failure in adults. It has been shown to lower the:

- risk of death that is caused from heart and blood vessel related problems
- need for hospitalisation due to heart failure.

How does Sacubitril-Valsartan work?

Sacubitril-Valsartan contains sacubitril and valsartan. These two ingredients work by blocking a specific enzyme and a specific receptor in your body.

Sacubitril-Valsartan helps treat heart failure by:
- relaxing your blood vessels. This makes it easier for your heart to pump blood around your body.
- helping your body retain less water.

What are the ingredients in Sacubitril-Valsartan?
Medicinal ingredients: sacubitril and valsartan, as sodium salt complex.

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide black, iron oxide red, iron oxide yellow, low-substituted hydroxypropylcellulose, Macrogol 4000, magnesium stearate (vegetable origin), microcrystalline cellulose, talc and titanium dioxide.

Sacubitril-Valsartan comes in the following dosage forms:
Film-coated tablet:

24 mg sacubitril/ 26 mg valsartan (violet white). Each tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium hydrate complex).

49 mg sacubitril/ 51 mg valsartan (pale yellow). Each tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium hydrate complex).

97 mg sacubitril/ 103 mg valsartan (light pink). Each tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium hydrate complex).

Do not use Sacubitril-Valsartan if you:

- are allergic to sacubitril or valsartan or any of the other ingredients in Sacubitril-Valsartan
- are taking angiotensin converting enzyme (ACE) inhibitors. **You must wait at least 36 hours after your last dose of the ACE Inhibitor before starting Sacubitril-Valsartan.**
- have had **angioedema**, a swelling of the face, lips, tongue and/or throat, with or without difficulty in breathing:
    - while taking an ACE inhibitor or an ARB in the past
    - due to any other reason. The exception is an allergic reaction to a bee sting, insect or snake bite.

  If this occurs, stop Sacubitril-Valsartan immediately, and contact your doctor.
- have an inherited condition called "hereditary angioedema," an increased risk of getting an allergic reaction (angioedema) that is passed down through families.
- are taking aliskiren-containing medicines, such as Rasilez, **and** have Diabetes or Kidney disease.
- are pregnant or planning to become pregnant. Taking Sacubitril-Valsartan during pregnancy can cause injury and even death to your baby.
- are breastfeeding. It is possible that Sacubitril-Valsartan passes into the breast milk.
- are having symptoms related to low blood pressure
- are 18 years or younger

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sacubitril-Valsartan. **Talk about any health conditions or problems you may have, including if you:**

- have severe kidney disease.
- have severe liver disease
- ever had a reaction called angioedema (swelling of the face, lips, tongue, and/or throat, difficulties in breathing).
- have low blood pressure, or are taking other drugs to lower your blood pressure, such as, a diuretic or water pill.
- are taking any drugs that increase the amount of potassium in your blood (such as potassium supplements, or salt substitutes containing potassium, potassium-sparing drugs, and heparin). Your doctor may check the potassium levels in your blood at regular times while you are taking Sacubitril-Valsartan

- have one or both of arteries to your kidney that are severely narrowed.

Other warnings you should know about:

Black patients may have a higher risk of **angioedema.**

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sacubitril-Valsartan:

- ACE inhibitors (such as enalapril, ramipril, lisinopril and fosinopril).
- Drugs used for lowering blood pressure or to treat heart failure:
    - ARB (such as losartan, telmisartan, valsartan and candesartan)
    - Aliskiren-containing drugs
- Drugs used to lower cholesterol levels. These are known as 'statins' (such as atorvastatin).
- Sildenafil, a drug used to treat erectile dysfunction
- Drugs that increase the amount of potassium in the blood (such as potassium supplements, or salt substitutes containing potassium, potassium-sparing diuretics or heparin).
- Drugs used to treat inflammation and pain:
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Cox-2 inhibitors (such as celecoxib)
- Lithium, a drug used to treat some types of depression, bipolar or hypomanic disorders.
- Drugs used after organ transplants to protect against transplant rejection (such as cyclosporin)
- Drugs used to treat HIV/AIDS (such as ritonavir)
- Warfarin, a drug used to make blood thinner and less likely to clot.
- Furosemide, a diuretic (water pill) used to reduce the fluid build-up in your body
- Metformin, used to treat diabetes.

Ask your doctor or pharmacist if you are not sure if any of the medicines you take are included in the list above.

How to take Sacubitril-Valsartan:

If you were taking ACE inhibitors, you **must** wait at least 36 hours after your last dose of the ACE inhibitor before starting Sacubitril-Valsartan.

Swallow the tablet **whole**. Do **NOT** break the tablet.

Take Sacubitril-Valsartan:

- exactly as prescribed;
- every 12 hours, at about the same time every day;
- with or without food

<u>Usual Adult Dose:</u>

Recommended starting dose: Sacubitril-Valsartan 49 mg sacubitril/ 51 mg valsartan twice a day
Maximum daily dose: Sacubitril-Valsartan 97 mg sacubitril/ 103 mg valsartan twice a day

Your doctor may start you on Sacubitril-Valsartan 24 mg sacubitril/ 26 mg valsartan twice a day if you:

- have previously taken low doses of an ACE inhibitor or ARB for the treatment of heart failure
- are 75 years of age or older
- have low blood pressure

Your doctor may change your dose depending on how Sacubitril-Valsartan works for you.

Do not take more than the maximum daily dose.

Do not reduce the dose or stop taking Sacubitril-Valsartan without consulting your doctor. This could make your disease worse.

Overdose:

If you think you have taken too much Sacubitril-Valsartan, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. You can take your next dose at the normal time, but do **NOT** double the dose to make up for the missed one.

What are possible side effects from using Sacubitril-Valsartan?

These are not all the possible side effects you may feel when taking Sacubitril-Valsartan. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

- low blood pressure
- excessively high level of potassium in the blood, as shown in a blood test
- kidney disorder (signs of renal impairment)
- dizziness
- tiredness (fatigue)
- sudden loss of consciousness
- feeling sick (nausea)
- weakness

- rash
- itchiness
- low blood pressure when switching from sitting or lying down to standing position
- spinning sensation

If you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON **Angioedema:** Swollen face, tongue or throat, difficulty breathing			X
Anaphylactic reaction or hypersensitivity: Difficulty breathing or swallowing, rash, itching, hives, dizziness			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store your tablets in the original package. Protect from moisture.
- Do not take this medicine after the expiry date, which is stated on the label.
- Do not store above 30°C.

Keep out of reach and sight of children.

If you want more information about Sacubitril-Valsartan:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website, (http://www.hc-sc.gc.ca); the manufacturer's website (novartis.ca) or by calling 1-800-363-8883
- by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:
  Novartis Pharmaceuticals Canada Inc.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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