NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Sacubitril/Valsartan Devatis 24/26 film coated tablets
Sacubitril/Valsartan Devatis 49/51 film coated tablets
Sacubitril/Valsartan Devatis 97/103 film coated tablets

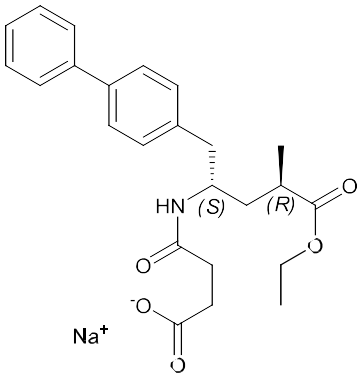
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sacubitril sodium

Active ingredient: Sacubitril sodium

Chemical name (IUPAC): sodium;4-[[(2S,4R)-5-ethoxy-4-methyl-5-oxo-1-(4-phenylphenyl)pentan-2-yl]amino]-4-oxobutanoate

Structure (schematic 2-dimensional):



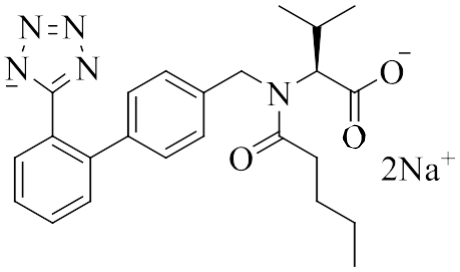
Molecular formula: $C_{24}H_{28}NNaO_5$
Relative molecular mass: 433.47 g/mol
CAS number: 149690-05-1

Valsartan disodium

Active ingredient: Valsartan disodium

Chemical name (IUPAC): N-[p-(o-1H-Tetrazol-5-ylphenyl)benzyl]-N-valeryl-L-valine, disodium salt

Structure (schematic 2-dimensional):



Molecular formula: $C_{24}H_{27}N_5Na_2O_3$
Relative molecular mass: 479.48 g/mol
CAS number: 391230-93-6

Sacubitril/Valsartan Devatis film coated tablets are available in 3 strengths:

Each Sacubitril/Valsartan Devatis 24/26 film coated tablet contains 25.6 mg of sacubitril sodium equivalent to 24.3 mg sacubitril and 28.3 mg of valsartan disodium equivalent to 25.7 mg valsartan.

Each Sacubitril/Valsartan Devatis 49/51 film-coated tablet contains 51.2 mg of sacubitril sodium equivalent to 48.6 mg sacubitril and 56.59 mg of valsartan disodium equivalent to 51.4 mg valsartan.

Each Sacubitril/Valsartan Devatis 97/103 film-coated tablet contains 102.39 mg of sacubitril sodium equivalent to 97.2 mg sacubitril and 113.18 mg of valsartan disodium equivalent to 102.8 mg valsartan.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Sacubitril sodium is almost white to yellow powder with a melting point of around 168°C (onset). It is freely soluble in water and in anhydrous ethanol, sparingly soluble in methylene chloride.

Valsartan disodium is off-white to yellow powder and deliquescent in nature. It is freely soluble in anhydrous ethanol and water; practically insoluble in methylene chloride.

Sacubitril/Valsartan Devatis 24/26 (24.3 mg sacubitril/25.7 mg valsartan): Violet-white, oblong film-coated tablet.

Sacubitril/Valsartan Devatis 49/51 (48.6 mg sacubitril/51.4 mg valsartan): Pale yellow, oblong film-coated tablet

Sacubitril/Valsartan Devatis 97/103 (97.2 mg sacubitril/102.8 mg valsartan): Light pink, oblong film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sacubitril/Valsartan Devatis is indicated in adult patients with chronic heart failure (NYHA Class II-IV) with a reduced ejection fraction.

Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat (see section 5.1).

4.2 Dose and method of administration

Sacubitril/Valsartan Devatis is administered in place of an ACE inhibitor or ARB.

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

The recommended starting dose of Sacubitril/Valsartan Devatis is one tablet of 49 mg/51 mg twice daily, except in the situations described below.

The dose of Sacubitril/Valsartan Devatis should be doubled after 2 to 4 weeks to the target maintenance dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient.

If patients experience tolerability issues (systolic blood pressure ≤95mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), consideration should be given to adjustment of concomitant medications, or to temporary down–titration or discontinuation of Sacubitril/Valsartan Devatis.

Starting dose of Sacubitril/Valsartan Devatis of 24 mg/26 mg for some populations

A starting dose of Sacubitril/Valsartan Devatis of one tablet of 24 mg/26 mg taken twice daily is recommended for patients not currently taking an ACE inhibitor or an ARB, or patients previously taking low doses of these agents (see sections 5.1 and 4.2).

A starting dose of Sacubitril/Valsartan Devatis of one tablet of 24 mg/26 mg taken twice daily should be considered for patients who have risk factors for hypotension, including patients ≥ 75 years old and patients with low systolic blood pressure (SBP ≥100 to 110 mmHg) (see section 4.4).

The dose of Sacubitril/Valsartan Devatis should be doubled every 2-4 weeks to the target dose of one tablet of Sacubitril/Valsartan Devatis 97 mg/103 mg twice daily, as tolerated by the patient.

See Special Populations section below for further starting dose recommendations in Renal insufficiency, Hepatic insufficiency and Geriatric patients.

Other important considerations for dosing

Sacubitril/Valsartan Devatis is contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. Due to the potential risk of angioedema when used concomitantly with an

ACE inhibitor, Sacubitril/Valsartan Devatis must not be administered until 36 hours after the last dose of ACE inhibitor therapy and similarly, at least 36 hours must elapse after the last dose of Sacubitril/Valsartan Devatis before ACE inhibitor therapy is initiated (see section 4.3*)*.

