1.4 Labelling and PI/PIL proposed in Singapore

1.4.3 Package Insert

The proposed Package Insert for Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is enclosed in following pages.

TRADE NAME
MERAVO® 50 mg
MERAVO® 100 mg
MERAVO® 200 mg

DESCRIPTION AND COMPOSITION

Pharmaceutical form
Film-coated tablets.

50 mg: Violet white, ovaloid, biconvex, film-coated tablet with beveled edges, unscored, debossed with "SV50" on one side and "B" on the other side.

100 mg: Pale yellow to yellow, ovaloid, biconvex, film-coated tablet with beveled edges, unscored, debossed with "SV100" on one side and "B" on the other side.

200 mg: Light pink to pink, ovaloid, biconvex, film-coated tablet with beveled edges, unscored, debossed with "SV200" on one side and "B" on the other side.

Active substances
MERAVO® 50 mg
Each film coated tablet contains:
24 mg of Sacubitril as Sacubitril Sodium
26 mg of Valsartan as Valsartan Disodium

MERAVO® 100 mg
Each film coated tablet contains:
49 mg of Sacubitril as Sacubitril Sodium
51 mg of Valsartan as Valsartan Disodium

MERAVO® 200 mg
Each film coated tablet contains:
97 mg of Sacubitril as Sacubitril Sodium
103 mg of Valsartan as Valsartan Disodium

Excipients
Microcrystalline cellulose, Low-substituted hydroxy propyl cellulose, Crospovidone, Magnesium stearate (vegetable origin), Talc and Colloidal silicon dioxide.

Excipients of film coating:

For 50 mg:
Talc, Titanium dioxide, Sodium lauryl sulphate, Ferrosoferric oxide , Iron oxide red , GMCC (glyceryl monocaprylocaprate) type 1 / Glycerol esters of fatty acids and Polyvinyl alcohol-Part. Hydrolyzed

For 100 mg:
Talc, Titanium dioxide, Sodium lauryl sulphate, Iron oxide yellow, Iron oxide red, GMCC (glyceryl monocaprylocaprate) type 1 / Glycerol esters of fatty acids and Polyvinyl alcohol-

Part. Hydrolyzed.

For 200 mg:
Talc, Titanium dioxide, Sodium lauryl sulfate, Iron oxide red, Ferrosoferric oxide, GMCC (glyceryl monocaprylocaprate) type 1 / Glycerol esters of fatty acids and Polyvinyl alcohol-Part. Hydrolyzed.

INDICATIONS
MERAVO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. MERAVO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

DOSAGE AND ADMINISTRATION
The target dose of MERAVO is 200 mg twice daily.
The recommended starting dose of MERAVO is 100 mg twice daily. A starting dose of 50 mg twice daily is recommended for patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and should be considered for patients previously taking low doses of these agents (see section CLINICAL STUDIES). The dose of MERAVO should be doubled every 2-4 weeks to the target dose of 200 mg twice daily, as tolerated by the patient.

Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, MERAVO must not be started until 36 hours after discontinuing ACE inhibitor therapy (see section CONTRAINDICATIONS).

MERAVO should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of MERAVO (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).
If patients experience tolerability issues (symptomatic hypotension, hyperkalemia, renal dysfunction), consideration should be given to adjustment of concomitant medications, or to temporary down–titration of MERAVO.

Special populations

Renal impairment
A starting dose of 50 mg twice daily is recommended in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2). Caution is recommended when using MERAVO in these patients due to limited data (see section CLINICAL PHARMACOLOGY).
No dose adjustment is required in patients with mild (eGFR 60-90 mL/min/1.73 m^2) to moderate (eGFR 30-60 mL/min/1.73 m^2) renal impairment.

Hepatic impairment
A starting dose of 50 mg twice daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification).
No dose adjustment is required when administering MERAVO to patients with mild hepatic impairment (Child-Pugh A classification).
No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification). Therefore use of MERAVO in these patients is not recommended (see section

CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years of age)
The safety and efficacy of MERAVO in pediatric patients aged below 18 years has not been established.

