For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

Rx

Sacubitril and Valsartan Tablets (24+26) 50mg

Sacubitril and Valsartan Tablets (49+51) 100mg

Sacubitril and Valsartan Tablets (97+103) 200mg

CARMADA™ 50 / 100 / 200

Qualitative and Quantitative Composition

Sacubitril and Valsartan Tablets (24+26) 50mg
Each film coated tablet contains:
Sacubitril 24 mg
Valsartan 26 mg
Colours: Titanium Dioxide IP, Ferric Oxide Red-USP-NF, Ferric Oxide Black-USP-NF

Sacubitril and Valsartan Tablets (49+51) 100mg
Each film coated tablet contains:
Sacubitril 49 mg
Valsartan 51 mg
Colours: Titanium Dioxide IP, Ferric Oxide Yellow-USP-NF, Ferric Oxide Red-USP-NF

Sacubitril and Valsartan Tablets (97+103) 200mg
Each film coated tablet contains:
Sacubitril 97 mg
Valsartan 103 mg
Colours: Titanium Dioxide IP, Ferric Oxide Red-USP-NF Ferric Oxide Black-USP-NF

Dosage Form and Strengths

Film coated tablets

Indications

Sacubitril/Valsartan tablets are 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.

These tablets are usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other Angiotensin receptor blockers (ARB).

Posology and Method of Administration
General Considerations
Sacubitril and valsartan tablets are contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to Sacubitril/Valsartan allow a washout period of 36 hours between administrations of the two drugs.

The recommended starting dose of Sacubitril/Valsartan tablets is 49mg/51mg orally twice daily.

Double the dose of Sacubitril/Valsartan tablets after 2 to 4 weeks to the target maintenance dose of 97mg/103mg twice daily, as tolerated by the patient.

Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents
In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start Sacubitril/ Valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults to follow the recommended dose escalation thereafter.

Dose Adjustment for Severe Renal Impairment
In adult patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), start Sacubitril/Valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter. No starting dose adjustment is needed for mild or moderate renal impairment.

Dose Adjustment for Hepatic Impairment
In adults with moderate hepatic impairment (Child-Pugh B classification), start Sacubitril/valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter. No starting dose adjustment is needed for mild hepatic impairment. Use in patients with severe hepatic impairment is not recommended.

Contraindications
Sacubitril/Valsartan tablets are contraindicated:
- In patients with hypersensitivity to any component.
- In patients with a history of angioedema related to previous ACE inhibitor or ARB therapy.
- With concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor.
- With concomitant use of aliskiren in patients with diabetes.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy.

Special Warnings and Precautions for Use

- **Fetal Toxicity**

Sacubitril/Valsartan tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue Sacubitril/valsartan tablets. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

- **Angioedema**

Sacubitril/Valsartan tablets may cause angioedema. If angioedema occurs, discontinue Sacubitril/Valsartan tablets immediately, provide appropriate therapy, and monitor for airway compromise. Sacubitril/Valsartan tablets 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, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

Sacubitril/Valsartan tablets have been associated with a higher rate of angioedema in Black than in non-Black patients.

Patients with a prior history of angioedema may be at increased risk of angioedema with Sacubitril/Valsartan tablets. Sacubitril/Valsartan tablets must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. Sacubitril/Valsartan should not be used in patients with hereditary angioedema.

- **Hypotension**

Sacubitril/Valsartan tablets lower blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of Sacubitril/Valsartan tablets or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue Sacubitril/valsartan tablets. Permanent discontinuation of therapy is usually not required.

- **Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with Sacubitril/valsartan tablets. 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 Sacubitril/Valsartan tablets in patients who develop a clinically significant decrease in renal function.

As with all drugs that affect the RAAS, Sacubitril/Valsartan tablets may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

- **Hyperkalemia**

Through its actions on the RAAS, hyperkalemia may occur with Sacubitril/Valsartan tablets. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of Sacubitril/Valsartan tablets may be required.

Drug Interactions

Effect of Co-administered Drugs on Sacubitril/Valsartan tablets:

Because CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, coadministration with drugs that impact CYP450 enzymes is not expected to affect the pharmacokinetics of Sacubitril/Valsartan tablets. Dedicated drug interaction studies demonstrated that coadministration of furosemide, warfarin, digoxin, carvedilol, a combination of levonorgestrel/ethinyl estradiol, amlodipine, omeprazole, hydrochlorothiazide (HCTZ), metformin, atorvastatin, and sildenafil, did not alter the systemic exposure to sacubitril, LBQ657 or valsartan.