Sacubitril/Valsartan Devatis should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Sacubitril/Valsartan Devatis (see sections 4.4 and 4.5).

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg (see section 4.4).

The valsartan contained within Sacubitril/Valsartan Devatis is more bioavailable than the valsartan in other marketed tablet formulations;

Table 4-1 Doses of Sacubitril and Valsartan in Sacubitril/Valsartan combination and doses of valsartan in other marketed formulations

Sacubitril/ Valsartan dose	Amount of Sacubitril delivered from the indicated Sacubitril/ Valsartan dose	Amount of Valsartan delivered from the indicated Sacubitril/ Valsartan dose	Dose of valsartan in other marketed formulations delivering an equivalent valsartan exposure (AUC) as the indicated Sacubitril/ Valsartan dose
24 mg/ 26 mg	24 mg	26 mg	40 mg
49 mg/ 51 mg	49 mg	51 mg	80 mg
97 mg/ 103 mg	97 mg	103 mg	160 mg

Special populations

Renal insufficiency

No dose adjustment is required in patients with mild (eGFR 60-90 mL/min/1.73 m^2) to moderate (eGFR 30-60 mL/min/1.73 m^2) renal impairment.

A starting dose of Sacubitril/Valsartan Devatis 24 mg/26 mg twice daily is recommended in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Caution is recommended when using Sacubitril/Valsartan Devatis in these patients as there are no adequate data (see section 5.2).

There is no experience in patients with end-stage renal disease and use of Sacubitril/Valsartan Devatis is not recommended.

Hepatic insufficiency

No dose adjustment is required when administering Sacubitril/Valsartan Devatis to patients with mild hepatic impairment (Child-Pugh A classification).

A starting dose of Sacubitril/Valsartan Devatis 24 mg/26 mg twice daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification).

Patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child Pugh C classification) should not take Sacubitril/Valsartan Devatis (see sections 4.3 and 5.2).

Paediatric patients

The safety and efficacy of Sacubitril/Valsartan Devatis in paediatric patients aged below 18 years have not been established.

Geriatric patients (older than 65 years)

No dose adjustment is required in patients over 65 years. However, sacubitril/valsartan has been studied in a limited number of patients over 80 years. In patients ≥ 75 years old, a starting dose of one tablet of Sacubitril/Valsartan Devatis 24 mg/26 mg taken twice daily should be considered.

Method of administration
For oral use. Sacubitril/Valsartan Devatis may be administered with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients.
- Concomitant use with ACE inhibitors. Do not administer Sacubitril/Valsartan Devatis within 36 hours of switching from or to an ACE inhibitor (see sections 4.4, 4.2, and 4.5).
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema (see section 4.4).
- Concomitant use with aliskiren in patients with Type 2 diabetes (see sections 4.4 and 4.5).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see section 4.2).
- Pregnancy (see section 4.4).

4.4 Special warnings and precautions for use

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

Sacubitril/Valsartan Devatis must not be administered with an ACE inhibitor due to the risk of angioedema. Sacubitril/Valsartan Devatis must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Sacubitril/Valsartan Devatis is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Sacubitril/Valsartan Devatis (see sections 4.3, 4.2, and 4.5).

Caution is required while co-administering Sacubitril/Valsartan Devatis with direct renin inhibitors such as aliskiren (see sections 4.3 and 4.5). Sacubitril/Valsartan Devatis must not be administered with aliskiren in patients with Type 2 diabetes (see section 4.3).

Sacubitril/Valsartan Devatis should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Sacubitril/Valsartan Devatis (see sections 4.2 and 4.5).

Hypotension

Sacubitril/Valsartan Devatis lowers blood pressure and may cause symptomatic hypotension, especially in patients ≥75 years old, patients with renal disease and patients with low systolic blood pressure (<112 mmHg) (see section 4.8). Patients with systolic blood pressure <100 mmHg at the time of initiation of sacubitril/valsartan have not been studied; use of Sacubitril/Valsartan Devatis in these patients is not recommended.

When initiating therapy or during dose titration with Sacubitril/Valsartan Devatis, blood pressure should be monitored routinely. 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.

If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. If hypotension persists despite such measures, the dosage of Sacubitril/Valsartan Devatis should be reduced or the product should be temporarily discontinued (see section 4.2). Permanent discontinuation of therapy is usually not required. 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 with Sacubitril/Valsartan Devatis.

Impaired renal function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, the use of sacubitril/valsartan may be associated with decreased renal function. In PARADIGM, the incidence of clinically relevant renal impairment was low and associated treatment discontinuation was observed less frequently in patients receiving sacubitril/valsartan (0.65%) compared to enalapril (1.28%). In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death.

Use of Sacubitril/Valsartan Devatis should include appropriate assessment of renal function, before initiation of therapy, and then during treatment, as appropriate. Closely monitor serum creatinine, and down-titrate or interrupt Sacubitril/Valsartan Devatis in patients who develop a clinically significant decrease in renal function (see section 5.2). As with all drugs that affect the RAAS, Sacubitril/ Valsartan Devatis may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

Patients with mild and moderate renal impairment are more at risk of developing hypotension. 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. Caution should be exercised when administering Sacubitril/Valsartan Devatis in patients with severe renal impairment. There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended (see sections 4.2 and 5.2).

