ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 24 mg/26 mg film-coated tablets
Neparvis 49 mg/51 mg film-coated tablets
Neparvis 97 mg/103 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Neparvis 24 mg/26 mg film-coated tablets

Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex).

Neparvis 49 mg/51 mg film-coated tablets

Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex).

Neparvis 97 mg/103 mg film-coated tablets

Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Neparvis 24 mg/26 mg film-coated tablets

Violet white ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “LZ” on the other side. Approximate tablet dimensions 13.1 mm x 5.2 mm.

Neparvis 49 mg/51 mg film-coated tablets

Pale yellow ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “L1” on the other side. Approximate tablet dimensions 13.1 mm x 5.2 mm.

Neparvis 97 mg/103 mg film-coated tablets

Light pink ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with “NVR” on one side and “L11” on the other side. Approximate tablet dimensions 15.1 mm x 6.0 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult heart failure

Neparvis is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1).

Paediatric heart failure

Neparvis is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction (see section 5.1).

4.2 Posology and method of administration

Posology

General considerations
Neparvis should not be co-administered with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB). Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy (see sections 4.3, 4.4 and 4.5).

The valsartan contained within Neparvis is more bioavailable than the valsartan in other marketed tablet formulations (see section 5.2).

If a dose is missed, the patient should take the next dose at the scheduled time.

Adult heart failure
The recommended starting dose of Neparvis is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient (see section 5.1).

If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of Neparvis is recommended (see section 4.4).

In PARADIGM-HF study, Neparvis was administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB (see section 5.1). There is limited experience in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, therefore a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended in these patients (see “Titration” in section 5.1).

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg (see section 4.4). A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg.

Paediatric heart failure
Table 1 shows the recommended dose for paediatric patients. The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient.

Neparvis film-coated tablets are not suitable for children weighing less than 40 kg. Neparvis granules are available for these patients.

Table 1 Recommended dose titration

Patient weight	To be given twice daily			
	Half the starting dose*	Starting dose	Intermediate dose	Target dose
Paediatric patients less than 40 kg	0.8 mg/kg[#]	1.6 mg/kg[#]	2.3 mg/kg[#]	3.1 mg/kg[#]
Paediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg[#]	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg
Paediatric patients at least 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg	97 mg/103 mg

* Half the starting dose is recommended in patients who have not been taking an ACE inhibitor or an ARB or have been taking low doses of these medicinal products, patients who have renal impairment (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2) and patients who have moderate hepatic impairment (see special populations).
[#]0.8 mg/kg, 1.6 mg/kg, 2.3 mg/kg and 3.1 mg/kg refer to the combined amount of sacubitril and valsartan and are to be given using granules.

In patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, half of the starting dose is recommended. For paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased to the standard starting dose following the recommended dose titration in Table 1 and adjusted every 3-4 weeks.

For example, a paediatric patient weighing 25 kg who has not previously taken an ACE inhibitor should start with half the standard starting dose, which corresponds to 20 mg (25 kg × 0.8 mg/kg) twice daily, given as granules. After rounding to the closest number of full capsules, this corresponds to 2 capsules of 6 mg/6 mg sacubitril/valsartan twice daily.

Treatment should not be initiated in patients with serum potassium level >5.3 mmol/l or with SBP <5th percentile for the age of the patient. If patients experience tolerability issues (SBP <5th percentile for the age of the patient, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of Neparvis is recommended (see section 4.4).

Special populations
Elderly
The dose should be in line with the renal function of the elderly patient.

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

Half of the starting dose should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) (see section 5.1), Neparvis should be used with caution and half of the starting dose is recommended. In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks.

There is no experience in patients with end-stage renal disease and use of Neparvis is not recommended.

Hepatic impairment
No dose adjustment is required when administering Neparvis to patients with mild hepatic impairment (Child-Pugh A classification).

There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with aspartate transaminase (AST)/alanine transaminase (ALT) values more than twice the upper limit of the normal range. Neparvis should be used with caution in these patients and half of the starting dose is recommended (see sections 4.4 and 5.2). In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks.

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

Paediatric population
The safety and efficacy of Neparvis in children aged below 1 year have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

Oral use.
Neparvis may be administered with or without food (see section 5.2). The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Concomitant use with ACE inhibitors (see sections 4.4 and 4.5). Neparvis must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy (see section 4.4).
- Hereditary or idiopathic angioedema (see section 4.4).
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections 4.4 and 4.5).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see section 4.2).
- Second and third trimesters of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

- The combination of sacubitril/valsartan with an ACE inhibitor is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.2, 4.3 and 4.5).

- The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 4.5). The combination of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections 4.3 and 4.5).

- Neparvis contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product (see sections 4.2 and 4.5).

Hypotension

Treatment should not be initiated unless SBP is ≥100 mmHg for adult patients or ≥5th percentile SBP for the age of the paediatric patient. Patients with SBP below these values were not studied (see section 5.1). Cases of symptomatic hypotension have been reported in adult patients treated with sacubitril/valsartan during clinical studies (see section 4.8), especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). When initiating therapy or during dose titration with sacubitril/valsartan, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended (see section 4.2). Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with sacubitril/valsartan, however, such corrective action must be carefully weighed against the risk of volume overload.

Renal impairment

Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension (see section 4.2). There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2) and these patients may be at greatest risk of hypotension (see section 4.2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended.

Worsening renal function

Use of sacubitril/valsartan may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs) (see section 4.5). Down-titration should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is >5.4 mmol/l in adult patients and >5.3 mmol/l in paediatric patients. Use of sacubitril/valsartan may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur (see section 4.8). Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists (see section 4.2). If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered.

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan. If angioedema occurs, 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. It must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, e.g. adrenaline solution 1 mg/1 ml (0.3-0.5 ml), and/or measures necessary to ensure a patent airway, should be promptly administered.

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

Black patients have an increased susceptibility to develop angioedema (see section 4.8).

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, sacubitril/valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Patients with renal artery stenosis

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

Patients with New York Heart Association (NYHA) functional classification IV

Caution should be exercised when initiating sacubitril/valsartan in patients with NYHA functional classification IV due to limited clinical experience in this population.

B-type natriuretic peptide (BNP)

BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate (see section 5.1).

Patients with hepatic impairment

There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In these patients, exposure may be increased and safety is not established. Caution is therefore recommended when using it in these patients (see section 4.2 and 5.2). Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).

Psychiatric disorders

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a contraindication

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

Aliskiren
The concomitant use of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see section 4.3). The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 4.4). Combination of sacubitril/valsartan with aliskiren is potentially associated with a higher frequency of adverse reactions such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) (see sections 4.3 and 4.4).

Interactions resulting in concomitant use not being recommended

Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product (see section 4.4).

Interactions requiring precautions

OATP1B1 and OATP1B3 substrates, e.g. statins
In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. Neparvis 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. Caution should be exercised when co-administering sacubitril/valsartan with statins. No clinically relevant interaction was observed when simvastatin and Neparvis were co-administered.

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

Potassium
Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if sacubitril/valsartan is co-administered with these agents (see section 4.4).

Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors
In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use 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 treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly (see section 4.4).

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

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

Nitrates, e.g. nitroglycerine
There was no interaction between sacubitril/valsartan and intravenously administered nitroglycerin with regard to blood pressure reduction. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone. A similar effect on the heart rate may occur when sacubitril/valsartan is co-administered with sublingual, oral or transdermal nitrates. In general no dose adjustment is required.

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

Metformin
Co-administration 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 in patients receiving metformin, the clinical status of the patient should be evaluated.

No significant interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

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

Should exposure to ARBs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension (see section 4.3).

Sacubitril
There are no data from the use of sacubitril in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Sacubitril/valsartan
There are no data from the use of sacubitril/valsartan in pregnant women. Animal studies with sacubitril/valsartan have shown reproductive toxicity (see section 5.3).

Breast-feeding

Limited data show that sacubitril and its active metabolite LBQ657 are excreted in human milk in very low amounts with an estimated relative infant dose of 0.01% for sacubitril and 0.46% for the active metabolite LBQ657 when administered to breast-feeding women at a dose of 24 mg/26 mg sacubitril/valsartan, twice daily. In the same data, valsartan was under the limit of detection. There is insufficient information on the effects of sacubitril/valsartan in newborns/infants. Because of the potential risk for adverse reactions in breast-fed newborns/infants, Neparvis is not recommended in women who are breast-feeding.

Fertility

There are no available data on the effect of sacubitril/valsartan on human fertility. No impairment of fertility was demonstrated in studies with it in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Sacubitril/valsartan has a minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in adults during treatment with sacubitril/valsartan were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%) (see section 4.4). Angioedema was reported in patients treated with sacubitril/valsartan (0.5%) (see description of selected adverse reactions).

Tabulated list of adverse reactions

Adverse reactions are ranked by System organ class and then by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 2 List of adverse reactions

System organ class	Preferred term	Frequency category
Blood and lymphatic system disorders	Anaemia	Common
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalaemia*	Very common
	Hypokalaemia	Common
	Hypoglycaemia	Common
	Hyponatraemia	Uncommon
Psychiatric disorders	Hallucinations**	Rare
	Sleep disorders	Rare
	Paranoia	Very rare
Nervous system disorders	Dizziness	Common
	Headache	Common
	Syncope	Common
	Dizziness postural	Uncommon
	Myoclonus	Not known
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension*	Very common
	Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
	Gastritis	Common
	Intestinal angioedema	Very rare
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Angioedema*	Uncommon
Renal and urinary disorders	Renal impairment*	Very common
	Renal failure (renal failure, acute renal failure)	Common
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common

*See description of selected adverse reactions.
**Including auditory and visual hallucinations

Description of selected adverse reactions

Angioedema
Angioedema has been reported in patients treated with sacubitril/valsartan. In PARADIGM-HF, angioedema was reported in 0.5% of patients treated with sacubitril/valsartan, compared with 0.2% of patients treated with enalapril. A higher incidence of angioedema was observed in Black patients treated with sacubitril/valsartan (2.4%) and enalapril (0.5%) (see section 4.4).

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

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

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

Paediatric population

In the PANORAMA-HF study, the safety of sacubitril/valsartan was assessed in a randomised, active-controlled, 52-week study of 375 paediatric heart failure (HF) patients aged 1 month to <18 years compared to enalapril. The 215 patients who rolled over into the long-term open-label extension study (PANORAMA-HF OLE) were treated for a median of 2.5 years, for up to 4.5 years. The safety profile observed in both studies was similar to that observed in adult patients. Safety data in patients aged 1 month to <1 year was limited.