Effect of Sacubitril/valsartan tablets on Co-administered Drugs:

In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Concomitant use of Sacubitril/Valsartan tablets with an ACE inhibitor is contraindicated because of the increased risk of angioedema.

Avoid use of Sacubitril/Valsartan tablets with an ARB, because Sacubitril/Valsartan tablets contain the angiotensin II receptor blocker Valsartan.

The concomitant use of Sacubitril/Valsartan tablets with aliskiren is contraindicated in patients with diabetes. Avoid use with aliskiren in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Potassium-Sparing Diuretics

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with Sacubitril/valsartan tablets may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

Lithium
Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with Sacubitril/valsartan tablets.

Use in Special Populations

Pregnancy
Risk Summary
Sacubitril/valsartan tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. In animal reproduction studies, Sacubitril/Valsartan tablets treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits. When pregnancy is detected, consider alternative drug treatment and discontinue Sacubitril/Valsartan tablets. However, if there is no appropriate alternative to therapy with drugs affecting the renin angiotensin system, and if the drug is considered life saving for the mother, advise a pregnant woman of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of in utero exposure to Sacubitril/Valsartan tablets for hypotension, oliguria, and hyperkalemia. In neonates with a history of in utero exposure to Sacubitril/ Valsartan tablets, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Animal Data
Sacubitril/Valsartan tablets treatment during organogenesis resulted in increased embryo-fetal lethality in rats. Sacubitril and valsartan tablets are teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits. The adverse embryo-fetal effects of Sacubitril and valsartan tablets are attributed to the angiotensin receptor antagonist activity.

Lactation
There is no information regarding the presence of Sacubitril/Valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril/ Valsartan is present in rat milk. Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with Sacubitril/ Valsartan tablets.

Paediatric Use
Safety and effectiveness have not been established in pediatric patients.

Geriatric Use
No relevant pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population.

Hepatic Impairment
No dose adjustment is required when administering Sacubitril/Valsartan tablets to patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in patients with moderate hepatic impairment (Child-Pugh B classification) is 24mg/26mg twice daily. The use of Sacubitril/Valsartan tablets in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients.

Renal Impairment
No dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) to moderate (eGFR 30 to 60 mL/min/1.73 m^2) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) is 24mg/26 mg twice daily.

Effects on Ability to Drive and Use Machines

Sacubitril/Valsartan tablets have 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.

Undesirable Effects

Clinically significant adverse reactions that appear include:

- Angioedema
- Hypotension
- Impaired Renal Function
- Hyperkalemia

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 (≥1/1000 to<1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

System Organ Class	Preferred term	Frequency category
Blood and lymphatic system disorders	Anemia	Common
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalemia	Very common
	Hypokalemia	Common
	Hypoglycemia	Common
Nervous system disorders	Dizziness	Common
	Headache	Common
	Syncope	Common
	Dizziness postural	Uncommon
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension	Very common
	Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Diarrhea	Common
	Nausea	Common
	Gastritis	Common
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Angioedema	Uncommon
Renal and urinary disorders	Renal impairment	Very common
	Renal failure (renal failure, acute renal failure)	Common
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common

Overdose

Limited data are available with regard to over dosage with Sacubitril/valsartan tablets. Hypotension is the most likely result of over dosage due to the blood pressure lowering effects of Sacubitril/valsartan tablets. Symptomatic treatment should be provided.

Sacubitril/valsartan tablets are unlikely to be removed by hemodialysis because of high protein binding.

PHARMACOLOGICAL PROPERTIES

Mechanism of action

Sacubitril/Valsartan tablets contain a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. Sacubitril/Valsartan tablets inhibit neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via valsartan. The cardiovascular and renal effects of Sacubitril/Valsartan tablets in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

Incompatibilities

None

Storage and Handling Instructions

Do not store above 30°C.
Store in the original package in order to protect from moisture.
Keep out of the sight and reach of children.

Patient Counselling Information

Pregnancy:
Advise female patients of childbearing age about the consequences of exposure to Sacubitril/valsartan during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physicians as soon as possible.

Angioedema:
Advise patients to discontinue use of their previous ACE inhibitor or ARB. Advise patients to allow a 36 hour wash-out period if switching from or to an ACE inhibitor.

Manufactured by:
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Sanofi India Ltd.
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Source:

1. Prescribing information of Sacubitril and Valsartan Tablets, MSN Laboratories Private Limited dated Apr 2023
2. US Prescribing Information of Entresto updated Feb 2021