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Through its action on the renin-angiotensin-aldosterone system, hyperkalaemia may occur with Sacubitril/Valsartan Devatis. In PARADIGM-HF, the incidence of clinically relevant hyperkalaemia was low, resulting in treatment discontinuation in 0.26% of sacubitril/valsartan treated patients compared to 0.35% of

enalapril treated patients. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalaemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of Sacubitril/Valsartan Devatis may be required (see section 4.2). Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution when co-administered with Sacubitril/Valsartan Devatis. If clinically significant hyperkalaemia occurs, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered. In addition, if serum potassium level is >5.4 mmol/l, discontinuation of Sacubitril/Valsartan Devatis should be considered.

Angioedema

If angioedema occurs, Sacubitril/Valsartan Devatis 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 Devatis 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/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly administered.

Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Sacubitril/Valsartan Devatis is used in these patients. Sacubitril/Valsartan Devatis must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema (see section 4.3).

Black patients may have increased susceptibility to develop angioedema.

Patients with renal artery stenosis

Similar to other drugs that affect the renin-angiotensin-aldosterone system, Sacubitril/Valsartan Devatis 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 Sacubitril/Valsartan Devatis in patients with NYHA functional classification IV due to limited clinical experience in this population.

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 sections 4.2 and 5.2). Sacubitril/Valsartan Devatis is

contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).

Effects on 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.

Use in Pregnancy (Category D)

Drugs that act on the renin-angiotensin-aldosterone system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific class of drugs acting on the RAAS).

As for other drugs that also act directly on the RAAS, Sacubitril/Valsartan Devatis must not be used during pregnancy (see section 4.3) or in women planning to become pregnant. Valsartan exerts its effects via angiotensin II antagonism. 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. Physicians prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. Patients should be advised to discontinue Sacubitril/Valsartan Devatis as soon as pregnancies occur and to inform their physicians.

The use of drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function. Oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

In animal studies, sacubitril/valsartan treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥ 49 mg sacubitril/51 mg valsartan/kg/day (≤ 0.06 [LBQ657 (sacubitrilat), the active metabolite] and 0.7 [valsartan]-fold the maximum recommended human dose [MRHD] of 97 mg/103 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses ≥ 5 mg sacubitril/5 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively). Sacubitril/valsartan is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril/valsartan dose of ≥ 5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo-fetal effects of sacubitril/valsartan are attributed to the angiotensin receptor antagonist activity.

Sacubitril
There are no data from the use of sacubitril in pregnant women. Studies in animals have shown reproductive toxicity.

Sacubitril/Valsartan
There are no data from the use of sacubitril/valsartan in pregnant women. Animal studies with sacubitril/valsartan have shown reproductive toxicity.
Use in Lactation

It is not known whether sacubitril/valsartan is excreted in human milk. The components of Sacubitril/Valsartan combination, sacubitril and valsartan, were excreted in the milk of lactating rats.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (1.1-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 AUC) indicate that treatment with sacubitril/valsartan during organogenesis, gestation and lactation may affect pup development and survival.

Because of the potential risk for adverse drug reactions in breastfed newborns/infants, Sacubitril/ Valsartan Devatis is not recommended during breastfeeding. A decision should be made whether to abstain from breast-feeding or to discontinue Sacubitril/Valsartan Devatis while breast-feeding, taking into account the importance of Sacubitril/Valsartan Devatis to the mother.

Effects on Fertility

There are no available data on the effect of sacubitril/valsartan on human fertility.
Sacubitril/valsartan did not show any effects on fertility or early embryonic development in male and female rats up to a dose of 73 mg sacubitril/77 mg valsartan /kg/day (≤1.0 fold and ≤0.13 fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively).

Females of child-bearing potential

Female patients of child-bearing potential should be advised about the consequences of exposure to Sacubitril/Valsartan Devatis during pregnancy and to use contraception during treatment with Sacubitril/Valsartan Devatis and for 1 week after their last dose.

Carcinogenicity

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for sacubitril/valsartan. The doses of sacubitril studied (high dose of 1200 and 400 mg/kg/day in mice and rats, respectively) were about 29 and 19 times, respectively, the maximum recommended human dose (MRHD) on a mg/m^2 basis. 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 maximum recommended human dose on a mg/m^2 basis.

Genotoxicity

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

Other preclinical safety findings, including amyloid-β findings

The effects of sacubitril/valsartan on amyloid-β concentrations in cerebrospinal fluid (CSF) and brain tissue were assessed in young (2-4 years old) cynomolgus monkeys treated with sacubitril/valsartan (24 mg sacubitril/26 mg valsartan /kg/day) for 2 weeks. In this study, sacubitril/valsartan had a pharmacodynamic effect on CSF Aβ clearance in cynomolgus monkeys, increasing CSF Aβ 1-40, 1-42, and 1-38 levels; there was no corresponding increase in Aβ levels in the brain. Increases in CSF Aβ 1-40 and 1-42 were not observed in a 2 week healthy volunteer study in humans (see section 5.1). Additionally, in a toxicology study in cynomolgus monkeys treated with sacubitril/valsartan at 146 mg sacubitril/154 mg valsartan /kg/day for 39-weeks, there was no amyloid-β plaque accumulation in the brain. The clinical relevance of these findings is not known. Studies in heart failure patients will investigate the potential effects of sacubitril/valsartan on cognitive function and brain amyloid-β deposition.

4.5 Interaction with other medicines and other forms of interaction

Anticipated interactions resulting in a contraindication:

ACE inhibitors: The concomitant use of Sacubitril/Valsartan Devatis with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE inhibitor therapy may increase the risk of angioedema. Sacubitril/Valsartan Devatis 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 Devatis (see sections 4.3 and 4.2).

Aliskiren: The concomitant use of Sacubitril/Valsartan Devatis with aliskiren is contraindicated in patients with Type 2 diabetes (see section 4.3). Combination of sacubitril/valsartan with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure).