Geriatric patients (65 years of age and above)
No dosage adjustment is required in patients 65 years of age and above.

Method of administration
For oral use. MERAVO may be administered with or without food (see section CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

- Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients.
- Concomitant use with ACE inhibitors (see sections WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, and INTERACTIONS). MERAVO must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary angioedema.
- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (eGFR < 60ml/min/1.73 m^2) (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).
- Pregnancy (see section FEMALES OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).
- Severe renal impairment with eGFR <10 ml/min/1.73 m^2 and patients undergoing dialysis due to lack of data.

WARNINGS AND PRECAUTIONS

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

- MERAVO must not be administered with an ACE inhibitor due to the risk of angioedema. MERAVO must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with MERAVO is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of MERAVO (see sections CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, and INTERACTIONS).
- Caution is required while co-administering MERAVO with direct renin inhibitors such as aliskiren (see sections CONTRAINDICATIONS and INTERACTIONS). MERAVO must not be administered with aliskiren-containing products in patients with diabetes mellitus or renal impairment (eGFR < 60ml/min/1.73m^2) (see section CONTRAINDICATIONS).
- MERAVO should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of MERAVO (see sections DOSAGE AND ADMINISTRATION and INTERACTIONS).

Hypotension
Cases of symptomatic hypotension have been reported in patients treated with MERAVO during clinical trials. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. If hypotension persists despite such measures, the dosage of MERAVO should be reduced or the product should be temporarily discontinued (see section DOSAGE AND ADMINISTRATION). Permanent discontinuation of therapy is usually not required**.** Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with MERAVO.

Impaired renal function
As for any drug that acts on the renin-angiotensin-aldosterone system, use of MERAVO may be associated with decreased renal function. In PARADIGM-HF, associated treatment discontinuation was observed less frequently in patients receiving MERAVO (0.65%) compared to enalapril (1.28%).

In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt MERAVO in patients who develop a clinically significant decrease in renal function. Caution should be exercised when administering MERAVO in patients with severe renal impairment (see sections DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS and CLINICAL PHARMACOLOGY).

Hyperkalemia
As for any drug that acts on the renin-angiotensin-aldosterone system, use of MERAVO may be associated with an increased risk of hyperkalemia. In PARADIGM-HF, hyperkalemia resulted in treatment discontinuation in 0.26% of MERAVO treated patients compared to 0.35% of enalapril treated patients. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution when co-administered with MERAVO. If clinically significant hyperkalemia occurs, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered. Dosage reduction or interruption of MERAVO may be required. Monitoring of serum potassium is recommended especially in patients with risk factors such as severe renal impairment, diabetes mellitus, hypoaldosteronism or receiving a high potassium diet (see section DOSAGE AND ADMINISTRATION).

Angioedema
Angioedema has been reported in patients treated with MERAVO. If angioedema occurs, MERAVO should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. MERAVO must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly administered.
Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if MERAVO is used in these patients. MERAVO must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or in patients with a history of hereditary or idiopathic angioedema (see section CONTRAINDICATIONS).

Black patients may have increased susceptibility to develop angioedema.

Patients with renal artery stenosis
Similar to other drugs that affect the renin-angiotensin-aldosterone system, MERAVO 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.

ADVERSE DRUG REACTIONS

Summary of the safety profile
The safety of MERAVO in patients with chronic heart failure was evaluated in the pivotal phase 3 study PARADIGM-HF, which compared patients treated twice daily with MERAVO 200 mg (n= 4,203) or enalapril 10 mg (n= 4,229). Patients randomized to MERAVO received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3271 patients were treated for more than one year.
Discontinuation of therapy due to an AE in the double-blind period of the PARADIGM-HF trial occurred in 450 (10.71%) of MERAVO treated patients and 516 (12.20%) of patients receiving enalapril. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalemia and renal impairment.

The overall incidence of adverse drug reactions (ADRs) of MERAVO in heart failure patients was comparable to enalapril. The pattern of the ADRs is consistent with the pharmacology of MERAVO and the patients underlying conditions.