Limited safety data are available in paediatric patients with moderate hepatic impairment or moderate to severe renal impairment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Limited data are available with regard to overdose in humans. A single dose of 583 mg sacubitril/617 mg valsartan and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) were studied in healthy adult volunteers and were well tolerated.

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

The medicinal product is unlikely to be removed by haemodialysis due to high protein binding (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II receptor blockers (ARBs), other combinations, ATC code: C09DX04

Mechanism of action

Sacubitril/valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits 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 LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

Pharmacodynamic effects

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 an initial increase in natriuresis, increased urine cGMP, and decreased plasma levels of mid-regional pro-atrial natriuretic peptide (MR-proANP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) compared to valsartan. In a 21-day study in HFrEF patients, sacubitril/valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. The AT1-receptor was also blocked as evidenced by increased plasma renin activity and plasma renin concentrations. In the PARADIGM-HF study, sacubitril/valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. In the PANORAMA-HF study, a reduction in NT-proBNP was observed at weeks 4 and 12 for sacubitril/valsartan (40.2% and 49.8%) and enalapril (18.0% and 44.9%) compared to baseline. The NT-proBNP levels continued to decrease over the duration of the study with a reduction of 65.1% for sacubitril/valsartan and 61.6% for enalapril at week 52 compared to baseline. BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because BNP is a neprilysin substrate (see section 4.4). NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

In a thorough QTc clinical study in healthy male subjects, single doses of sacubitril/valsartan 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 sacubitril/valsartan 194 mg sacubitril/206 mg valsartan once daily for two weeks to healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo; there were no changes in concentrations of CSF Aβ1-40 and 1-42. The clinical relevance of this finding is not known (see section 5.3).

Clinical efficacy and safety

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

PARADIGM-HF

PARADIGM-HF, the pivotal phase 3 study, was a multinational, randomised, double-blind study of 8 442 patients comparing sacubitril/valsartan to enalapril, both given to adult patients with chronic heart failure, NYHA class II-IV and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤40%, amended later to ≤35%) in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalisation for heart failure (HF). Patients with SBP <100 mmHg, severe renal impairment (eGFR <30 ml/min/1.73 m^2) and severe hepatic impairment were excluded at screening and therefore not prospectively studied.

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

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and enter a sequential single-blind run-in period during which they received treatment with enalapril 10 mg twice

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

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

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

Sacubitril/valsartan was superior to enalapril, reducing the risk of cardiovascular death or heart failure hospitalisations to 21.8% compared to 26.5% for enalapril treated patients. The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalisation, 3.1% for CV death alone, and 2.8% for first HF hospitalisation alone. The relative risk reduction was 20% versus enalapril (see Table 3). This effect was observed early and was sustained throughout the duration of the study (see Figure 1). Both components contributed to the risk reduction. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in sacubitril/valsartan-treated patients compared to enalapril-treated patients (hazard ratio [HR] 0.80, p=0.0082). Pump failure accounted for 26% of cardiovascular deaths and was reduced by 21% in sacubitril/valsartan-treated patients compared to enalapril-treated patients (HR 0.79, p=0.0338).

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

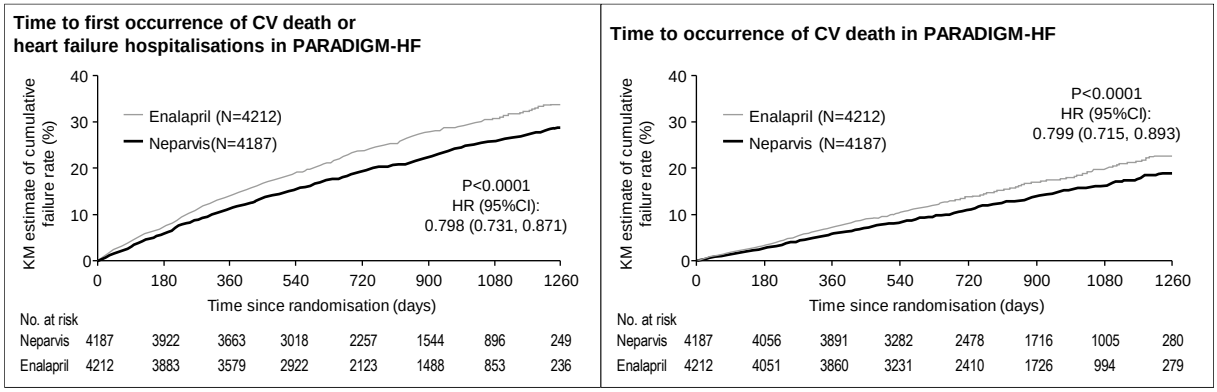
Sacubitril/valsartan improved survival with a significant reduction in all-cause mortality of 2.8% (sacubitril/valsartan, 17%, enalapril, 19.8%). The relative risk reduction was 16% compared with enalapril (see Table 3).

Table 3 Treatment effect for the primary composite endpoint, its components and all-cause mortality over a median follow-up of 27 months

	Sacubitril/ valsartan N=4 187[♯] n (%)	**Enalapril N=4 212[♯] n (%)**	**Hazard ratio (95% CI)**	**Relative risk reduction**	**p-value *****
Primary composite endpoint of CV death and heart failure hospitalisations*	914 (21.83)	1 117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual components of the primary composite endpoint					
CV death**	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	0.00004
First heart failure hospitalisation	537 (12.83)	658 (15.62)	0.79 (0.71, 0.89)	21%	0.00004
Secondary endpoint					
All-cause mortality	711 (16.98)	835 (19.82)	0.84 (0.76, 0.93)	16%	0.0005

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

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



TITRATION

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

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

Paediatric population

PANORAMA-HF

PANORAMA-HF, a phase 3 study, was a multinational, randomised, double-blind study comparing sacubitril/valsartan and enalapril in 375 paediatric patients aged 1 month to <18 years with heart failure due to systemic left ventricular systolic dysfunction (LVEF ≤45% or fractional shortening ≤22.5%). The primary objective was to determine whether sacubitril/valsartan was superior to enalapril in paediatric HF patients over a 52-week treatment duration based on a global rank endpoint. The global rank primary endpoint was derived by ranking patients (worst-to-best outcome) based on clinical events such as death, initiation of mechanical life support, listing for urgent heart transplant, worsening HF, measures of functional capacity (NYHA/ROSS scores), and patient-reported HF symptoms (Patient Global Impression Scale [PGIS]). Patients with systemic right ventricles or single ventricles and patients with restrictive or hypertrophic cardiomyopathy were excluded from the study. The target maintenance dose of sacubitril/valsartan was 2.3 mg/kg twice daily in paediatric patients aged 1 month to <1 year and 3.1 mg/kg twice daily in patients aged 1 to <18 years with a maximum dose of 200 mg twice daily. The target maintenance dose of enalapril was 0.15 mg/kg twice daily in paediatric patients aged 1 month to <1 year and 0.2 mg/kg twice daily in patients aged 1 to <18 years with a maximum dose of 10 mg twice daily.

In the study, 9 patients were aged 1 month to <1 year, 61 patients were aged 1 year to <2 years, 85 patients were aged 2 to <6 years and 220 patients were aged 6 to <18 years. At baseline, 15.7% of patients were NYHA/ROSS class I, 69.3% were class II, 14.4% were class III and 0.5% were class IV. The mean LVEF was 32%. The most common underlying causes of heart failure were cardiomyopathy related (63.5%). Prior to study participation, patients were treated most commonly with ACE inhibitors/ARBs (93%), beta-blockers (70%), aldosterone antagonists (70%), and diuretics (84%).

The Mann-Whitney Odds of the global rank primary endpoint was 0.907 (95% CI 0.72, 1.14), numerically in favour of sacubitril/valsartan (see Table 4). Sacubitril/valsartan and enalapril showed comparable clinically relevant improvements in the secondary endpoints of NYHA/ROSS class and

PGIS score change compared to baseline. At week 52, the NYHA/ROSS functional class changes from baseline were: improved in 37.7% and 34.0%; unchanged in 50.6% and 56.6%; worsened in 11.7% and 9.4% of patients for sacubitril/valsartan and enalapril respectively. Similarly, the PGIS score changes from baseline were: improved in 35.5% and 34.8%; unchanged in 48.0% and 47.5%; worsened in 16.5% and 17.7% of patients for sacubitril/valsartan and enalapril respectively. NT-proBNP was substantially reduced from baseline in both treatment groups. The magnitude of NT-proBNP reduction with Neparvis was similar to that observed in adult heart failure patients in PARADIGM-HF. Because sacubitril/valsartan improved outcomes and reduced NT-proBNP in PARADIGM-HF, the reductions in NT-proBNP coupled with the symptomatic and functional improvements from baseline seen in PANORAMA-HF were considered a reasonable basis to infer clinical benefits in paediatric heart failure patients. There were too few patients aged below 1 year to evaluate the efficacy of sacubitril/valsartan in this age group.

Table 4 Treatment effect for the primary global rank endpoint in PANORAMA-HF

	Sacubitril/valsartan N=187	**Enalapril N=188**	**Treatment effect**
Global rank primary endpoint	Probability of favourable outcome (%)*	Probability of favourable outcome (%)*	Odds** (95% CI)
	52.4	47.6	0.907 (0.72, 1.14)

*The probability of favourable outcome or Mann-Whitney probability (MWP) for the given treatment was estimated based on percentage of wins in pairwise comparisons of global rank score between sacubitril/valsartan-treated patients versus enalapril-treated patients (each higher score counts as one win and each equal score counts as half a win).
**Mann-Whitney Odds was calculated as the estimated MWP for enalapril divided by the estimated MWP for sacubitril/valsartan, with odds <1 in favour of sacubitril/valsartan and >1 in favour of enalapril.

5.2 Pharmacokinetic properties

The valsartan contained within sacubitril/valsartan is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in sacubitril/valsartan is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.

Adult population

Absorption
Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657. These reach peak plasma concentrations in 2 hours, 1 hour, and 2 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60% and 23%, respectively.

Following twice daily dosing of sacubitril/valsartan, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1.6-fold. Administration with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. Sacubitril/valsartan can be administered with or without food.

Distribution
Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94-97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volume of distribution of valsartan and sacubitril were 75 litres to 103 litres, respectively.

Biotransformation
Sacubitril is readily converted to LBQ657 by carboxylesterases 1b and 1c; LBQ657 is not further metabolised to a significant extent. Valsartan is minimally metabolised, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite of valsartan has been identified in plasma at low concentrations (<10%).

Since CYP450-enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with medicinal products that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

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

Elimination
Following oral administration, 52-68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37-48% of sacubitril (primarily as LBQ657) and 86% of valsartan and its metabolites are excreted in faeces.

Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life ($T_{½}$) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Linearity/non-linearity
The pharmacokinetics of sacubitril, LBQ657 and valsartan were approximately linear over a sacubitril/valsartan dose range of 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan.

Special populations

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

Renal impairment
A correlation was observed between renal function and systemic exposure to LBQ657 in patients with mild to severe renal impairment. The exposure of LBQ657 in patients with moderate (30 ml/min/1.73 m^2 ≤ eGFR <60 ml/min/1.73 m^2) and severe renal impairment (15 ml/min/1.73 m^2 ≤ eGFR <30 ml/min/1.73 m^2) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60 ml/min/1.73 m^2 ≤ eGFR <90 ml/min/1.73 m^2), the largest group of patients enrolled in PARADIGM-HF. The exposure of valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild renal impairment. No studies have been performed in patients undergoing dialysis. However, LBQ657 and valsartan are highly bound to plasma protein and therefore unlikely to be effectively removed by dialysis.

Hepatic impairment
In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, LBQ657 increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects. However, in patients with mild to moderate hepatic impairment, the exposures of free concentrations of LBQ657 increased by 1.47- and 3.08-fold, respectively, and the exposures of free concentrations of valsartan increased by 1.09-fold and 2.20-fold, respectively, compared to matching healthy subjects. Sacubitril/valsartan has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (see sections 4.3 and 4.4).

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

Paediatric population

The pharmacokinetics of sacubitril/valsartan were evaluated in paediatric heart failure patients aged 1 month to <1 year and 1 year to <18 years and indicated that the pharmacokinetic profile of sacubitril/valsartan in paediatric and adult patients is similar.

5.3 Preclinical safety data

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

Fertility, reproduction and development

Sacubitril/valsartan treatment during organogenesis resulted in increased embryofoetal lethality in rats at doses ≥49 mg sacubitril/51 mg valsartan/kg/day (≤0.72-fold the maximum recommended human dose [MRHD] on the basis of AUC) and rabbits at doses ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). It is teratogenic based on a low incidence of foetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril/valsartan dose of ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day. Cardiovascular abnormalities (mainly cardiomegaly) were observed in rabbit foetuses at a maternally non-toxic dose (1.46 mg sacubitril/1.54 mg valsartan/kg/day). A slight increase in two foetal skeletal variations (misshapen sternebra, sternebra bipartite ossification) was observed in rabbits at a sacubitril/valsartan dose of 4.9 mg sacubitril/5.1 mg valsartan/kg/day. The adverse embryofoetal effects of sacubitril/valsartan are attributed to the angiotensin receptor antagonist activity (see section 4.6).

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

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

Other preclinical findings

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

Sacubitril
In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation at approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, based on sacubitril/valsartan paediatric clinical dose of 3.1 mg/kg twice daily. The mechanism for these findings in juvenile rats, and consequently the relevance to the human paediatric population, is unknown. A study in adult rats showed only a minimal transient inhibitory effect on bone mineral density but not on any other parameters relevant for bone growth, suggesting no relevant effect of sacubitril on bone in adult patient populations under normal conditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults cannot be excluded. Clinical data in paediatric patients (PANORAMA-HF study) did not show evidence that sacubitril/valsartan has an impact on body weight, height, head circumference and fracture rate. Bone density was not measured in the study. Long-term data in paediatric patients (PANORAMA-HF OLE) showed no evidence of adverse effects of sacubitril/valsartan on (bone) growth or fracture rates.

Valsartan
In juvenile rats treated with valsartan (postnatal days 7 to 70), doses as low as 1 mg/kg/day produced persistent irreversible kidney changes consisting of tubular nephropathy (sometimes accompanied by tubular epithelial necrosis) and pelvic dilatation. These kidney changes represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in paediatric patients less than 1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for paediatric patients older than 1 year.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Low-substituted hydroxypropylcellulose
Crospovidone, type A
Magnesium stearate
Talc
Silica colloidal anhydrous

Film coat

Neparvis 24 mg/26 mg film-coated tablets
Hypromellose, substitution type 2910 (3 mPa·s)
Titanium dioxide (E171)
Macrogol (4000)
Talc
Iron oxide red (E172)
Iron oxide black (E172)

Neparvis 49 mg/51 mg film-coated tablets
Hypromellose, substitution type 2910 (3 mPa·s)
Titanium dioxide (E171)
Macrogol (4000)
Talc
Iron oxide red (E172)
Iron oxide yellow (E172)

Neparvis 97 mg/103 mg film-coated tablets
Hypromellose, substitution type 2910 (3 mPa·s)
Titanium dioxide (E171)
Macrogol (4000)
Talc
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters.

Neparvis 24 mg/26 mg film-coated tablets

Pack sizes: 14, 20, 28 or 56 film-coated tablets and multipacks containing 196 (7 packs of 28) film-coated tablets.

Neparvis 49 mg/51 mg film-coated tablets

Pack sizes: 14, 20, 28 or 56 film-coated tablets and multipacks containing 168 (3 packs of 56) or 196 (7 packs of 28) film-coated tablets.

Neparvis 97 mg/103 mg film-coated tablets

Pack sizes: 14, 20, 28 or 56 film-coated tablets and multipacks containing 168 (3 packs of 56) or 196 (7 packs of 28) film-coated tablets.

Not all pack sizes 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. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Neparvis 24 mg/26 mg film-coated tablets

EU/1/16/1103/001
EU/1/16/1103/008-010
EU/1/16/1103/017

Neparvis 49 mg/51 mg film-coated tablets

EU/1/16/1103/002-004
EU/1/16/1103/011-013

Neparvis 97 mg/103 mg film-coated tablets

EU/1/16/1103/005-007
EU/1/16/1103/014-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2016
Date of latest renewal: 11 February 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 6 mg/6 mg granules in capsules for opening
Neparvis 15 mg/16 mg granules in capsules for opening

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Neparvis 6 mg/6 mg granules in capsules for opening

Each capsule contains four granules equivalent to 6.1 mg sacubitril and 6.4 mg valsartan (as sacubitril valsartan sodium salt complex).

Neparvis 15 mg/16 mg granules in capsules for opening

Each capsule contains ten equivalent to 15.18 mg sacubitril and 16.07 mg valsartan (as sacubitril valsartan sodium salt complex).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules in capsules for opening (granules in capsule)

The granules are white to slightly yellow in colour and round, biconvex in shape and approximately 2 mm in diameter. They are provided in a hard capsule which must be opened prior to administration.

Neparvis 6 mg/6 mg granules in capsules for opening

The capsule consists of a white coloured cap, marked “04” in red and a transparent body, marked “NVR” in red. An arrow is printed on both the body and the cap.

Neparvis 15 mg/16 mg granules in capsules for opening

The capsule consists of a yellow coloured cap, marked “10” in red and a transparent body, marked “NVR” in red. An arrow is printed on both the body and the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paediatric heart failure

Neparvis is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction (see section 5.1).

4.2 Posology and method of administration

Posology

General considerations
Neparvis should not be co-administered with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB). Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy (see sections 4.3, 4.4 and 4.5).

The valsartan contained within Neparvis is more bioavailable than the valsartan in other marketed tablet formulations (see section 5.2).

If a dose is missed, the patient should take the next dose at the scheduled time.

Paediatric heart failure
Table 1 shows the recommended dose for paediatric patients. The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient.

The lowest recommended dose is 6 mg/6 mg. Doses can be rounded up or down to the closest combination of full 6 mg/6 mg and/or 15 mg/16 mg capsules. When rounding the dose up or down during the up-titration phase, consideration should be given to ensuring progressive increase to the target dose.

For patients weighing more than 40 kg, Neparvis film-coated tablets can be used.

Table 1 Recommended dose titration

Patient weight	To be given twice daily			
	Half the starting dose*	Starting dose	Intermediate dose	Target dose
Paediatric patients less than 40 kg	0.8 mg/kg[#]	1.6 mg/kg[#]	2.3 mg/kg[#]	3.1 mg/kg[#]
Paediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg[#]	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg
Paediatric patients at least 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg	97 mg/103 mg

* Half the starting dose is recommended in patients who have not been taking an ACE inhibitor or an ARB or have been taking low doses of these medicinal products, patients who have renal impairment (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2) and patients who have moderate hepatic impairment (see special populations).
[#]0.8 mg/kg, 1.6 mg/kg, 2.3 mg/kg and 3.1 mg/kg refer to the combined amount of sacubitril and valsartan and are to be given using granules.

In patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, half of the starting dose is recommended. For paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased to the standard starting dose following the recommended dose titration in Table 1 and adjusted every 3-4 weeks.

For example, a paediatric patient weighing 25 kg who has not previously taken an ACE inhibitor should start with half the standard starting dose, which corresponds to 20 mg (25 kg × 0.8 mg/kg) twice daily, given as granules. After rounding to the closest number of full capsules, this corresponds to 2 capsules of 6 mg/6 mg sacubitril/valsartan twice daily.

Treatment should not be initiated in patients with serum potassium level >5.3 mmol/l or with systolic blood pressure (SBP) <5th percentile for the age of the patient. If patients experience tolerability issues (SBP <5th percentile for the age of the patient, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of Neparvis is recommended (see section 4.4).

Special populations
Renal impairment
No dose adjustment is required in patients with mild (eGFR 60-90 ml/min/1.73 m^2) renal impairment.

Half of the starting dose should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) (see section 5.1), Neparvis should be used with caution and half of the starting dose is recommended. In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily is recommended. After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks.

There is no experience in patients with end-stage renal disease and use of Neparvis is not recommended.

Hepatic impairment
No dose adjustment is required when administering Neparvis to patients with mild hepatic impairment (Child-Pugh A classification).

There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with aspartate transaminase (AST)/alanine transaminase (ALT) values more than twice the upper limit of the normal range. Neparvis should be used with caution in these patients and half of the starting dose is recommended (see sections 4.4 and 5.2). In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily is recommended. After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks.

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

Paediatric population
The safety and efficacy of Neparvis in children aged below 1 year have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

Oral use.

Neparvis granules are administered by opening the capsule and sprinkling the contents onto a small amount of soft food (1 to 2 teaspoons). Food containing the granules must be consumed immediately. Patients may receive either the 6 mg/6 mg (white cap) or 15 mg/16 mg (yellow cap) capsules or both to reach the required doses (see section 6.6). The capsule must not be swallowed. The empty shells must be discarded after use and not swallowed.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Concomitant use with ACE inhibitors (see sections 4.4 and 4.5). Neparvis must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy (see section 4.4).
- Hereditary or idiopathic angioedema (see section 4.4).
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections 4.4 and 4.5).
- Severe hepatic impairment, biliary cirrhosis and cholestasis (see section 4.2).
- Second and third trimesters of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

- The combination of sacubitril/valsartan with an ACE inhibitor is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.2, 4.3 and 4.5).