Anticipated interactions resulting in concomitant use not being recommended:

Sacubitril/Valsartan Devatis should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Sacubitril/Valsartan Devatis (see section 4.4).

Concomitant use with aliskiren should be avoided in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2) (see section 4.4).

Observed interactions to be considered:

Statins: *In vitro* data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. Sacubitril/Valsartan Devatis may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of sacubitril/valsartan increased the C_{max} of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Therefore, caution should be exercised upon co-administration of Sacubitril/Valsartan Devatis with statins.

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

Anticipated interactions to be considered:
Potassium: Concomitant use of potassium-sparing diuretics (e.g, triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if Sacubitril/Valsartan Devatis is co-administered with these agents (see section 4.4).

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 Inhibitors): In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of sacubitril/ valsartan and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on Sacubitril/Valsartan Devatis who are taking NSAIDs concomitantly.

Lithium: 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. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use with Sacubitril/Valsartan Devatis. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Frusemide: Co-administration of sacubitril/valsartan and frusemide had no effect on the pharmacokinetics of sacubitril/valsartan but reduced C_{max} and AUC of frusemide 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 frusemide was unchanged from baseline until the end of the PARADIGM-HF study in patients treated with sacubitril/valsartan.

Transporters: The active metabolite of sacubitril (sacubitrilat) 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 to sacubitrilat or valsartan, respectively. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

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

No significant interactions:
No clinically meaningful drug-drug interaction was observed upon co-administration of sacubitril/ valsartan and digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol, intravenous nitroglycerin or a combination of levonorgestrel/ethinyloestradiol. No interaction is expected with atenolol, indomethacin, glyburide, or cimetidine.

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Sacubitril/valsartan did not show any effects on fertility or early embryonic development in male and female rats up to a dose of 73 mg sacubitril/77 mg valsartan /kg/day (≤1.0 fold and ≤0.13 fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively).

Females of child-bearing potential

Female patients of child-bearing potential should be advised about the consequences of exposure to Sacubitril/Valsartan Devatis during pregnancy and to use contraception during treatment with Sacubitril/Valsartan Devatis and for 1 week after their last dose.

Use in Pregnancy (Category D)

Drugs that act on the renin-angiotensin-aldosterone system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors (a specific class of drugs acting on the RAAS).

As for other drugs that also act directly on the RAAS, Sacubitril/Valsartan Devatis must not be used during pregnancy (see section 4.3) or in women planning to become pregnant. Valsartan exerts its effects via angiotensin II antagonism. 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. Physicians prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. Patients should be advised to discontinue Sacubitril/Valsartan Devatis as soon as pregnancies occur and to inform their physicians.

The use of drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function. Oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

In animal studies, sacubitril/valsartan treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥ 49 mg sacubitril/51 mg valsartan/kg/day (≤ 0.06 [sacubitrilat, the active metabolite] and 0.7 [valsartan]-fold the maximum recommended human dose [MRHD] of 97 mg/103 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses ≥ 5 mg sacubitril/5 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD

on the basis of valsartan and sacubitrilat AUC, respectively). Sacubitril/valsartan is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril/valsartan dose of ≥ 5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo-fetal effects of sacubitril/valsartan are attributed to the angiotensin receptor antagonist activity.

Sacubitril

There are no data from the use of sacubitril in pregnant women. Studies in animals have shown reproductive toxicity.

Sacubitril/Valsartan

There are no data from the use of sacubitril/valsartan in pregnant women. Animal studies with sacubitril/valsartan have shown reproductive toxicity.

Use in Lactation

It is not known whether sacubitril/valsartan is excreted in human milk. The components of sacubitril/valsartan combination, sacubitril and valsartan, were excreted in the milk of lactating rats.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (1.1-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 AUC) indicate that treatment with sacubitril/valsartan during organogenesis, gestation and lactation may affect pup development and survival.

Because of the potential risk for adverse drug reactions in breastfed newborns/infants, Sacubitril/Valsartan Devatis is not recommended during breastfeeding. A decision should be made whether to abstain from breast-feeding or to discontinue Sacubitril/Valsartan Devatis while breast-feeding, taking into account the importance of Sacubitril/Valsartan Devatis to the mother.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Summary of the safety profile
A total of 4,203 heart failure patients with reduced ejection fraction were treated with sacubitril/valsartan in the PARADIGM-HF (vs. enalapril) clinical trial. Of these, 3,271 were exposed for at least 1 year.

The safety of sacubitril/valsartan in patients with chronic heart failure was evaluated in the pivotal phase 3 study PARADIGM-HF, which compared patients treated twice daily with sacubitril/valsartan 97 mg/103 mg (n= 4203) or enalapril 10 mg (n= 4229). Patients randomised to sacubitril/valsartan received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3271 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 AE in the double-blind period of the PARADIGM-HF trial occurred in 450 (10.71%) of sacubitril/valsartan treated patients and 516 (12.20%) of patients receiving enalapril. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalaemia and renal impairment. The overall incidence of adverse drug reactions (ADRs) of sacubitril/valsartan in heart failure patients was comparable to enalapril. The pattern of the ADRs is consistent with the pharmacology of sacubitril/valsartan and the patients underlying conditions.

The overall frequency of adverse reactions was not related to gender, age, or race.

