

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SACUBITRIL AND VALSARTAN TABLETS safely and effectively. See full prescribing information for SACUBITRIL AND VALSARTAN TABLETS.

SACUBITRIL AND VALSARTAN tablets, for oral use

Initial U.S. Approval: 2015

WARNING: FETAL TOXICITY See full prescribing information for complete boxed warning. - When pregnancy is detected, discontinue sacubitril and valsartan as soon as possible. (5.1) - Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

RECENT MAJOR CHANGES

- Dosage and Administration. (2.3)

INDICATIONS AND USAGE

- Sacubitril and valsartan tablets are a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, and is indicated:
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. (1.1)
 - for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Sacubitril and valsartan tablets reduce NT-proBNP and are expected to improve cardiovascular outcomes. (1.2)

DOSAGE AND ADMINISTRATION

- The recommended starting dose for adults is 49 mg/51 mg orally twice daily. The target maintenance dose is 97 mg/103 mg orally twice daily. (2.2)
- Adjust adult doses every 2 to 4 weeks to the target maintenance dose, as tolerated by the patient. (2.2)
 - For pediatric patients, see the Full Prescribing Information for recommended dosage, titrations, preparation and administration instructions. (2.3, 2.4)
 - Reduce starting dose to half the usually recommended starting dosage for:

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY When pregnancy is detected, discontinue sacubitril and valsartan as soon as possible (5.1) Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus(5.1)

1 INDICATIONS AND USAGE

1.1 Adult Heart Failure

Sacubitril and valsartan tablets are indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical Studies (14.1)].

1.2 Pediatric Heart Failure

Sacubitril and valsartan tablets are indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Sacubitril and valsartan tablets reduce NT-proBNP and are expected to improve cardiovascular outcomes.

2 DOSAGE AND ADMINISTRATION

2.1 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 and valsartan tablets, use a washout period of 36 hours between administration of the two drugs [see Contraindications (4) and Drug Interactions (7.1)].

2.2 Adult Heart Failure

The recommended starting dose of sacubitril and valsartan tablets is 49/51 mg orally twice-daily. Double the dose of sacubitril and valsartan tablets after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient.

2.3 Pediatric Heart Failure

For the recommended dosage for pediatric patients aged 1 year and older, refer to Table 1 if using the tablets.

Take the recommended dose orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient.

Table 1: Recommended Dose and Titration for Pediatric Patients Using Tablets

Weight (kg)	Titration Step Dose (twice daily)		
	Starting	Second	Final
Less than 40 kg ^a	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
At least 40 kg, less than 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg ^b
At least 50 kg	49 mg/51 mg	72 mg/78 mg ^c	97 mg/103 mg ^c

^a Use of the oral suspension is recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan [see Dosage and Administration (2.4)].

^b Doses of 72 mg/78 mg can be achieved using three 24 mg/26 mg tablets [see Dosage Forms and Strengths (3)].

2.4 Preparation of Oral Suspension Using Tablets

Sacubitril and valsartan oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets.

Sacubitril and valsartan 800 mg/200 mL oral suspension can be prepared in a concentration of 4 mg/mL (sacubitril) and 1.96/2.04 mg/mL. Use sacubitril and valsartan 49/51 mg tablets in the preparation of the suspension.

To make an 800 mg/200 mL (4 mg/mL) oral suspension, transfer eight tablets of sacubitril and valsartan 49/51 mg film-coated tablets into a mortar. Crush the tablets into a fine powder using a pestle. Add 60 mL of Ora-Plus[®] into the mortar and triturate gently with pestle for 10 minutes, to form a uniform suspension. Add 140 mL of Ora-Sweet[®] SF into the mortar and triturate with pestle for another 10 minutes, to form a uniform suspension. Transfer the entire contents from the mortar into a clean 200 mL amber colored PET or glass bottle. Place a press-in bottle adapter and close the bottle with a child resistant cap.

The oral suspension can be stored for up to 15 days. Do not store above 25°C (77°F) and do not refrigerate. Shake before each use.

^cOra-Sweet SF[®] and Ora-Plus[®] are registered trademarks of Paddock Laboratories, Inc.

2.5 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 and valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter [see Dosage and Administration (2.2, 2.3)].