- The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 4.5). The combination of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections 4.3 and 4.5).

- Neparvis contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product (see sections 4.2 and 4.5).

Hypotension

Treatment should not be initiated unless SBP is ≥100 mmHg for adult patients or ≥5^{th} percentile SBP for the age of the paediatric patient. Patients with SBP below these values were not studied (see section 5.1). Cases of symptomatic hypotension have been reported in adult patients treated with sacubitril/valsartan during clinical studies (see section 4.8), especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). When initiating therapy or during dose titration with sacubitril/valsartan, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended (see section 4.2). Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with sacubitril/valsartan, however, such corrective action must be carefully weighed against the risk of volume overload.

Renal impairment

Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension (see section 4.2). There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2) and these patients may be at greatest risk of hypotension (see section 4.2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended.

Worsening renal function

Use of sacubitril/valsartan may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs) (see section 4.5). Down-titration should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is >5.4 mmol/l in adult patients and >5.3 mmol/l in paediatric patients. Use of sacubitril/valsartan may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur (see section 4.8). Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid

antagonists (see section 4.2). If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered.

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan. If angioedema occurs, 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. It must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, e.g. adrenaline solution 1 mg/1 ml (0.3-0.5 ml), and/or measures necessary to ensure a patent airway, should be promptly administered.

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

Black patients have an increased susceptibility to develop angioedema (see section 4.8).

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, sacubitril/valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Patients with renal artery stenosis

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

Patients with New York Heart Association (NYHA) functional classification IV

Caution should be exercised when initiating sacubitril/valsartan in patients with NYHA functional classification IV due to limited clinical experience in this population.

B-type natriuretic peptide (BNP)

BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate (see section 5.1).

Patients with hepatic impairment

There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In these patients, exposure may be increased and safety is not established. Caution is therefore recommended when using it in these patients (see section 4.2 and 5.2). Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).

Psychiatric disorders

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a contraindication

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

Aliskiren
The concomitant use of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see section 4.3). The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended (see section 4.4). Combination of sacubitril/valsartan with aliskiren is potentially associated with a higher frequency of adverse reactions such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) (see sections 4.3 and 4.4).

Interactions resulting in concomitant use not being recommended

Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product (see section 4.4).

Interactions requiring precautions

OATP1B1 and OATP1B3 substrates, e.g. statins
In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. Neparvis 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. Caution should be exercised when co-administering sacubitril/valsartan with statins. No clinically relevant interaction was observed when simvastatin and Neparvis were co-administered.

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

Potassium
Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium, and to increases

in serum creatinine. Monitoring of serum potassium is recommended if sacubitril/valsartan is co-administered with these agents (see section 4.4).

Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors
In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use 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 treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly (see section 4.4).

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

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

Nitrates, e.g. nitroglycerine
There was no interaction between sacubitril/valsartan and intravenously administered nitroglycerin with regard to blood pressure reduction. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone. A similar effect on the heart rate may occur when sacubitril/valsartan is co-administered with sublingual, oral or transdermal nitrates. In general no dose adjustment is required.

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

Metformin
Co-administration 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 in patients receiving metformin, the clinical status of the patient should be evaluated.

No significant interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

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

Should exposure to ARBs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension (see section 4.3).

Sacubitril
There are no data from the use of sacubitril in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Sacubitril/valsartan
There are no data from the use of sacubitril/valsartan in pregnant women. Animal studies with sacubitril/valsartan have shown reproductive toxicity (see section 5.3).

Breast-feeding

Limited data show that sacubitril and its active metabolite LBQ657 are excreted in human milk in very low amounts with an estimated relative infant dose of 0.01% for sacubitril and 0.46% for the active metabolite LBQ657 when administered to breast-feeding women at a dose of 24 mg/26 mg sacubitril/valsartan, twice daily. In the same data, valsartan was under the limit of detection. There is insufficient information on the effects of sacubitril/valsartan in newborns/infants. Because of the potential risk for adverse reactions in breast-fed newborns/infants, Neparvis is not recommended in women who are breast-feeding.

Fertility

There are no available data on the effect of sacubitril/valsartan on human fertility. No impairment of fertility was demonstrated in studies with it in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Sacubitril/valsartan has a minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in adults during treatment with sacubitril/valsartan were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%) (see section 4.4). Angioedema was reported in patients treated with sacubitril/valsartan (0.5%) (see description of selected adverse reactions).

Tabulated list of adverse reactions

Adverse reactions are ranked by System organ class and then by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 2 List of adverse reactions

System organ class	Preferred term	Frequency category
Blood and lymphatic system disorders	Anaemia	Common
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalaemia*	Very common
	Hypokalaemia	Common
	Hypoglycaemia	Common
	Hyponatraemia	Uncommon
Psychiatric disorders	Hallucinations**	Rare
	Sleep disorders	Rare
	Paranoia	Very rare
Nervous system disorders	Dizziness	Common
	Headache	Common
	Syncope	Common
	Dizziness postural	Uncommon
	Myoclonus	Not known
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension*	Very common
	Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
	Gastritis	Common
	Intestinal angioedema	Very rare
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Angioedema*	Uncommon
Renal and urinary disorders	Renal impairment*	Very common
	Renal failure (renal failure, acute renal failure)	Common
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common

*See description of selected adverse reactions.
**Including auditory and visual hallucinations

Description of selected adverse reactions

Angioedema
Angioedema has been reported in patients treated with sacubitril/valsartan. In PARADIGM-HF, angioedema was reported in 0.5% of patients treated with sacubitril/valsartan, compared with 0.2% of patients treated with enalapril. A higher incidence of angioedema was observed in Black patients treated with sacubitril/valsartan (2.4%) and enalapril (0.5%) (see section 4.4).

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

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

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

Paediatric population

In the PANORAMA-HF study, the safety of sacubitril/valsartan was assessed in a randomised, active-controlled, 52-week study of 375 paediatric heart failure (HF) patients aged 1 month to <18 years compared to enalapril. The 215 patients who rolled over into the long-term open-label extension study (PANORAMA-HF OLE) were treated for a median of 2.5 years, for up to 4.5 years. The safety profile observed in both studies was similar to that observed in adult patients. Safety data in patients aged 1 month to <1 year was limited.

Limited safety data are available in paediatric patients with moderate hepatic impairment or moderate to severe renal impairment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Limited data are available with regard to overdose in humans. A single dose of 583 mg sacubitril/617 mg valsartan and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) were studied in healthy adult volunteers and were well tolerated.

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

The medicinal product is unlikely to be removed by haemodialysis due to high protein binding (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II receptor blockers (ARBs), other combinations, ATC code: C09DX04

Mechanism of action

Sacubitril/valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits 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 LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

Pharmacodynamic effects

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 an initial increase in natriuresis, increased urine cGMP, and decreased plasma levels of mid-regional pro-atrial natriuretic peptide (MR-proANP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) compared to valsartan. In a 21-day study in HFrEF patients, sacubitril/valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. The AT1-receptor was also blocked as evidenced by increased plasma renin activity and plasma renin concentrations. In the PARADIGM-HF study, sacubitril/valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. In the PANORAMA-HF study, a reduction in NT-proBNP was observed at weeks 4 and 12 for sacubitril/valsartan (40.2% and 49.8%) and enalapril (18.0% and 44.9%) compared to baseline. The NT-proBNP levels continued to decrease over the duration of the study with a reduction of 65.1% for sacubitril/valsartan and 61.6% for enalapril at week 52 compared to baseline. BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because BNP is a neprilysin substrate (see section 4.4). NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

In a thorough QTc clinical study in healthy male subjects, single doses of sacubitril/valsartan 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 sacubitril/valsartan 194 mg sacubitril/206 mg valsartan once daily for two weeks to healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo; there were no changes in concentrations of CSF Aβ1-40 and 1-42. The clinical relevance of this finding is not known (see section 5.3).

Clinical efficacy and safety

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

PARADIGM-HF
PARADIGM-HF, the pivotal phase 3 study, was a multinational, randomised, double-blind study of 8 442 patients comparing sacubitril/valsartan to enalapril, both given to adult patients with chronic heart failure, NYHA class II-IV and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤40%, amended later to ≤35%) in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalisation for heart failure (HF). Patients with SBP <100 mmHg, severe renal impairment (eGFR <30 ml/min/1.73 m^2) and severe hepatic impairment were excluded at screening and therefore not prospectively studied.

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

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and enter a sequential single-blind run-in period during which they received treatment with enalapril 10 mg twice daily, followed by single-blind treatment with sacubitril/valsartan 100 mg twice daily, increasing to 200 mg twice daily (see section 4.8 for discontinuations during this period). They were then randomised to the double-blind period of the study, during which they received either sacubitril/valsartan 200 mg or enalapril 10 mg twice daily [sacubitril/valsartan (n=4 209); enalapril (n=4 233)].

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

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

Sacubitril/valsartan was superior to enalapril, reducing the risk of cardiovascular death or heart failure hospitalisations to 21.8% compared to 26.5% for enalapril treated patients. The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalisation, 3.1% for CV death alone, and 2.8% for first HF hospitalisation alone. The relative risk reduction was 20% versus enalapril (see Table 3). This effect was observed early and was sustained throughout the duration of the study (see Figure 1). Both components contributed to the risk reduction. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in sacubitril/valsartan-treated patients compared to enalapril-treated patients (hazard ratio [HR] 0.80, p=0.0082). Pump failure accounted for 26% of cardiovascular deaths and was reduced by 21% in sacubitril/valsartan-treated patients compared to enalapril-treated patients (HR 0.79, p=0.0338).

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

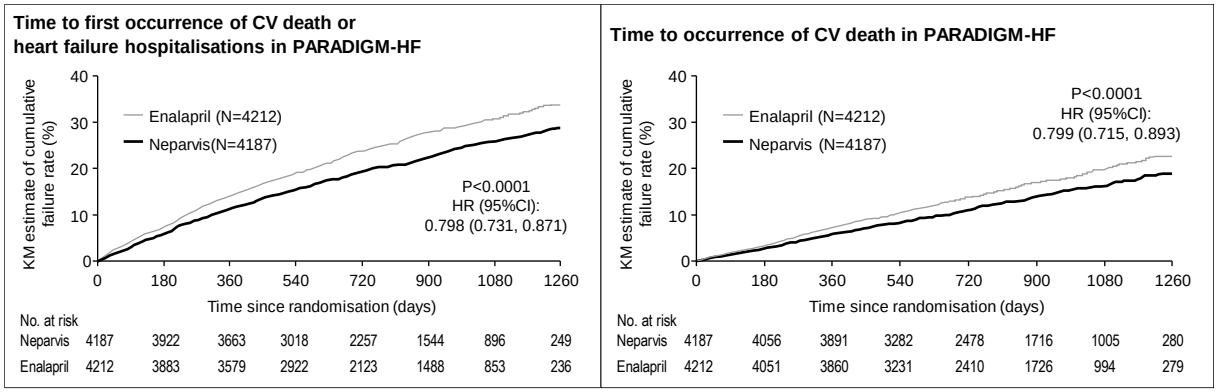
Sacubitril/valsartan improved survival with a significant reduction in all-cause mortality of 2.8% (sacubitril/valsartan, 17%, enalapril, 19.8%). The relative risk reduction was 16% compared with enalapril (see Table 3).