Tabulated summary of adverse drug reactions from clinical trials

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

Table 4-2 Frequency of emergent adverse effects regardless of causality (reported by > 2% of patients in the sacubitril/valsartan group, N=4203) in the PARADIGM-HF study in the heart failure population

System organ class **Preferred term**	**Sacubitril/valsartan** **97 mg/103 mg twice daily** (%) **N=4203**	**Enalapril** **10 mg twice daily** (%) **N=4229**
Blood and lymphatic system disorders		
Anaemia	4.00	4.75
Cardiac disorders		
Angina pectoris	4.09	4.02
Atrial fibrillation	5.97	5.58
Cardiac failure	17.37	19.67
Cardiac failure chronic	3.21	3.67
Cardiac failure congestive	3.16	3.95
Ventricular tachycardia	2.57	3.24
Gastrointestinal disorders		
Constipation	2.05	2.93
Diarrhoea	4.62	4.47

Nausea	2.09	2.36
General disorders and administration site conditions		
Asthenia	2.09	1.84
Cardiac death	2.05	2.70
Fatigue	2.97	3.05
Non-cardiac chest pain	2.52	2.88
Oedema peripheral	5.12	5.04
Infections and infestations		
Bronchitis	4.35	5.30
Influenza	3.78	3.12
Nasopharyngitis	4.85	4.14
Pneumonia	5.40	5.60
Upper respiratory tract infection	4.83	4.75
Urinary tract infection	4.73	4.61
Metabolism and nutrition disorders		
Diabetes mellitus	2.93	3.17
Gout	2.88	2.84
Hyperkalaemia	11.61	14.00
Hyperuricaemia	2.57	3.57
Hypokalaemia	3.31	2.53
Musculoskeletal and connective tissue disorders		
Arthralgia	3.00	2.81
Back pain	3.90	3.26
Pain in extremity	2.19	2.36
Nervous system disorders		
Dizziness	6.33	4.87
Headache	2.45	2.51
Syncope	2.24	2.70
Psychiatric disorders		
Insomnia	2.19	2.18
Renal and urinary disorders		
Renal failure	2.66	3.41
Renal impairment	10.14	11.52
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	2.21	2.51
Cough	8.78	12.60
Dyspnoea	5.07	7.24
Vascular disorders		
Hypertension	3.00	4.56
Hypotension	17.61	11.97

Table 4-3 Adverse Drug Reactions in the PARADIGM-HF safety set[#]

Adverse drug reactions	Sacubitril/valsartan 97 mg/103 mg twice daily (%)	Enalapril 10 mg twice daily (%)	Frequency category
Blood and lymphatic system disorders			
Anaemia	4.00	4.75	Common
Immune system disorders			
Hypersensitivity	0.24	0.26	Uncommon
Metabolism and nutrition disorders			
Hyperkalaemia*	11.61	14.00	Very common
Hypokalaemia	3.31	2.53	Common
Hypoglycaemia	1.36	1.06	Common
Nervous system disorders			
Dizziness	6.33	4.87	Common
Dizziness postural	0.57	0.28	Uncommon
Headache	2.45	2.51	Common
Syncope	2.24	2.70	Common
Ear and labyrinth disorders			
Vertigo	1.45	1.40	Common
Vascular disorders			
Hypotension*	17.61	11.97	Very common
Orthostatic hypotension	1.52	0.80	Common
Respiratory, thoracic and mediastinal disorders			
Cough	8.78	12.60	Common
Gastrointestinal disorders			
Diarrhoea	4.62	4.47	Common
Nausea	2.09	2.36	Common
Gastritis	1.48	1.66	Common
Skin and subcutaneous tissue disorders			
Pruritus	0.86	0.59	Uncommon
Rash	0.81	0.97	Uncommon
Angioedema*	0.45	0.24	Uncommon
Renal and urinary disorders			
Renal impairment*	10.14	11.52	Very common
Renal failure (renal failure, acute renal failure)	4.76	5.30	Common
General disorders and administration site conditions			
Fatigue	2.97	3.05	Common
Asthenia	2.09	1.84	Common

[#] *safety analysis set*
**see description of selected adverse reactions*

Description of selected adverse reactions

Angioedema

In the PARADIGM-HF trial, the incidence of angioedema was 0.1% in both the enalapril and sacubitril/valsartan run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with sacubitril/valsartan than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with sacubitril/valsartan and 0.5% with enalapril (see section 4.4).

Hyperkalaemia and serum potassium

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

Blood pressure

In PARADIGM-HF, hypotension and clinically relevant low systolic blood pressure (<90 mmHg and decrease from baseline of >20 mmHg) were reported in 17.6% and 4.76% of sacubitril/valsartan-treated patients compared with 11.9% and 2.67% of enalapril-treated patients, respectively. Orthostasis was reported in 2.1% of patients treated with sacubitril/valsartan compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with sacubitril/valsartan compared to 1.3% of patients treated with enalapril.

Renal impairment

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

Laboratory Abnormalities

Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of >20% were observed in approximately 5% of both sacubitril/valsartan- and enalapril treated patients in the double-blind period in PARADIGM-HF.

Serum Creatinine

During the double-blind period in PARADIGM-HF, approximately 16% of both sacubitril/valsartan- and enalapril-treated patients had increases in serum creatinine of >50%.

Serum Potassium

During the double-blind period in PARADIGM-HF, approximately 16% of both sacubitril/valsartan- and enalapril treated patients had potassium concentrations >5.5 mEq/L.

Adverse events leading to study drug discontinuation in the TITRATION study (see section 5.1) are shown in the table below.

Table 4-4 Number (%) of patients with most frequently reported (N≥2) AEs leading to study drug discontinuation during post-randomisation period by preferred term (Safety set)

	Sacubitril/valsartan Condensed titration regimen N=246 n (%)	Sacubitril/valsartan Conservative titration regimen N=251 n (%)
Discontinuation in post-randomisation 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)

Post-marketing experience - Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

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 categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA.

Table 4-5 Adverse Drug Reactions from spontaneous reports and literature cases (frequency not known)

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

Additional adverse event information for valsartan may be found in the Australian approved Valsartan Product Information.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Limited data are available with regards to over dosage in human subjects with sacubitril/valsartan. In healthy volunteers, a single dose of 583 mg sacubitril/617 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated.