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension [see Dosage and Administration (2.3, 2.4)].

2.7 Dose Adjustment for Severe Renal Impairment

In adults and pediatric patients with severe renal impairment estimated glomerular filtration rate (eGFR less than 30 mL/min/1.73 m²), start sacubitril and valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter [see Dosage and Administration (2.2, 2.3)].

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension [see Dosage and Administration (2.3, 2.4)].

No starting dose adjustment is needed for mild or moderate renal impairment.

2.8 Dose Adjustment for Hepatic Impairment

In adults and pediatric patients with moderate hepatic impairment (Child-Pugh B classification), start sacubitril and valsartan tablets at half the usually recommended starting dose. After initiation, increase

- patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents. (2.6)
- patients with severe renal impairment. (2.7)
- patients with moderate hepatic impairment. (2.8)

DOSAGE FORMS AND STRENGTHS

- Film-coated tablets: 24/26 mg; 49/51 mg; 97/103 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to any component. (4)
- History of angioedema related to previous ACEi or ARB therapy. (4)
- Concomitant use with ACE inhibitors. (4, 7.1)
- Concomitant use with aldiskiren in patients with diabetes. (4, 7.1)

WARNINGS AND PRECAUTIONS

- Observe for signs and symptoms of angioedema and hypotension. (5.2, 5.3)
- Monitor renal function and potassium in susceptible patients. (5.4, 5.5)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact **Laurus Generics Inc.** at **1-833-334-LAURUS (1-833-352-8787)** or **FDA at 1-800-(FDA-1088)** or **www.fda.gov/medwatch**.

DRUG INTERACTIONS

- Avoid concomitant use with aldiskiren in patients with estimated glomerular filtration rate (eGFR) less than 60. (7.1)
- Potassium-sparing diuretics: May lead to increased serum potassium. (7.2)
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): May lead to increased risk of renal impairment. (7.3)
- Lithium: Increased risk of lithium toxicity. (7.4)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)
- Severe Hepatic Impairment: Use not recommended. (2.8, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2024

- Potassium-Sparing Diuretics
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
- Lithium

USE IN SPECIFIC POPULATIONS

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*Sections or subsections omitted from the full prescribing information are not listed.

the dose to follow the recommended dose escalation thereafter [see Dosage and Administration (2.2, 2.3)].

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension [see Dosage and Administration (2.3, 2.4)].

No starting dose adjustment is needed for mild hepatic impairment.

Use in patients with severe hepatic impairment is not recommended.

DOSAGE FORMS AND STRENGTHS

Sacubitril and valsartan tablets are supplied in the following strengths: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.

Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.

Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

4 CONTRAINDICATIONS

Sacubitril and valsartan is contraindicated:

- in patients with hypersensitivity to any component
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy [see Warnings and Precautions (5.2)]
- with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from to an ACE inhibitor [see Drug Interactions (7.1)]
- with concomitant use of aldiskiren in patients with diabetes [see Drug Interactions (7.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Sacubitril and valsartan 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 and valsartan. 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 [see Use in Specific Populations (8.1)].

5.2 Angioedema

Sacubitril and valsartan may cause angioedema [see Adverse Reactions (6.1)]. If angioedema occurs, discontinue sacubitril and valsartan immediately, provide appropriate therapy, and monitor for airway compromise. Sacubitril and valsartan must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1,000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

Sacubitril and valsartan has 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 and valsartan [see Adverse Reactions (6.1)]. Sacubitril and valsartan must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy [see Contraindications (4)]. Sacubitril and valsartan should not be used in patients with hereditary angioedema.

5.3 Hypotension

Sacubitril and valsartan lowers blood pressure and may cause symptomatic hypotension [see Adverse Reactions (6.1)]. 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 and valsartan 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 dose or temporarily discontinue sacubitril and valsartan. Permanent discontinuation of therapy is usually not required.

5.4 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 and valsartan [see Adverse Reactions (6.1)]. 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 and valsartan in patients who develop a clinically significant decrease in renal function [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

As with all drugs that affect the RAAS, sacubitril and valsartan 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.