Table 3 Treatment effect for the primary composite endpoint, its components and all-cause mortality over a median follow-up of 27 months

	Sacubitril/ valsartan N=4 187[♯] n (%)	**Enalapril N=4 212[♯] n (%)**	**Hazard ratio (95% CI)**	**Relative risk reduction**	**p-value *****
Primary composite endpoint of CV death and heart failure hospitalisations*	914 (21.83)	1 117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual components of the primary composite endpoint					
CV death**	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	0.00004
First heart failure hospitalisation	537 (12.83)	658 (15.62)	0.79 (0.71, 0.89)	21%	0.00004
Secondary endpoint					
All-cause mortality	711 (16.98)	835 (19.82)	0.84 (0.76, 0.93)	16%	0.0005

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

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



TITRATION

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

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

Paediatric population

PANORAMA-HF

PANORAMA-HF, a phase 3 study, was a multinational, randomised, double-blind study comparing sacubitril/valsartan and enalapril in 375 paediatric patients aged 1 month to <18 years with heart failure due to systemic left ventricular systolic dysfunction (LVEF ≤45% or fractional shortening ≤22.5%). The primary objective was to determine whether sacubitril/valsartan was superior to enalapril in paediatric HF patients over a 52-week treatment duration based on a global rank endpoint. The global rank primary endpoint was derived by ranking patients (worst-to-best outcome) based on clinical events such as death, initiation of mechanical life support, listing for urgent heart transplant, worsening HF, measures of functional capacity (NYHA/ROSS scores), and patient-reported HF symptoms (Patient Global Impression Scale [PGIS]). Patients with systemic right ventricles or single ventricles and patients with restrictive or hypertrophic cardiomyopathy were excluded from the study. The target maintenance dose of sacubitril/valsartan was 2.3 mg/kg twice daily in paediatric patients aged 1 month to <1 year and 3.1 mg/kg twice daily in patients aged 1 to <18 years with a maximum dose of 200 mg twice daily. The target maintenance dose of enalapril was 0.15 mg/kg twice daily in paediatric patients aged 1 month to <1 year and 0.2 mg/kg twice daily in patients aged 1 to <18 years with a maximum dose of 10 mg twice daily.

In the study, 9 patients were aged 1 month to <1 year, 61 patients were aged 1 year to <2 years, 85 patients were aged 2 to <6 years and 220 patients were aged 6 to <18 years. At baseline, 15.7% of patients were NYHA/ROSS class I, 69.3% were class II, 14.4% were class III and 0.5% were class IV. The mean LVEF was 32%. The most common underlying causes of heart failure were cardiomyopathy related (63.5%). Prior to study participation, patients were treated most commonly with ACE inhibitors/ARBs (93%), beta-blockers (70%), aldosterone antagonists (70%), and diuretics (84%).

The Mann-Whitney Odds of the global rank primary endpoint was 0.907 (95% CI 0.72, 1.14), numerically in favour of sacubitril/valsartan (see Table 4). Sacubitril/valsartan and enalapril showed comparable clinically relevant improvements in the secondary endpoints of NYHA/ROSS class and PGIS score change compared to baseline. At week 52, the NYHA/ROSS functional class changes from baseline were: improved in 37.7% and 34.0%; unchanged in 50.6% and 56.6%; worsened in 11.7% and 9.4% of patients for sacubitril/valsartan and enalapril respectively. Similarly, the PGIS score changes from baseline were: improved in 35.5% and 34.8%; unchanged in 48.0% and 47.5%; worsened in 16.5% and 17.7% of patients for sacubitril/valsartan and enalapril respectively. NT-proBNP was substantially reduced from baseline in both treatment groups. The magnitude of NT-proBNP reduction with Neparvis was similar to that observed in adult heart failure patients in PARADIGM-HF. Because sacubitril/valsartan improved outcomes and reduced NT-proBNP in PARADIGM-HF, the reductions in NT-proBNP coupled with the symptomatic and functional improvements from baseline seen in PANORAMA-HF were considered a reasonable basis to infer clinical benefits in paediatric heart failure patients. There were too few patients aged below 1 year to evaluate the efficacy of sacubitril/valsartan in this age group.

Table 4 Treatment effect for the primary global rank endpoint in PANORAMA-HF

	Sacubitril/valsartan N=187	**Enalapril N=188**	**Treatment effect**
Global rank primary endpoint	Probability of favourable outcome (%)*	Probability of favourable outcome (%)*	Odds** (95% CI)
	52.4	47.6	0.907 (0.72, 1.14)

*The probability of favourable outcome or Mann-Whitney probability (MWP) for the given treatment was estimated based on percentage of wins in pairwise comparisons of global rank score between sacubitril/valsartan-treated patients versus enalapril-treated patients (each higher score counts as one win and each equal score counts as half a win).

**Mann-Whitney Odds was calculated as the estimated MWP for enalapril divided by the estimated MWP for sacubitril/valsartan, with odds <1 in favour of sacubitril/valsartan and >1 in favour of enalapril.

5.2 Pharmacokinetic properties

The valsartan contained within sacubitril/valsartan is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in sacubitril/valsartan is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.

Paediatric population

The pharmacokinetics of sacubitril/valsartan were evaluated in paediatric heart failure patients aged 1 month to <1 year and 1 year to <18 years and indicated that the pharmacokinetic profile of sacubitril/valsartan in paediatric and adult patients is similar.

Adult population

Absorption
Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657. These reach peak plasma concentrations in 2 hours, 1 hour, and 2 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60% and 23%, respectively.

Following twice daily dosing of sacubitril/valsartan, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1.6-fold. Administration with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. Sacubitril/valsartan can be administered with or without food.

Distribution
Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94-97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volume of distribution of valsartan and sacubitril were 75 litres to 103 litres, respectively.

Biotransformation
Sacubitril is readily converted to LBQ657 by carboxylesterases 1b and 1c; LBQ657 is not further metabolised to a significant extent. Valsartan is minimally metabolised, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite of valsartan has been identified in plasma at low concentrations (<10%).

Since CYP450-enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with medicinal products that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

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

Elimination
Following oral administration, 52-68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37-48% of sacubitril (primarily as LBQ657) and 86% of valsartan and its metabolites are excreted in faeces.

Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life ($T_{½}$) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Linearity/non-linearity
The pharmacokinetics of sacubitril, LBQ657 and valsartan were approximately linear over a sacubitril/valsartan dose range of 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan.

Special populations

Renal impairment
A correlation was observed between renal function and systemic exposure to LBQ657 in patients with mild to severe renal impairment. The exposure of LBQ657 in patients with moderate (30 ml/min/1.73 m^2 ≤ eGFR <60 ml/min/1.73 m^2) and severe renal impairment (15 ml/min/1.73 m^2 ≤ eGFR <30 ml/min/1.73 m^2) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60 ml/min/1.73 m^2 ≤ eGFR <90 ml/min/1.73 m^2), the largest group of patients enrolled in PARADIGM-HF. The exposure of valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild renal impairment. No studies have been performed in patients undergoing dialysis. However, LBQ657 and valsartan are highly bound to plasma protein and therefore unlikely to be effectively removed by dialysis.

Hepatic impairment
In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, LBQ657 increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects. However, in patients with mild to moderate hepatic impairment, the exposures of free concentrations of LBQ657 increased by 1.47- and 3.08-fold, respectively, and the exposures of free concentrations of valsartan increased by 1.09-fold and 2.20-fold, respectively, compared to matching healthy subjects. Sacubitril/valsartan has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (see sections 4.3 and 4.4).

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

5.3 Preclinical safety data

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

Fertility, reproduction and development

Sacubitril/valsartan treatment during organogenesis resulted in increased embryofoetal lethality in rats at doses ≥49 mg sacubitril/51 mg valsartan/kg/day (≤0.72-fold the maximum recommended human dose [MRHD] on the basis of AUC) and rabbits at doses ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). It is teratogenic based on a low incidence of foetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril/valsartan dose of ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day. Cardiovascular abnormalities (mainly cardiomegaly) were observed in rabbit foetuses at a maternally non-toxic dose (1.46 mg sacubitril/1.54 mg valsartan/kg/day). A slight increase in two foetal skeletal variations (misshapen sternebra, sternebra bipartite ossification) was observed in rabbits at a sacubitril/valsartan dose of 4.9 mg sacubitril/5.1 mg valsartan/kg/day. The adverse embryofoetal effects of sacubitril/valsartan are attributed to the angiotensin receptor antagonist activity (see section 4.6).

Sacubitril treatment during organogenesis resulted in embryo-foetal lethality and embryo-foetal toxicity (decreased foetal body weights and skeletal malformations) in rabbits at doses associated with maternal toxicity (500 mg/kg/day; 5.7-fold the MRHD on the basis of LBQ657 AUC). A slight generalised delay in ossification was observed at doses of >50 mg/kg/day. This finding is not

considered adverse. No evidence of embryo-foetal toxicity or teratogenicity was observed in rats treated with sacubitril. The embryo-foetal no-observed adverse effect level (NOAEL) for sacubitril was at least 750 mg/kg/day in rats and 200 mg/kg/day in rabbits (2.2-fold the MRHD on the basis of LBQ657 AUC).

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

Other preclinical findings

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

Sacubitril
In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation at approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, based on sacubitril/valsartan paediatric clinical dose of 3.1 mg/kg twice daily. The mechanism for these findings in juvenile rats, and consequently the relevance to the human paediatric population, unknown. A study in adult rats showed only a minimal transient inhibitory effect on bone mineral density but not on any other parameters relevant for bone growth, suggesting no relevant effect of sacubitril on bone in adult patient populations under normal conditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults cannot be excluded. Clinical data in paediatric patients (PANORAMA-HF study) did not show evidence that sacubitril/valsartan has an impact on body weight, height, head circumference and fracture rate. Bone density was not measured in the study. Long-term data in paediatric patients (PANORAMA-HF OLE) showed no evidence of adverse effects of sacubitril/valsartan on (bone) growth or fracture rates.