Hypotension is the most likely symptom of over dosage due to the blood pressure lowering effects of sacubitril/valsartan. Symptomatic treatment should be provided.

Sacubitril/valsartan is unlikely to be removed by haemodialysis due to high protein binding.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Sacubitril/valsartan exhibits the novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via sacubitrilat, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits and renal effects of sacubitril/valsartan in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitrilat and the simultaneous inhibition of the deleterious 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), thereby promoting 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. Sustained activation of the renin-angiotensin-aldosterone system results in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

5.1 Pharmacodynamic properties

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 RAAS blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), 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 compared to baseline. Sacubitril/valsartan also blocked the AT1-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 and urine cGMP compared with enalapril. While BNP is a neprilysin substrate, NT-proBNP is not. Therefore, NT-proBNP (but not BNP) is a suitable biomarker for monitoring of heart failure patients treated with sacubitril/valsartan.

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.

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;

there were no changes in concentrations of CSF Aβ 1-40 and 1-42. The clinical relevance of this finding is unknown.

Clinical efficacy and safety

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

PARADIGM-HF

The PARADIGM-HF trial was a multinational, randomised, double-blind trial comparing sacubitril/valsartan to enalapril in 8,442 adult patients with symptomatic chronic heart failure and reduced ejection fraction (left ventricular ejection fraction ≤ 40% amended later to ≤ 35%), in NYHA Class II-IV, in addition to other heart failure therapy. 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 ACE inhibitor 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 severe hepatic impairment, 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 endpoint was the composite of cardiovascular (CV) death or hospitalisation for heart failure.

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 (83%). The median follow- up duration was 27 months and patients were treated for up to 4.3 years.

The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years (19% of patients were 75 years or older); and 78% were male. At randomisation, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV. The mean left ventricular ejection fraction was 29%. There were 11.4% of patients with a baseline left ventricular ejection fraction > 35 and ≤40%. Median NTproBNP level at study enrollment was 1,629 pg/mL for sacubitril/valsartan-treated patients, and 1,593 pg/mL for enalapril-treated patients. Median BNP levels at study enrollment was 255 pg/mL for sacubitril/valsartan-treated patients, and 251 pg/mL for enalapril-treated patients. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR < 60 mL/min/1.73m^2, and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronisation therapy-defibrillator (CRT-D) (15%).

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and entered a sequential single-blind run-in period during which patients received treatment with enalapril 10 mg twice daily, followed by treatment with sacubitril/valsartan 49 mg/51 mg twice daily, increasing to sacubitril/valsartan 97 mg/103 mg twice daily. Patients were then randomised to the double-blind

period of the study to receive either sacubitril/valsartan 97 mg/103 mg or enalapril 10 mg twice daily [sacubitril/valsartan (n= 4209); enalapril (n= 4233)].

In the sacubitril/valsartan group, 76% of patients remained on the target dose of sacubitril/valsartan 97 mg/103 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 demonstrated clinically relevant and statistically significant superiority to enalapril, 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 <0.0001) versus enalapril. This effect was observed early and was sustained throughout the duration of the trial. The absolute risk reduction was 4.69%. A statistically significant reduction for CV death and first HF hospitalisation was observed (CV death, RRR 20%, HR 0.80; 95% CI [0.71, 0.89]; and hospitalisation for heart failure RRR 21%; HR 0.79; 95% CI [0.71, 0.89]) - *see Table 5-1 and Figure 5-1*. 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). 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).

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

Sacubitril/valsartan also significantly reduced all-cause mortality by 16% compared with enalapril (RRR 16%, HR 0.84; 95% CI [0.76 to 0.93], 1-sided p=0.0005) - *see Table 5-1*. The absolute risk reduction was 2.84%.

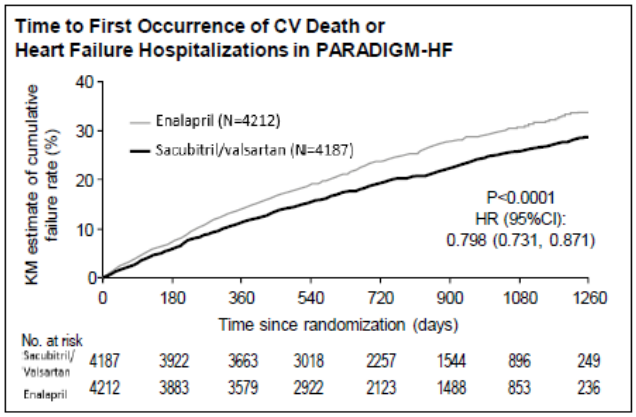
Table 5-1 Treatment effect for the primary composite endpoint, its components and all-cause mortality – PARADIGM-HF

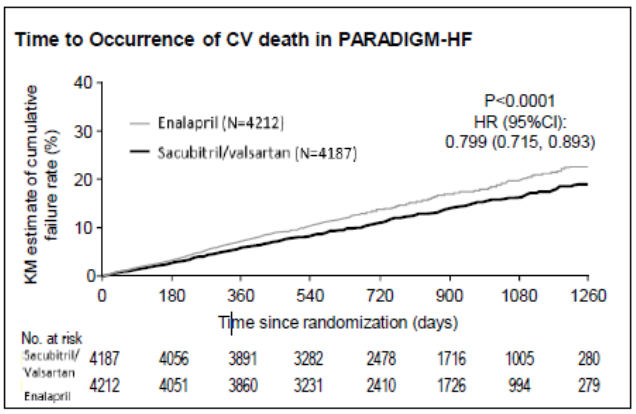
	Sacubitril/ valsartan N = 4187 ^ n (%)	**Enalapril N = 4212^ n (%)**	**Hazard Ratio (95% CI)**	**Relative Risk Reduction**	**Absolute Risk Reduction**	**p-value[c]**
Primary Composite Endpoint of CV Death and Heart Failure Hospitalisations[a]	914 (21.83)	1117 (26.52)	0.80 (0.73, 0.87)	20%	4.69%	<0.0001
Individual Components of the primary composite endpoint						
CV Death [b]	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	3.13%	
First Heart Failure Hospitalisation	537 (12.83)	658 (15.62)	0.79 (0.71, 0.89)	21%	2.80%	
Secondary Endpoint						
All-cause mortality	711 (16.98)	835 (19.82)	0.84 (0.76, 0.93)	16%	2.84%	0.0005