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

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

Table 1 Adverse Drug Reactions in the PARADIGM-HF, Safety Set

Adverse drug reactions	**MERAVO** 200mg twice daily (%)*	**Enalapril** 10 mg twice daily (%)*	**Frequency category**
Metabolism and nutrition disorders			
Hyperkalaemia	11.61	14.00	Very common
Hypokalaemia	3.31	2.53	Common
Nervous system disorders			
Dizziness	6.33	4.87	Common
Dizziness postural	0.57	0.28	Uncommon
Headache	2.45	2.51	Common
Syncope	2.24	2.70	Common
Ear and labyrinth disorders			
Vertigo	1.45	1.40	Common
Vascular disorders			
Hypotension	17.61	11.97	Very common
Orthostatic hypotension	1.52	0.80	Common
Respiratory, thoracic and mediastinal disorders			
Cough	8.78	12.60	Common
Gastrointestinal disorders			
Diarrhoea	4.62	4.47	Common
Nausea	2.09	2.36	Common
Skin and subcutaneous tissue disorders			
Angioedema	0.45	0.24	Uncommon
Renal and urinary disorders			
Renal impairment	10.14	11.52	Very Common
Renal failure (renal failure, acute renal failure)	4.76	5.30	Common
General disorders and administration site conditions			
Fatigue	2.97	3.05	Common
Asthenia	2.09	1.84	Common

* Safety analysis set

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

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

Table 2 Adverse Drug Reactions from spontaneous reports and literature cases (frequency not known)

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

INTERACTIONS

Anticipated interactions resulting in a contraindication

ACE inhibitors: The concomitant use of MERAVO with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE inhibitor therapy may increase the risk of angioedema. MERAVO 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 MERAVO (see sections CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).

Aliskiren: The concomitant use of MERAVO with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (eGFR < 60ml/min/1.73 m^2) (see section CONTRAINDICATIONS).

The combination of MERAVO with direct renin inhibitors such as aliskiren is not recommended. Combination of MERAVO with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) (see sections CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Anticipated interactions resulting in concomitant use not being recommended

MERAVO should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of MERAVO (see section WARNINGS AND PRECAUTIONS).

Observed interactions to be considered

Statins: *In vitro* data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. MERAVO may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of MERAVO increased the Cmax of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Caution should be exercised upon co- administration of MERAVO with statins. No clinically relevant drug-drug interaction was observed when simvastatin and MERAVO were co-administered.

Sildenafil: Addition of a 50mg single dose of sildenafil to MERAVO at steady state (400mg MERAVO once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (-5/4 mmHg, systolic/diastolic 24h-ambulatory BP) compared to administration of MERAVO alone. Therefore, caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with MERAVO.

Anticipated interactions to be considered

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

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

Lithium: The potential for a drug interaction between MERAVO and lithium has not been investigated. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use with MERAVO. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Transporters: The active metabolite of sacubitril (sacubitrilat), and valsartan are OATP1B1, OATP1B3 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of MERAVO with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) or MRP2 (e.g. ritonavir) may increase the systemic exposure to sacubitrilat or valsartan, respectively. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

Furosemide: Co-administration of MERAVO and furosemide had no effect on the pharmacokinetics of MERAVO but reduced Cmax, 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 MERAVO.

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

No significant interactions
No clinically meaningful drug-drug interaction was observed upon co-administration of MERAVO and digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol, intravenous nitroglycerin or a combination of levonorgestrel/ethinyl estradiol.
CYP 450 Interactions: In vitro metabolism studies indicate that the potential for CYP 450 - based drug interactions is low since there is limited metabolism of MERAVO via the CYP450 enzymes. MERAVO does not induce or inhibit CYP450 enzymes.

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

Females of child-bearing potential (and contraceptive measures if applicable)
Female patients of child-bearing potential should be advised about the consequences of exposure to MERAVO during pregnancy and to use contraception during treatment with MERAVO and for 1 week after their last dose.