Valsartan
In juvenile rats treated with valsartan (postnatal days 7 to 70), doses as low as 1 mg/kg/day produced persistent irreversible kidney changes consisting of tubular nephropathy (sometimes accompanied by tubular epithelial necrosis) and pelvic dilatation. These kidney changes represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in paediatric patients less than 1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for paediatric patients older than 1 year.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granule core

Microcrystalline cellulose
Hydroxypropylcellulose
Magnesium stearate
Silica colloidal anhydrous
Talc

Film coat

Basic butylated methacrylate copolymer
Talc
Stearic acid
Sodium laurilsulfate

Capsule shell component

Neparvis 6 mg/6 mg granules in capsules for opening
Hypromellose
Titanium dioxide (E171)

Neparvis 15 mg/16 mg granules in capsules for opening
Hypromellose
Titanium dioxide (E171)
Iron oxide, yellow (E172)

Printing ink

Shellac
Propylene glycol
Iron oxide, red (E172)
Ammonia solution (concentrated)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PA/Alu/PVC blisters

Neparvis 6 mg/6 mg granules in capsules for opening

Pack size: 60 capsules

Neparvis 15 mg/16 mg granules in capsules for opening

Pack size: 60 capsules

6.6 Special precautions for disposal and other handling

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

Use in the paediatric population

Patients and caregivers must be instructed to open the capsule(s) carefully to avoid spillage or dispersion of the capsule contents into the air. It is recommended to hold the capsule upright with the coloured cap on top and to pull the cap away from the body of the capsule.

The contents of the capsule must be sprinkled onto 1 to 2 teaspoons of soft food in a small container.

Food containing the granules must be consumed immediately.

The empty capsule shells must be discarded immediately.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Neparvis 6 mg/6 mg granules in capsules for opening

EU/1/16/1103/018

Neparvis 15 mg/16 mg granules in capsules for opening

EU/1/16/1103/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2016
Date of latest renewal: 11 February 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Film-coated tablets
Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
1000 Ljubljana
Slovenia

Novartis Farma S.p.A
Via Provinciale Schito 131
80058 Torre Annunziata (NA)
Italy

LEK farmacevtska družba d. d., Poslovna enota PROIZVODNJA LENDAVA
Trimlini 2D
Lendava 9220
Slovenia

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

Granules in capsules for opening
Lek farmacevtska družba d.d.
Verovskova Ulica 57
1526 Ljubljana
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
1000 Ljubljana
Slovenia

Novartis Farmaceutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 24 mg/26 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
20 film-coated tablets
28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/001	28 film-coated tablets
EU/1/16/1103/008	14 film-coated tablets
EU/1/16/1103/009	20 film-coated tablets
EU/1/16/1103/010	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 24 mg/26 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 24 mg/26 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 196 (7 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/017 196 film-coated tablets (7 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 24 mg/26 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 24 mg/26 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/017 196 film-coated tablets (7 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 24 mg/26 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 24 mg/26 mg tablets
sacubitril/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 49 mg/51 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
20 film-coated tablets
28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/002	28 film-coated tablets
EU/1/16/1103/003	56 film-coated tablets
EU/1/16/1103/011	14 film-coated tablets
EU/1/16/1103/012	20 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 49 mg/51 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 49 mg/51 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 168 (3 packs of 56) film-coated tablets
Multipack: 196 (7 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/004	168 film-coated tablets (3 packs of 56)
EU/1/16/1103/013	196 film-coated tablets (7 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 49 mg/51 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 49 mg/51 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets. Component of a multipack. Not to be sold separately.
56 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/004	168 film-coated tablets (3 packs of 56)
EU/1/16/1103/013	196 film-coated tablets (7 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 49 mg/51 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 49 mg/51 mg tablets
sacubitril/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 97 mg/103 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
20 film-coated tablets
28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/005	28 film-coated tablets
EU/1/16/1103/006	56 film-coated tablets
EU/1/16/1103/014	14 film-coated tablets
EU/1/16/1103/015	20 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 97 mg/103 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 97 mg/103 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 168 (3 packs of 56) film-coated tablets
Multipack: 196 (7 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/007	168 film-coated tablets (3 packs of 56)
EU/1/16/1103/016	196 film-coated tablets (7 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 97 mg/103 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 97 mg/103 mg film-coated tablets
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets. Component of a multipack. Not to be sold separately.
56 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/007	168 film-coated tablets (3 packs of 56)
EU/1/16/1103/016	196 film-coated tablets (7 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 97 mg/103 mg film-coated tablets, abbreviated form accepted, if required for technical reasons

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 97 mg/103 mg tablets
sacubitril/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 6 mg/6 mg granules in capsules for opening
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 granules equivalent to 6.1 mg sacubitril and 6.4 mg valsartan (as sacubitril valsartan sodium salt complex).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in capsules for opening

60 capsules each containing 4 granules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Open the capsule and sprinkle the granules onto food.
Do not swallow capsules.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/018 60 capsules each containing 4 film-coated granules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 6 mg/6 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 6 mg/6 mg granules in capsule
sacubitril/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not swallow capsules.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 15 mg/16 mg granules in capsules for opening
sacubitril/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 10 granules equivalent to 15.18 mg sacubitril and 16.07 mg valsartan (as sacubitril valsartan sodium salt complex).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in capsules for opening

60 capsules each containing 10 granules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Open the capsule and sprinkle the granules onto food.
Do not swallow capsules.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1103/019 60 capsules each containing 10 granules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neparvis 15 mg/16 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Neparvis 15 mg/16 mg granules in capsule
sacubitril/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not swallow capsules.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Neparvis 24 mg/26 mg film-coated tablets
Neparvis 49 mg/51 mg film-coated tablets
Neparvis 97 mg/103 mg film-coated tablets
sacubitril/valsartan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Neparvis is and what it is used for
2. What you need to know before you take Neparvis
3. How to take Neparvis
4. Possible side effects
5. How to store Neparvis
6. Contents of the pack and other information

1. What Neparvis is and what it is used for

Neparvis is a heart medicine containing an angiotensin receptor neprilysin inhibitor. It delivers two active substances, sacubitril and valsartan.

Neparvis is used to treat a type of long-term heart failure in adults, children and adolescents (one year and older).

This type of heart failure occurs when the heart is weak and cannot pump enough blood to the lungs and the rest of the body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

2. What you need to know before you take Neparvis

Do not take Neparvis
- if you are allergic to sacubitril, valsartan or any of the other ingredients of this medicine (listed in section 6).
- if you are taking another type of medicine called an angiotensin converting enzyme (ACE) inhibitor (for example enalapril, lisinopril or ramipril), which is used to treat high blood pressure or heart failure. If you have been taking an ACE inhibitor, wait for 36 hours after taking the last dose before you start to take Neparvis (see “Other medicines and Neparvis”).
- if you have ever had a reaction called angioedema (rapid swelling under the skin in areas such as the face, throat, arms and legs which can be life threatening if throat swelling blocks the airway) when taking an ACE inhibitor or an angiotensin receptor blocker (ARB) (such as valsartan, telmisartan or irbesartan).
- if you have a history of angioedema which is hereditary or for which the cause is unknown (idiopathic).
- if you have diabetes or impaired kidney function and you are being treated with a blood pressure lowering medicine containing aliskiren (see “Other medicines and Neparvis”).

- if you have severe liver disease.
- if you are more than 3 months pregnant (see "Pregnancy and breast-feeding").

If any of the above applies to you, do not take Neparvis and talk to your doctor.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before or when taking Neparvis:
- if you are being treated with an angiotensin receptor blocker (ARB) or aliskiren (see "Do not take Neparvis").
- if you have ever had angioedema (see "Do not take Neparvis" and section 4 "Possible side effects").
- if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Neparvis. Your doctor will decide on further treatment. Do not stop taking Neparvis on your own.
- if you have low blood pressure or are taking any other medicines that reduce your blood pressure (for example, a medicine that increases urine production (diuretic)) or are suffering from vomiting or diarrhoea, especially if you are aged 65 years or more, or if you have kidney disease and low blood pressure.
- if you have kidney disease.
- if you are suffering from dehydration.
- if your kidney artery has narrowed.
- if you have liver disease.
- if you experience hallucinations, paranoia or changes in sleeping pattern while taking Neparvis.
- if you have hyperkalaemia (high levels of potassium in the blood).
- if you suffer from heart failure classified as NYHA class IV (unable to carry on any physical activity without discomfort and may have symptoms even when resting).

If any of the above applies to you, tell your doctor, pharmacist or nurse before you take Neparvis.

Your doctor may check the amount of potassium and sodium in your blood at regular intervals during Neparvis treatment. In addition, your doctor may check your blood pressure at start of treatment and when the doses are increased.

Children and adolescents
Do not give this medicine to children aged below 1 year because it has not been studied in this age group. For children one year and older with a body weight below 40 kg, this medicine will be given as granules (instead of tablets).

Other medicines and Neparvis
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. It may be necessary to change the dose, to take other precautions, or even to stop taking one of the medicines. This is particularly important for the following medicines:
- ACE inhibitors. Do not take Neparvis with ACE inhibitors. If you have been taking an ACE inhibitor, wait 36 hours after taking the last dose of the ACE inhibitor before starting to take Neparvis (see "Do not take Neparvis"). If you stop taking Neparvis, wait 36 hours after taking your last dose of Neparvis before starting an ACE inhibitor.
- other medicines used to treat heart failure or lower blood pressure, such as angiotensin receptor blockers or aliskiren (see "Do not take Neparvis").
- some medicines known as statins that are used to lower high cholesterol levels (for example atorvastatin).
- sildenafil, tadalafil, vardenafil or avanafil, which are medicines used to treat erectile dysfunction or lung hypertension.
- medicines that increase the amount of potassium in the blood. These include potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin.

- painkillers of the type called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 (Cox-2) inhibitors. If you are taking one of these, your doctor may want to check your kidney function when starting or adjusting treatment (see "Warnings and precautions").
- lithium, a medicine used to treat some types of psychiatric illness.
- furosemide, a medicine belonging to the type known as diuretics, which are used to increase the amount of urine you produce.
- nitroglycerine, a medicine used to treat angina pectoris.
- some types of antibiotics (rifamycin group), ciclosporin (used to prevent rejection of transplanted organs) or antivirals such as ritonavir (used to treat HIV/AIDS).
- metformin, a medicine used to treat diabetes.