[a] *The primary endpoint was defined as the time to first event.*
b CV death includes all patients who died up to the cut-off date irrespective of previous hospitalisation.
c One-sided p-value
^ *Full analysis set*

The Kaplan-Meier presented in the figure below (left) shows time to first occurrence of the primary composite endpoint of CV death or heart failure hospitalisation. Sacubitril/valsartan treatment effect was evident early and sustained for the duration of the study. The Kaplan-Meier figure presented below (right) shows the time to CV death endpoint.

Figure 5-1 Kaplan-Meier curves for the primary composite endpoint and the CV death component – PARADIGM-HF

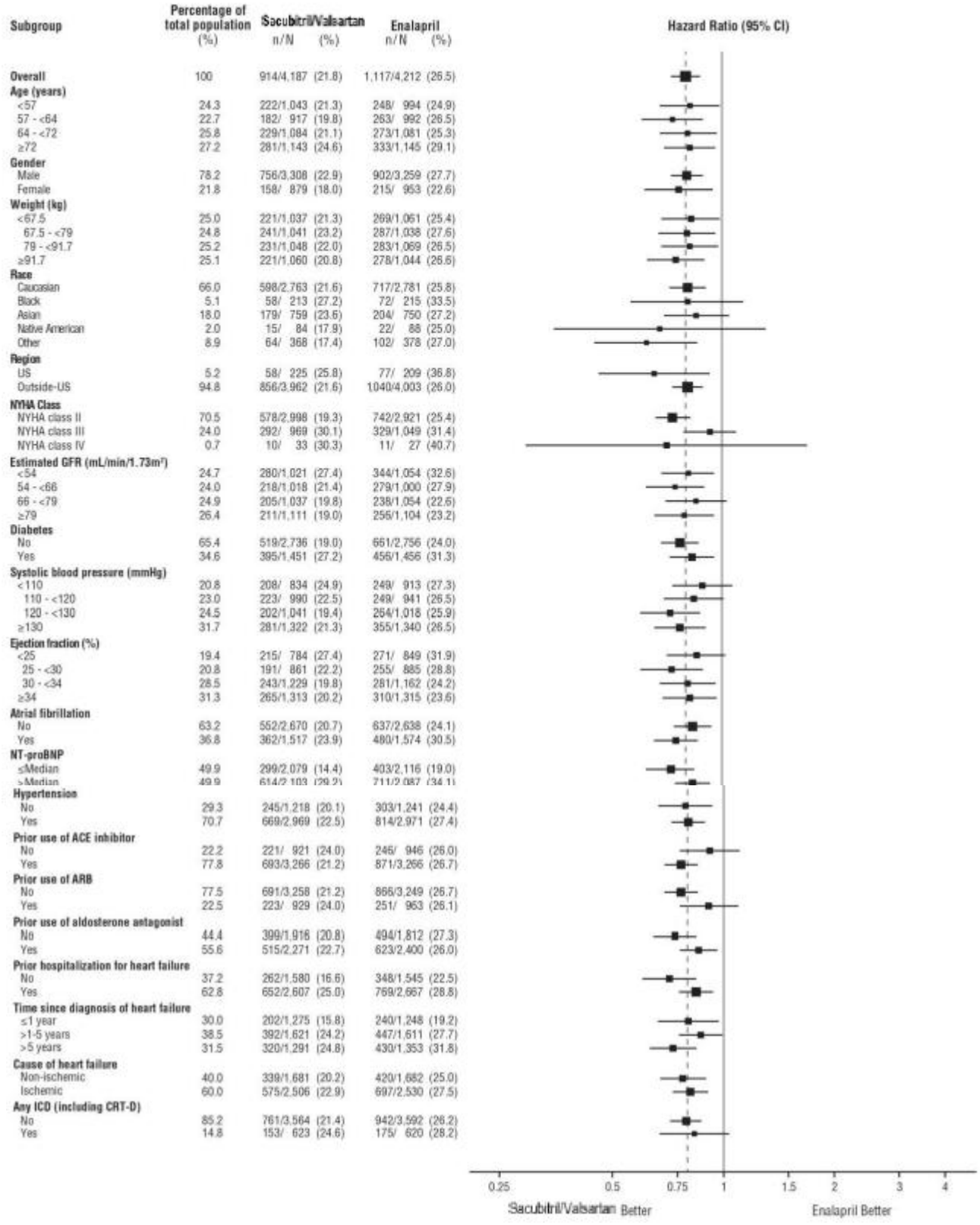




Overall, there were fewer all cause hospital admissions in patients treated with sacubitril/valsartan compared to enalapril, including a 12% relative risk reduction for the first hospitalisation (HR 0.88 [95% CI: 0.82, 0.94], P<0.001), and a 16% relative rate reduction for total number of hospitalisations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

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. The results of the primary composite endpoint were consistent across the subgroups examined (Figure 5-2).