Pregnancy
As for other drugs that also act directly on the RAAS, MERAVO must not be used during pregnancy (see section CONTRAINDICATIONS). MERAVO exerts its effects via angiotensin II antagonism. As a result, a risk to the fetus cannot be excluded. There have been reports of injury to the developing fetus (e.g. spontaneous abortion, oligohydramnios and newborn renal dysfunction), when pregnant women have taken valsartan. Patients should be advised to discontinue MERAVO as soon as pregnancies occur and to inform their physicians.

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

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

OVERDOSAGE
Limited data are available with regards to overdosage in human subjects with MERAVO. In healthy volunteers, a single dose of MERAVO 1200 mg, and 900 mg multiple doses (14 days) have been studied and were well tolerated.

Hypotension is the most likely symptom of overdosage due to the blood pressure lowering effects of MERAVO. Symptomatic treatment should be provided. MERAVO is unlikely to be removed by hemodialysis due to high protein binding.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

MERAVO exhibits the novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via sacubitrilat, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits and renal effects of MERAVO in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitrilat and the simultaneous inhibition of the deleterious effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), thereby promoting vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti- hypertrophic and anti-fibrotic effects. Sustained activation of the renin-angiotensin-aldosterone system results in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

Pharmacodynamics (PD)

The pharmacodynamic effects of MERAVO 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 MERAVO resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan. In a 21-day study in HFrEF patients, MERAVO significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. MERAVO also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, MERAVO decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. While BNP is a neprilysin substrate, NT-proBNP is not. Therefore, NT-proBNP (but not BNP) is a suitable biomarker for monitoring of heart failure patients treated with MERAVO.

In a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1,200 mg MERAVO had no effect on cardiac repolarization.

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-beta (A-beta) from the brain and cerebrospinal fluid (CSF). Administration of MERAVO 400 mg once daily for 2 weeks to healthy subjects was associated with an increase in CSF A-beta 1-38 compared to placebo; there were no changes in concentrations of CSF A-beta 1-40 and 1-42. The clinical relevance of this finding is unknown (see section NON-CLINICAL SAFETY DATA).

Pharmacokinetics (PK)

Absorption
Following oral administration, MERAVO dissociates into sacubitril, which is further metabolized to sacubitrilat, and valsartan, which reach peak plasma concentrations in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be ≥ 60% and 23%, respectively. The valsartan in MERAVO is more bioavailable than the valsartan in other marketed tablet formulations.

Following twice daily dosing of MERAVO, steady state levels of sacubitril, sacubitrilat, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, while sacubitrilat accumulates by 1.6-fold. MERAVO administration with food has no clinically significant impact on the systemic exposures of sacubitril, sacubitrilat and valsartan. Although there is a decrease in exposure to valsartan when MERAVO is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. MERAVO can therefore be administered with or without food.

Distribution
MERAVO is highly bound to plasma proteins (94% - 97%). Based on the comparison of plasma and CSF exposures, sacubitrilat does cross the blood brain barrier to a limited extent (0.28%). The average apparent volumes of distribution of valsartan and sacubitril are 75 to and 103L respectively.

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

Elimination
Following oral administration, 52 to 68% of sacubitril (primarily as sacubitrilat) and ~13% of valsartan and its metabolites are excreted in urine; 37 to 48% of sacubitril (primarily as sacubitrilat), and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, sacubitrilat, and valsartan are eliminated from plasma with a mean elimination half- life (T1/2) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Linearity/non-linearity
The pharmacokinetics of sacubitril, sacubitrilat, and valsartan are linear in the dose range tested (50 to 400 mg of MERAVO).

Special populations

Elderly patients (aged over 65 years)
The exposures of sacubitrilat and valsartan are increased in elderly subjects by 42% and 30%, respectively, compared to younger subjects. However, this is not associated with clinically relevant effects and therefore no dosage adjustment is necessary.

Pediatric patients (aged below 18 years)
MERAVO has not been studied in pediatric patients.

