HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENTRESTO safely and effectively. See full prescribing information for ENTRESTO.

ENTRESTO® (sacubitril and valsartan) tablets, for oral use
ENTRESTO® SPRINKLE (sacubitril and valsartan) oral pellets
Initial U.S. Approval: 2015

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue ENTRESTO 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, 2.5) 4/2024

----------INDICATIONS AND USAGE----------

ENTRESTO is a combination of sacubitril, a neprilisin 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. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage for adults is 49 mg/51 mg orally twice daily. The target maintenance dose is 97 mg/103mg 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, 2.5)
- Reduce starting dose to half the usually recommended starting dosage for:
  - 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)
- Film-coated oral pellets within capsules: 6 mg/6 mg; 15 mg/16 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 aliskiren 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 Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Avoid concomitant use with aliskiren 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: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue ENTRESTO 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

ENTRESTO 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.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat *[see Clinical Studies (14.1)]*.

1.2 Pediatric Heart Failure

ENTRESTO is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

ENTRESTO is contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to ENTRESTO allow 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 ENTRESTO is 49/51 mg orally twice-daily.

Double the dose of ENTRESTO 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, or Table 2 if using the oral pellets.

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[†]	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[‡]
At least 50 kg	49 mg/51 mg	72 mg/78 mg[‡]	97 mg/103 mg

[†]Use of the oral suspension or oral pellets (see Table 2) 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, 2.5)]*.
[‡]Doses of 72 mg/78 mg can be achieved using three 24 mg/26 mg tablets *[see Dosage Forms and Strengths (3)]*.

Table 2: Recommended Dose and Titration for Pediatric Patients using ENTRESTO SPRINKLE†

Weight (kg)*	Titration Step Dose (twice daily)		
	Starting	Second	Final
Less than 13 (use oral suspension‡)	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
13 to less than 19	**12 mg/12 mg** (Two 6 mg/6 mg capsules)	**18 mg/18 mg** (Three 6 mg/6 mg capsules)	**24 mg/24 mg** (Four 6 mg/6 mg capsules)
19 to less than 26	**18 mg/18 mg** (Three 6 mg/6 mg capsules)	**24 mg/24 mg** (Four 6 mg/6 mg capsules)	**30 mg/32 mg** (Two 15 mg/16 mg capsules)
26 to less than 34	**24 mg/24 mg** (Four 6 mg/6 mg capsules)	**30 mg/32 mg** (Two 15 mg/16 mg capsules)	**45 mg/48 mg** (Three 15 mg/16 mg capsules)
34 to less than 50*	**30 mg/32 mg** (Two 15 mg/16 mg capsules)	**45 mg/48 mg** (Three 15 mg/16 mg capsules)	**60 mg/64 mg** (Four 15 mg/16 mg capsules)

† When using capsules, more than one capsule may be needed to achieve recommended doses. Oral pellets are contained within each capsule. Use the entire contents of the capsules to achieve the dose.
‡ Recommended mg/kg doses are of the combined amount of sacubitril and valsartan *[see Dosage and administration (2.4)]*.
* For patients 50 kg or more, see Table 1.

2.4 Preparation of Oral Suspension Using Tablets

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

ENTRESTO 800 mg/200 mL oral suspension can be prepared in a concentration of 4 mg/mL (sacubitril/valsartan 1.96/2.04 mg/mL). Use ENTRESTO 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 ENTRESTO 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 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.

*Ora-Sweet SF® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.

2.5 Preparation and Administration of Oral Pellets

ENTRESTO SPRINKLE are oral pellets contained within capsules. Do not swallow the capsules. Do not chew or crush the oral pellets.

ENTRESTO SPRINKLE can also be substituted in patients unable to swallow tablets.

Use the entire contents of the capsules to achieve the dose.

To administer ENTRESTO oral pellets, open the capsule and sprinkle the full content onto 1 to 2 teaspoons of soft food. Consume the food containing the oral pellets immediately after adding them. Empty capsule shells must be discarded after use and not swallowed. Do not administer ENTRESTO oral pellets via nasogastric, gastrostomy, or other enteral tubes because it may cause obstruction of enteral tubes.

2.6 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 ENTRESTO 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

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension or oral pellets *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

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 m^2), start ENTRESTO 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 or oral pellets *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

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 ENTRESTO 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 or oral pellets *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

No starting dose adjustment is needed for mild hepatic impairment.

Use in patients with severe hepatic impairment is not recommended.

3 DOSAGE FORMS AND STRENGTHS

ENTRESTO film-coated tablets are supplied as unscored, ovaloid tablets in the following strengths:

- ENTRESTO 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white and debossed with “NVR” on one side and “LZ” on the other side.
- ENTRESTO 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow and debossed with “NVR” on one side and “L1” on the other side.
- ENTRESTO 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink and debossed with “NVR” on one side and “L11” on the other side.

ENTRESTO SPRINKLE film-coated oral pellets are contained in a hard capsule in the following strengths:

- ENTRESTO SPRINKLE 6/6 mg, (sacubitril 6 mg and valsartan 6 mg) consists of a white colored cap with “04” and a transparent body with “NVR” and both parts with arrows.
- ENTRESTO SPRINKLE 15/16 mg, (sacubitril 15 mg and valsartan 16 mg) consists of a yellow colored cap with “10” and a transparent body with “NVR” and both parts with arrows.

4 CONTRAINDICATIONS

ENTRESTO 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 or to an ACE inhibitor *[see Drug Interactions (7.1)]*
- with concomitant use of aliskiren in patients with diabetes *[see Drug Interactions (7.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

ENTRESTO 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

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

ENTRESTO may cause angioedema *[see Adverse Reactions (6.1)]*. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO 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.

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

5.3 Hypotension

ENTRESTO 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 ENTRESTO 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 ENTRESTO. 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 ENTRESTO *[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 ENTRESTO 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, ENTRESTO 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 ENTRESTO *[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, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of ENTRESTO 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)]*

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