If any of the above applies to you, tell your doctor or pharmacist before you take Neparvis.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You must tell your doctor if you think that you are (or might become) pregnant. Your doctor will normally advise you to stop taking this medicine before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Neparvis.

This medicine is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

Breast-feeding
Neparvis is not recommended for mothers who are breast-feeding. Tell your doctor if you are breast-feeding or about to start breast-feeding.

Driving and using machines
Before you drive a vehicle, use tools or operate machines, or carry out other activities that require concentration, make sure you know how Neparvis affects you. If you feel dizzy or very tired while taking this medicine, do not drive a vehicle, cycle or use any tools or machines.

Neparvis contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose, that is to say essentially 'sodium free'.

3. How to take Neparvis

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults
You will usually start by taking a 24 mg/26 mg or 49 mg/51 mg tablet twice a day (one tablet in the morning and one tablet in the evening). Your doctor will decide your exact starting dose based on which medicines you have been taking previously and your blood pressure. Your doctor will then adjust the dose every 2-4 weeks depending on how you respond to the treatment until the best dose for you is found.

The usual recommended target dose is 97 mg/103 mg twice a day (one tablet in the morning and one tablet in the evening).

Children and adolescents (one year and older)
Your (or your child's) doctor will decide the starting dose based on body weight and other factors including previously taken medicines. The doctor will adjust the dose every 2-4 weeks until the best dose is found.

Neparvis should be given twice a day (one tablet in the morning and one tablet in the evening).

Neparvis film-coated tablets are not meant to be used in children who weigh less than 40 kg. For these patients, Neparvis granules are available.

Patients taking Neparvis can develop low blood pressure (dizziness, light-headedness), a high level of potassium in the blood (which would be detected when your doctor performed a blood test) or decreased kidney function. If this happens, your doctor may reduce the dose of any other medicine you are taking, temporarily reduce the Neparvis dose, or stop Neparvis treatment completely.

Swallow the tablets with a glass of water. You can take Neparvis with or without food. Splitting or crushing of the tablets is not recommended.

If you take more Neparvis than you should
If you have accidentally taken too many Neparvis tablets, or if someone else has taken your tablets, contact your doctor immediately. If you experience severe dizziness and/or fainting, tell your doctor as quickly as possible and lie down.

If you forget to take Neparvis
It is advisable to take your medicine at the same time each day. However, if you forget to take a dose, you should simply take the next one at the scheduled time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Neparvis
Stopping your treatment with Neparvis may cause your condition to get worse. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects may be serious.
- Stop taking Neparvis and seek immediate medical attention if you notice any swelling of the face, lips, tongue and/or throat, which may cause difficulties in breathing or swallowing. These may be signs of angioedema (an uncommon side effect which may affect up to 1 in 100 people).

Other possible side effects:
If any of the side effects listed below becomes severe, tell your doctor or pharmacist.

Very common (may affect more than 1 in 10 people)
- low blood pressure, which can cause symptoms of dizziness and light-headedness (hypotension)
- high level of potassium in the blood, shown in a blood test (hyperkalaemia)
- decreased kidney function (renal impairment)

Common (may affect up to 1 in 10 people)
- cough
- dizziness
- diarrhoea
- low level of red blood cells, shown in a blood test (anaemia)
- tiredness (fatigue)
- (acute) inability of the kidney to work properly (renal failure)
- low level of potassium in the blood, shown in a blood test (hypokalaemia)
- headache
- fainting (syncope)
- weakness (asthenia)
- feeling sick (nausea)
- low blood pressure (dizziness, light-headedness) when switching from sitting or lying to standing position
- gastritis (stomach pain, nausea)
- spinning sensation (vertigo)
- low level of sugar in the blood, shown in a blood test (hypoglycaemia)

Uncommon (may affect up to 1 in 100 people)
- allergic reaction with rash and itching (hypersensitivity)
- dizziness when switching from sitting to standing position (dizziness postural)
- low level of sodium in the blood, shown in a blood test (hyponatraemia)

Rare (may affect up to 1 in 1 000 people)
- seeing, hearing or feeling things that are not there (hallucinations)
- changes in sleeping pattern (sleep disorder)

Very rare (may affect up to 1 in 10 000 people)
- paranoia
- intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea

Not known (frequency cannot be estimated from the available data)
- sudden involuntary muscle twitching (myoclonus)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neparvis

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
This medicine does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.
Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.
Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Neparvis contains

- The active substances are sacubitril and valsartan.
  - Each 24 mg/26 mg film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex).
  - Each 49 mg/51 mg film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex).
  - Each 97 mg/103 mg film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex).
- The other ingredients in the tablet core are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate, talc and silica colloidal anhydrous (see end of section 2 under 'Neparvis contains sodium').
- The 24 mg/26 mg and the 97 mg/103 mg tablet coatings contain hypromellose, titanium dioxide (E171), Macrogol (4000), talc, iron oxide red (E172) and iron oxide black (E172).
- The 49 mg/51 mg tablet coating contains hypromellose, titanium dioxide (E171), Macrogol (4000), talc, iron oxide red (E172) and iron oxide yellow (E172).

What Neparvis looks like and contents of the pack

Neparvis 24 mg/26 mg film-coated tablets are violet-white oval tablets with "NVR" on one side and "LZ" on the other side. Approximate tablet dimensions 13.1 mm x 5.2 mm.
Neparvis 49 mg/51 mg film-coated tablets are pale yellow oval tablets with "NVR" on one side and "L1" on the other side. Approximate tablet dimensions 13.1 mm x 5.2 mm
Neparvis 97 mg/103 mg film-coated tablets are light pink oval tablets with "NVR" on one side and "L11" on the other side. Approximate tablet dimensions 15.1 mm x 6.0 mm.

The tablets are supplied in packs containing 14, 20, 28 or 56 tablets and in multipacks comprising 7 cartons, each containing 28 tablets. The 49 mg/51 mg and 97 mg/103 mg tablets are also supplied in multipacks comprising 3 cartons, each containing 56 tablets.

Not all pack sizes may be marketed.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Package leaflet: Information for the user

Neparvis 6 mg/6 mg granules in capsules for opening
Neparvis 15 mg/16 mg granules in capsules for opening
sacubitril/valsartan

Read all of this leaflet carefully before you (or your child) start taking this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you (or your child) only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you (or your child) get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Neparvis is and what it is used for
2. What you need to know before you (or your child) take Neparvis
3. How to take Neparvis
4. Possible side effects
5. How to store Neparvis
6. Contents of the pack and other information

1. What Neparvis is and what it is used for

Neparvis is a heart medicine containing an angiotensin receptor neprilysin inhibitor. It delivers two active substances, sacubitril and valsartan.

Neparvis is used to treat a type of long-term heart failure in children and adolescents (one year and older).

This type of heart failure occurs when the heart is weak and cannot pump enough blood to the lungs and the rest of the body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

2. What you need to know before you (or your child) take Neparvis

Do not take Neparvis
- if you (or your child) are allergic to sacubitril, valsartan or any of the other ingredients of this medicine (listed in section 6).
- if you (or your child) are taking another type of medicine called an angiotensin converting enzyme (ACE) inhibitor (for example enalapril, lisinopril or ramipril), which is used to treat high blood pressure or heart failure. If you have been taking an ACE inhibitor, wait for 36 hours after taking the last dose before you start to take Neparvis (see “Other medicines and Neparvis”).
- if you (or your child) have ever had a reaction called angioedema (rapid swelling under the skin in areas such as the face, throat, arms and legs which can be life threatening if throat swelling blocks the airway) when taking an ACE inhibitor or an angiotensin receptor blocker (ARB) (such as valsartan, telmisartan or irbesartan).
- if you (or your child) have a history of angioedema which is hereditary or for which the cause is unknown (idiopathic).
- if you (or your child) have diabetes or impaired kidney function and you are being treated with a blood pressure lowering medicine containing aliskiren (see “Other medicines and Neparvis”).

- if you (or your child) have severe liver disease.
- if you (or your child) are more than 3 months pregnant (see "Pregnancy and breast-feeding").

If any of the above applies to you, do not take Neparvis and talk to your doctor.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before or when taking Neparvis:
- if you (or your child) are being treated with an angiotensin receptor blocker (ARB) or aliskiren (see "Do not take Neparvis").
- if you (or your child) have ever had angioedema (see "Do not take Neparvis" and section 4 "Possible side effects").
- if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Neparvis. Your doctor will decide on further treatment. Do not stop taking Neparvis on your own.
- if you (or your child) have low blood pressure or are taking any other medicines that reduce your blood pressure (for example, a medicine that increases urine production (diuretic)) or are suffering from vomiting or diarrhoea, especially if you are aged 65 years or more, or if you have kidney disease and low blood pressure.
- if you (or your child) have kidney disease.
- if you (or your child) are suffering from dehydration.
- if your (or your child's) kidney artery has narrowed.
- if you (or your child) have liver disease.
- if you (or your child) experience hallucinations, paranoia or changes in sleeping pattern while taking Neparvis.
- if you (or your child) have hyperkalaemia (high levels of potassium in the blood).
- if you (or your child) suffer from heart failure classified as NYHA class IV (unable to carry on any physical activity without discomfort and may have symptoms even when resting).

If any of the above applies to you, tell your doctor, pharmacist or nurse before you take Neparvis.

Your doctor may check the amount of potassium and sodium in your blood at regular intervals during Neparvis treatment. In addition, your doctor may check your blood pressure at start of treatment and when the doses are increased.

Children (below one year of age)
Use in children below one year of age is not recommended. There is limited experience on use in children in this age group. Neparvis film-coated tablets are available for children who weigh more than 40 kg.

Other medicines and Neparvis
Tell your doctor, pharmacist or nurse if you (or your child) are taking, have recently taken or might take any other medicines. It may be necessary to change the dose, to take other precautions, or even to stop taking one of the medicines. This is particularly important for the following medicines:
- ACE inhibitors. Do not take Neparvis with ACE inhibitors. If you have been taking an ACE inhibitor, wait 36 hours after taking the last dose of the ACE inhibitor before starting to take Neparvis (see "Do not take Neparvis"). If you stop taking Neparvis, wait 36 hours after taking your last dose of Neparvis before starting an ACE inhibitor.
- other medicines used to treat heart failure or lower blood pressure, such as angiotensin receptor blockers or aliskiren (see "Do not take Neparvis").
- some medicines known as statins that are used to lower high cholesterol levels (for example atorvastatin).
- sildenafil, tadalafil, vardenafil or avanafil, which are medicines used to treat erectile dysfunction or lung hypertension.
- medicines that increase the amount of potassium in the blood. These include potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin.