Impaired renal function
A correlation was observed between renal function and systemic exposure to sacubitrilat, but not to valsartan. In patients with mild (60 mL/min/1.73 m^2 ≤eGFR<90 mL/min/1.73 m^2) to moderate (30 mL/min/1.73 m^2 ≤ eGFR< 60 mL/min/1.73 m^2) renal impairment, the AUC for sacubitrilat was up to 2-fold higher. No dosage adjustment is required in patients with mild or moderate renal impairment. A 2.7-fold higher AUC for sacubitrilat was observed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2). A starting dose of 50 mg twice daily is recommended in patients with severe renal impairment. Caution is recommended when administering MERAVO to these patients due to limited data.
No studies have been performed in patients undergoing dialysis. However, sacubitrilat and valsartan are highly bound to plasma protein and, therefore, unlikely to be effectively removed by dialysis.

Impaired hepatic function
In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, sacubitrilat increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects. No dosage adjustment is recommended when administering MERAVO to patients with mild hepatic impairment (Child- Pugh A classification) including patients with biliary obstructive disorders. A starting dose of 50 mg twice daily is recommended in patients with moderate hepatic impairment (Child-Pugh B classification). MERAVO has not been studied in patients with severe hepatic impairment. Therefore, its use is not recommended in patients with severe hepatic impairment.

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

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

CLINICAL STUDIES

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind study of 8,442 patients comparing MERAVO to enalapril, both given to adult patients with chronic heart failure, NYHA class II – IV, and systolic dysfunction (left ventricular ejection fraction ≤ 40%), in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF).

Prior to study participation, patients were well treated with standard of care therapy which included ACE inhibitors/ARBs (>99%), beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (83%). The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and entered a sequential single-blind run-in period during which patients received treatment with enalapril 10 mg twice daily, followed by treatment with MERAVO 100 mg twice daily, increasing to 200 mg twice daily. Patients were then randomized to the double-blind period of the study to receive either MERAVO 200 mg or enalapril 10 mg twice daily [MERAVO (n= 4,209); enalapril (n= 4,233)].

The mean age of the population studied was 64 years of age and 19% were 75 years or older. At randomization, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV.

In the MERAVO 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).

MERAVO demonstrated clinically relevant and statistically significant superiority to enalapril, reducing the risk of cardiovascular death or heart failure hospitalizations by 20% (hazard ratio (HR): 0.80, 95% CI [0.73; 0.87], 1-sided p =0.0000002) versus enalapril. This effect was observed early and was sustained throughout the duration of the trial. The absolute risk reduction was 4.69%. A statistically significant reduction for CV death and first HF hospitalization was observed (CV death, RRR 20%, HR 0.80; 95% CI [0.71, 0.89], 1-sided p= 0.00004; and hospitalization for heart failure RRR 21%; HR 0.79; 95% CI 0.71, 0.89], 1-sided p= 0.00004); see Table 2 and Figure 1. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in MERAVO treated patients compared to enalapril treated patients (HR 0.80, p= 0.0082). Pump failure accounted for 26% of cardiovascular deaths and was reduced by 21% in MERAVO treated patients compared to enalapril treated patients (HR 0.79, p = 0.0338).

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

MERAVO also significantly reduced all-cause mortality by 16% compared with enalapril (RRR 16%, HR 0.84; 95% CI [0.76 to 0.93], 1-sided p=0.0005) (Table 2). The absolute risk reduction was 2.84%.

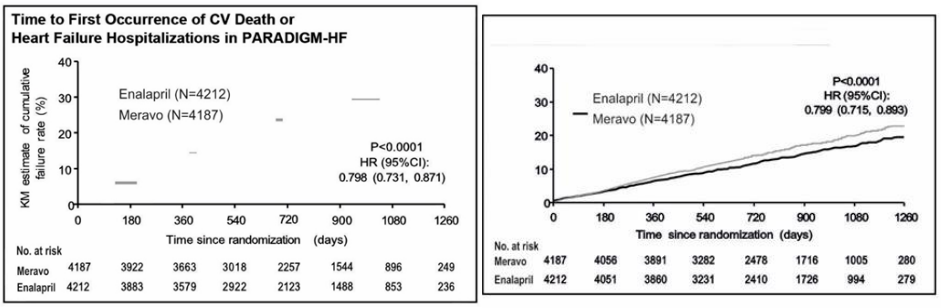
Table 3 Treatment effect for the primary composite endpoint, its components and all-cause mortality