5.5 Hyperkalemia

Through its actions on the RAAS, hyperkalemia may occur with sacubitril and valsartan [see Adverse Reactions (6.1)]. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoadosteronism, or a high potassium diet. Dosage reduction or interruption of sacubitril and valsartan may be required [see Dosage and Administration (2.7)].

6 ADVERSE REACTIONS

- Clinically significant adverse reactions that appear in other sections of the labeling include:
- Angioedema [see Warnings and Precautions (5.2)]

- Hypotension [see Warnings and Precautions (5.3)]
- Impaired Renal Function [see Warnings and Precautions (5.4)]
- Hyperkalemia [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 6,622 heart failure patients were treated with sacubitril and valsartan in the PARADIGM-HF (vs. enalapril) and PARAGON-HF (vs. valsartan) clinical trials. Of these, 5,085 were exposed for at least 1 year.

Adult Heart Failure

In PARADIGM-HF, patients were required to complete sequential enalapril and sacubitril and valsartan run-in periods of (median) 15 and 28 days, respectively, prior to entering the randomized double-blind period comparing sacubitril and valsartan and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the sacubitril and valsartan run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice.

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

Adverse reactions occurring at an incidence of greater than or equal to 5% in patients who were treated with sacubitril and valsartan in the double-blind period of PARADIGM-HF are shown in Table 3.

In PARADIGM-HF, the incidence of angioedema was 0.1% in both the enalapril and sacubitril and valsartan run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with sacubitril and valsartan than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with sacubitril and valsartan and 0.5% with enalapril [see Warnings and Precautions (5.2)].

Othostasis was reported in 2.1% of patients treated with sacubitril and valsartan compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with sacubitril and valsartan compared to 1.3% of patients treated with enalapril.

Table 3: Adverse Reactions Reported in greater than or equal to 5% of Patients Treated with Sacubitril and Valsartan in the Double-Blind Period of PARADIGM-HF

	Sacubitril and Valsartan (n = 4,203) %	Enalapril (n = 4,229) %
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

In PARAGON-HF, no new adverse reactions were identified.

Pediatric Heart Failure

The adverse reactions observed in pediatric patients 1 year to less than 18 years old who received treatment with sacubitril and valsartan were consistent with those observed in adult patients.

Laboratory Abnormalities

Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of greater than 20% were observed in approximately 5% of both sacubitril and valsartan- and enalapril-treated patients in the double-blind period in PARADIGM-HF. Decreases in hemoglobin/hematocrit of greater than 20% were observed in approximately 7% of sacubitril and valsartan-treated patients and 9% of valsartan-treated patients in the double-blind period in PARAGON-HF.

Serum Creatinine

During the double-blind period in PARADIGM-HF, approximately 16% of both sacubitril and valsartan- and enalapril-treated patients had increases in serum creatinine of greater than 50%. During the double-blind period in PARAGON-HF, approximately 17% of sacubitril and valsartan-treated patients and 21% of valsartan-treated patients had increases in serum creatinine of greater than 50%.

Serum Potassium

During the double-blind period of PARADIGM-HF, approximately 16% of both sacubitril and valsartan- and enalapril-treated patients had potassium concentrations greater than 5.5 mEq/L. During the double-blind period of PARAGON-HF, approximately 18% of sacubitril and valsartan-treated patients and 20% of valsartan-treated patients had potassium concentrations greater than 5.5 mEq/L.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity including rash, pruritus, and anaphylactic reaction

7 DRUG INTERACTIONS

7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System

Concomitant use of sacubitril and valsartan with an ACE inhibitor is contraindicated because of the increased risk of angioedema [see Contraindications (4)].

Avoid use of sacubitril and valsartan with an ARB, because sacubitril and valsartan contains the angiotensin II receptor blocker valsartan.

The concomitant use of sacubitril and valsartan with aldiskiren is contraindicated in patients with diabetes [see Contraindications (4)]. Avoid use with aldiskiren in patients with renal impairment (eGFR less than 60 mL/min/1.73 m²).

7.2 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 [see Warnings and Precautions (5.5)].

7.3 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 and valsartan may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

7.4 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 and valsartan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Sacubitril and valsartan 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 [see Clinical Contraindications]. 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 and valsartan treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits [see Data]. When pregnancy is detected, consider alternative drug treatment and discontinue sacubitril and valsartan. 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.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

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