- painkillers of the type called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 (Cox-2) inhibitors. If you are taking one of these, your doctor may want to check your kidney function when starting or adjusting treatment (see "Warnings and precautions").
- lithium, a medicine used to treat some types of psychiatric illness.
- furosemide, a medicine belonging to the type known as diuretics, which are used to increase the amount of urine you produce.
- nitroglycerine, a medicine used to treat angina pectoris.
- some types of antibiotics (rifamycin group), ciclosporin (used to prevent rejection of transplanted organs) or antivirals such as ritonavir (used to treat HIV/AIDS).
- metformin, a medicine used to treat diabetes.

If any of the above applies to you, tell your doctor or pharmacist before you take Neparvis.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You must tell your doctor if you think that you (or your child) are (or might become) pregnant. Your doctor will normally advise you to stop taking this medicine before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Neparvis.

This medicine is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

Breast-feeding
Neparvis is not recommended for mothers who are breast-feeding. Tell your doctor if you are breast-feeding or about to start breast-feeding.

Driving and using machines
Before you drive a vehicle, use tools or operate machines, or carry out other activities that require concentration, make sure you know how Neparvis affects you. If you feel dizzy or very tired while taking this medicine, do not drive a vehicle, cycle or use any tools or machines.

Neparvis contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose, that is to say essentially 'sodium free'.

3. How to take Neparvis

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your (or your child's) doctor will decide the starting dose based on body weight and other factors including previously taken medicines. The doctor will adjust the dose every 2-4 weeks until the best dose is found.

Neparvis should be given twice a day (once in the morning and once in the evening).

See the instructions for use for how to prepare and take Neparvis granules.

Patients taking Neparvis can develop low blood pressure (dizziness, light-headedness), a high level of potassium in the blood (which would be detected when your doctor performed a blood test) or decreased kidney function. If this happens, your doctor may reduce the dose of any other medicine you

(or your child) are taking, temporarily reduce the Neparvis dose, or stop Neparvis treatment completely.

If you take more Neparvis than you should
If you (or your child) have accidentally taken too many Neparvis granules, or if someone else has taken your granules, contact your doctor immediately. If you (or your child) experience severe dizziness and/or fainting, tell your doctor as quickly as possible and lie down.

If you (or your child) forget to take Neparvis
It is advisable to take your medicine at the same time each day. However, if you (or your child) forget to take a dose, you should simply take the next one at the scheduled time. Do not take a double dose to make up for a forgotten dose.

If you (or your child) stop taking Neparvis
Stopping your treatment with Neparvis may cause your condition to get worse. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects may be serious.
- Stop taking Neparvis and seek immediate medical attention if you (or your child) notice any swelling of the face, lips, tongue and/or throat, which may cause difficulties in breathing or swallowing. These may be signs of angioedema (an uncommon side effect which may affect up to 1 in 100 people).

Other possible side effects:
If any of the side effects listed below becomes severe, tell your doctor or pharmacist.

Very common (may affect more than 1 in 10 people)
- low blood pressure, which can cause symptoms of dizziness and light-headedness (hypotension)
- high level of potassium in the blood, shown in a blood test (hyperkalaemia)
- decreased kidney function (renal impairment)

Common (may affect up to 1 in 10 people)
- cough
- dizziness
- diarrhoea
- low level of red blood cells, shown in a blood test (anaemia)
- tiredness (fatigue)
- (acute) inability of the kidney to work properly (renal failure)
- low level of potassium in the blood, shown in a blood test (hypokalaemia)
- headache
- fainting (syncope)
- weakness (asthenia)
- feeling sick (nausea)
- low blood pressure (dizziness, light-headedness) when switching from sitting or lying to standing position
- gastritis (stomach pain, nausea)
- spinning sensation (vertigo)
- low level of sugar in the blood, shown in a blood test (hypoglycaemia)

Uncommon (may affect up to 1 in 100 people)
- allergic reaction with rash and itching (hypersensitivity)
- dizziness when switching from sitting to standing position (dizziness postural)
- low level of sodium in the blood, shown in a blood test (hyponatraemia)

Rare (may affect up to 1 in 1 000 people)
- seeing, hearing or feeling things that are not there (hallucinations)
- changes in sleeping pattern (sleep disorder)

Very rare (may affect up to 1 in 10 000 people)
- paranoia
- intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea

Not known (frequency cannot be estimated from the available data)
- sudden involuntary muscle twitching (myoclonus)

Reporting of side effects
If you (or your child) get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neparvis

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
This medicine does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.
Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.
Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Neparvis contains
- The active substances are sacubitril and valsartan.
  - Each Neparvis 6 mg/6 mg granules in capsule for opening (granules in capsule) contains four film-coated granules equivalent to 6.1 mg sacubitril and 6.4 mg valsartan (as sacubitril valsartan sodium salt complex).
  - Each Neparvis 15 mg/16 mg granules in capsule for opening (granules in capsule) contains ten film-coated granules equivalent to 15.18 mg sacubitril and 16.07 mg valsartan (as sacubitril valsartan sodium salt complex).
- The other ingredients of the granules are microcrystalline cellulose, hydroxypropylcellulose, magnesium stearate, silica colloidal anhydrous and talc.
- The ingredients of the film coat are basic butylated methacrylate copolymer, talc, stearic acid and sodium laurilsulfate (see end of section 2 under ‘Neparvis contains sodium’).
- The ingredients of the capsule shell are hypromellose, titanium dioxide (E171), iron oxide (yellow) (E172) (Neparvis 15 mg/16 mg only) and printing ink.
  - The ingredients of the printing ink are shellac, propylene glycol, iron oxide (red) (E172), ammonia solution (concentrated) and potassium hydroxide.

What Neparvis looks like and contents of the pack
Neparvis 6 mg/6 mg granules are white to slightly yellow in colour, round in shape, approximately 2 mm in diameter and provided in a capsule. The capsule consists of a white cap, marked “04” in red and a transparent body, marked “NVR” in red. An arrow is printed on both the body and the cap.
Neparvis 15 mg/16 mg granules are white to slightly yellow in colour, round in shape, approximately 2 mm in diameter and provided in a capsule. The capsule consists of a yellow cap, marked “10” in red and a transparent body, marked “NVR” in red. An arrow is printed on both the body and the cap.

Neparvis 6 mg/6 mg granules in capsules for opening and Neparvis 15 mg/16 mg granules in capsules for opening are supplied in packs containing 60 capsules.

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Other sources of information
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Instructions for use for Neparvis 6 mg/6 mg granules in capsules for opening and Neparvis 15 mg/16 mg granules in capsules for opening

To ensure that you use Neparvis granules correctly for your child, it is important that you follow these instructions. Your doctor, pharmacist or nurse will show you how to do this. Ask one of them if you have any questions.

Neparvis granules are contained within capsules and are available in two strengths: 6 mg/6 mg granules and 15 mg/16 mg granules. The capsules are packaged in blister cards. You may receive one or both strengths depending on the dose your child needs.

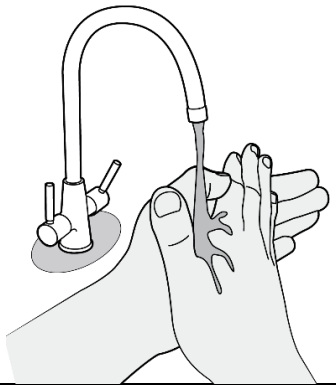
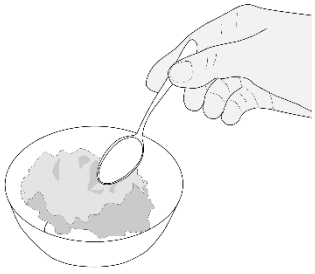
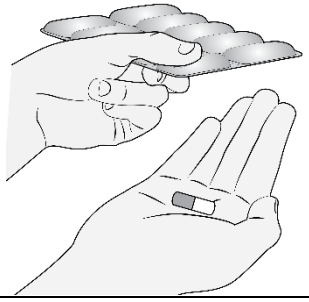
You can see the difference between the two strengths by the colour of the capsule cap and the imprint on it.

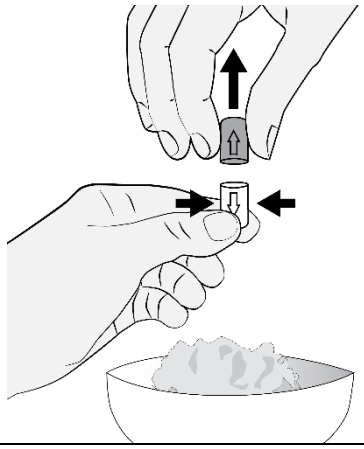
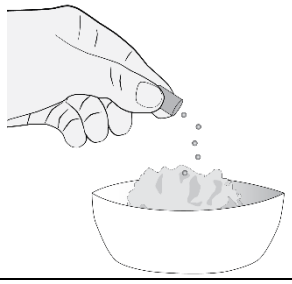
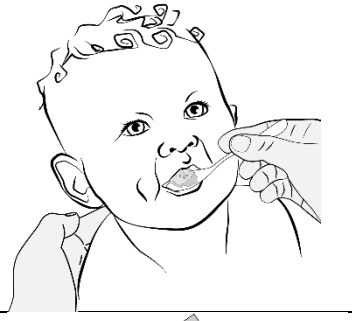
- The capsule containing the 6 mg/6 mg granules has a white cap with number 04 printed on it.
- The capsule containing the 15 mg/16 mg granules has a yellow cap with number 10 printed on it.

The capsules containing Neparvis granules must be opened before use.

Do NOT swallow the whole capsule. Do NOT swallow the empty capsule shells.

If you use both strengths of Neparvis granules, make sure you use the correct number of capsules of each strength as instructed by your doctor, pharmacist or nurse.

Step 1	• Wash and dry your hands	
Step 2	• Place the following items on a clean flat surface: o A small bowl, cup or spoon with a small amount of soft food the child likes. o Blister card(s) with capsules containing Neparvis granules. • Check that you have the correct strength(s) of Neparvis granules.	
Step 3	• Push the blister(s) to remove the capsule(s).	

Step 4	To open the capsule: • Hold the capsule upright (with the coloured cap on top) so that the granules are in the bottom of the capsule. • Hold the capsule over the soft food. • Gently pinch the middle of the capsule and pull slightly to separate the two ends of the capsule. Take care not to spill the contents.	
Step 5	• Empty all of the granules from the capsule onto the food. • Make sure that you do not miss any granules. Repeat steps 4 and 5 if you need more than one capsule to reach the prescribed dose.	
Step 6	Feed the food with the granules to the child immediately, making sure your child eats all of it. Make sure your child does not chew the granules to avoid change of taste.	
Step 7	Throw away the empty shells of the capsule.	