	MERAVO N = 4187♯ n (%)	**Enalapril N = 4212♯ n (%)**	**Hazard Ratio (95% CI)**	**Relative Risk Reduction**	**p-value *****
Primary Composite Endpoint of CV Death and Heart Failure Hospitalizations*	914 (21.83)	1117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual Components of the primary composite endpoint					
CV Death **	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	0.00004
First Heart Failure Hospitalization	537 (12.83)	658 (15.62)	0.79 (0.71, 0.89)	21%	0.00004
Secondary Endpoint					
All-cause mortality	711 (16.98)	835 (19.82)	0.84 (0.76, 0.93)	16%	0.0005

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

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

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



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

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%) naive to ACE inhibitor or ARB therapy or on varying doses of ACE inhibitors or ARBs prior to study entry. Patients initiated MERAVO 50 mg twice daily, were uptitrated to 100 mg twice daily and then to the target dose of 200 mg twice daily with either a 3-week or 6-week regimen.

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

NON-CLINICAL SAFETY DATA
Non-clinical safety studies conducted with MERAVO included assessment of safety pharmacology, repeated dose toxicity genotoxicity carcinogenicity and reproductive and development toxicity MERAVO had no adverse effects on vital organ systems. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of AT_1 receptor blockade.

Carcinogenicity, mutagenesis and genetic toxicity
Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for MERAVO. The doses of sacubitril studied (high dose of 1,200 and 400 mg/kg/day in mice and rats, respectively) were about 29 and 19 times, respectively, the maximum recommended human dose (MRHD) on a mg/m^2 basis. The doses of valsartan studied (high dose of 160 and 200 mg/kg/day in mice and rats, respectively) were about 4 and 10 times, respectively, the maximum recommended human dose on a mg/m^2 basis.
Mutagenicity and clastogenicity studies conducted with MERAVO, sacubitril, and valsartan did not reveal any effects at either the gene or chromosome level.

Fertility, reproduction and development
MERAVO did not show any effects on fertility or early embryonic development in rats up to a dose of 150 mg/kg/day (≤1.0 fold and ≤0.18 fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively).

MERAVO treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥100 mg/kg/day [≤0.72-fold the MRHD on the basis of AUC] and rabbits at doses ≥ 10 mg/kg/day [2-fold and 0.03-fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively]. MERAVO is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a MERAVO dose of ≥ 10 mg/kg/day. The adverse embryo-fetal effects of MERAVO are attributed to the angiotensin receptor antagonist activity (see section FEMALES OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).

Pre- and postnatal development studies in rats conducted with sacubitril at 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 MERAVO during organogenesis, gestation and lactation may affect pup development and survival.

Other preclinical findings
The effects of MERAVO on amyloid-beta concentrations in cerebrospinal fluid (CSF) and brain tissue were assessed in young (2 to4 years old) cynomolgus monkeys treated with MERAVO (50 mg/kg/day) for 2 weeks. In this study, MERAVO had a pharmacodynamic effect on CSF A- beta clearance in cynomolgus monkeys, increasing CSF A-beta 1-40, 1-42, and 1-38 levels; there was no corresponding increase in A-beta levels in the brain. Increases in CSF A-beta 1- 40 and 1-42 were not observed in a 2 week healthy volunteer study in humans (see section CLINICAL PHARMACOLOGY). Additionally, in a toxicology study in cynomolgus monkeys treated with MERAVO at 300 mg/kg/day for 39-weeks, there was no amyloid-beta accumulation in the brain.

INCOMPATIBILITIES
Not applicable.

SHELF LIFE
36 months

STORAGE

Store at or below 30˚C. Protect from moisture.

MERAVO should not be used after the date marked "EXP" on the pack. MERAVO must be kept out of the reach and sight of children.

PRESENTATION
28 Tablets, 56 Tablets and 154 Tablets Alu-Alu Blister pack (Each blister contains 14 Tablets in 2, 4 and 11 blisters packed in a carton).

Not all pack sizes may be marketed.

INSTRUCTIONS FOR USE AND HANDLING
Not applicable.

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