Figure 5-2 Primary Composite Endpoint (CV Death or HF Hospitalisation) - Subgroup Analysis (PARADIGM-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. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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 initiated sacubitril/valsartan 24 mg/26 mg twice daily, were uptitrated to sacubitril/valsartan 49 mg/51 mg twice daily and then to the target dose of sacubitril/valsartan 97 mg/103 mg twice daily with either a 3-week or 6-week regimen.

Overall, 76% of patients achieved and maintained the target dose of sacubitril/valsartan 97 mg/103 mg twice daily without any dose interruption or down-titration over 12-weeks. More patients who were naïve to previous ACE inhibitor or ARB therapy or on low dose therapy (equivalent to < 10 mg of enalapril/day) were able to achieve and maintain sacubitril/valsartan 97 mg/103 mg when uptitrated over 6 weeks versus 3 weeks.

5.2 PHARMACOKINETIC PROPERTIES

The valsartan contained within sacubitril/valsartan combination is more bioavailable than the valsartan in other marketed tablet formulations:

Table 5-3 Doses of sacubitril and valsartan in sacubitril/valsartan combination and doses of valsartan in other marketed formulations

Sacubitril/ Valsartan dose	Amount of Sacubitril delivered from the indicated Sacubitril/ Valsartan dose	Amount of Valsartan delivered from the indicated Sacubitril/ Valsartan dose	Dose of valsartan in other marketed formulations delivering an equivalent valsartan exposure (AUC) as the indicated Sacubitril/ Valsartan dose
24 mg/26 mg	24 mg	26 mg	40 mg
49 mg/51 mg	49 mg	51 mg	80 mg
97 mg/ 103 mg	97 mg	103 mg	160 mg

Absorption
Following oral administration, sacubitril/valsartan combination dissociates into sacubitril, which is 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.

Following twice daily dosing of sacubitril/valsartan combination, 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 and valsartan. Although there is a decrease in exposure to valsartan when sacubitril/ valsartan is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. Sacubitril/Valsartan Devatis can therefore be administered with or without food.

Distribution

Sacubitril/valsartan is 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 limited extent (0.28%). Sacubitril/valsartan has an apparent volume of distribution ranging from 75 L to 103 L.

Metabolism
Sacubitril is readily converted to sacubitrilat by esterases; sacubitrilat is not further metabolised to a significant extent. Valsartan is minimally metabolised, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (<10%). Since CYP450 enzyme mediated metabolism of sacubitril and valsartan is minimal, co-administration with drugs that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

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

Sacubitril, sacubitrilat, and valsartan are eliminated from plasma with a mean elimination half-life (T1/2) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Linearity/non-linearity
The pharmacokinetics of sacubitril, sacubitrilat, and valsartan are linear in the dose range tested (24 mg sacubitril/26 mg valsartan - 194 mg sacubitril/206 mg valsartan).

Special populations

Elderly patients (aged over 65 years)

The exposures of sacubitrilat and valsartan are increased in elderly subjects by 42% and 30%, respectively, compared to younger subjects. However, this is not associated with clinically relevant effects and therefore no dosage adjustment is necessary in patients over 65 years. In patients ≥ 75 years old, a lower starting dose of Sacubitril/Valsartan Devatis 24 mg/26 mg should be considered (see section 4.2).

Paediatric patients (aged below 18 years)

Sacubitril/valsartan has not been studied in paediatric patients.

Impaired renal function
A correlation was observed between renal function and systemic exposure to sacubitrilat, but not to valsartan. In patients with mild (60 mL/min/1.73 m^2 ≤eGFR<90 mL/min/1.73 m^2) to moderate (30 mL/min/1.73 m^2 ≤ eGFR< 60 mL/min/1.73 m^2) renal impairment, the AUC for sacubitrilat was up to 2-fold higher. No dosage adjustment is required in patients with mild or moderate renal impairment. A 2.7-fold higher AUC for sacubitrilat was observed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2). A starting dose of sacubitril/valsartan 24 mg/26 mg twice daily is recommended in patients with severe renal impairment. Caution is recommended when administering Sacubitril/Valsartan Devatis to these patients due to limited data.

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.

Impaired hepatic function

In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, sacubitrilat increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects. No dosage adjustment is recommended when administering Sacubitril/Valsartan Devatis to patients with mild hepatic impairment (Child-Pugh A classification) including patients with biliary obstructive disorders. A starting dose of Sacubitril/Valsartan Devatis 24 mg/26 mg twice daily is recommended in patients with moderate hepatic impairment (Child-Pugh B classification). Sacubitril/valsartan has not been studied in patients with severe hepatic impairment. Therefore, its use is not recommended in patients with severe hepatic impairment.

Ethnic Group

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

Gender

The pharmacokinetics of sacubitril/valsartan combination (sacubitril, sacubitrilat and valsartan) are similar between male and female subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

All tablets also contain colloidal anhydrous silica, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, talc, polyvinyl alcohol, titanium dioxide, glycerol, sodium lauril sulphate, red iron oxide.

Sacubitril/Valsartan Devatis 24/26 and Sacubitril/Valsartan Devatis 97/103 Film Coated Tablets tablets also contain black iron oxide black, while the Sacubitril/Valsartan Devatis 49/51 tablets also contain yellow iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C. Protect from moisture.
Store in the original package. Keep out of the reach and sight of children.

6.5 Nature and contents of container

14, 28, 56 and 60 film coated tablets in blister packs of clear PVC/PCTFE (ACLAR) sealed with aluminum foil.
**Not all pack sizes or presentations may be marketed.*

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Devatis Limited
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9. DATE OF FIRST APPROVAL

30.10.2025

10. DATE OF REVISION OF THE TEXT