Indications and Usage
Entresto 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. Entresto is usually administered in conjunction with other heart failure therapies, in place of an angiotensin-converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).

Mechanism of Action
Entresto contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. Entresto inhibits 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 Entresto 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.

Dosage and Administration
Entresto is contraindicated with concomitant use of an ACE inhibitor. If switching from an ACE inhibitor to Entresto allow a washout period of 36 hours between administration of the two drugs. The recommended starting dose of Entresto is 49/51 mg 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.

Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents
A starting dose of 24/26 mg twice-daily is recommended for patients not currently taking an ACE inhibitor or an ARB and for patients previously taking low doses of these agents. Double the dose of Entresto every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient.

Dose Adjustment for Severe Renal Impairment
A starting dose of 24/26 mg twice-daily is recommended for patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2). Double the dose of Entresto every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient. No starting dose adjustment is needed for mild or moderate renal impairment.

Dose Adjustment for Hepatic Impairment
A starting dose of 24/26 mg twice-daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification). Double the dose of Entresto every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient. No starting dose adjustment is needed for mild hepatic impairment. Use in patients with severe hepatic impairment is not recommended.

Efficacy
Dosing in clinical trials was based on the total amount of both components of Entresto, i.e., 24/26 mg, 49/51 mg and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.

The efficacy and safety of Entresto was evaluated in PARADIGM-HF, a multinational, randomized, double-blind trial comparing Entresto and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤ 40%).

- Patients had to have been on an ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure of < 100 mmHg at screening were excluded.
- The primary objective of PARADIGM-HF was to determine whether Entresto, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF).
- After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by Entresto 100 mg twice-daily, increasing to 200 mg twice daily. Patients who successfully completed the sequential run-in periods were randomized to receive either Entresto 200 mg (N=4,209) twice-daily or enalapril 10 mg (N=4,233) twice-daily.
- The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.
- The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years and 78% were male. At randomization, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV. The mean left ventricular ejection fraction was 29%. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR < 60 mL/min/1.73m², and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) (15%).
- PARADIGM-HF demonstrated that Entresto, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril), in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR]: 0.80, 95% confidence interval [CI]: 0.73, 0.87, p <0.0001. The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization. Sudden death accounted for 45% of cardiovascular deaths, followed by pump failure, which accounted for 26%.
- Entresto also improved overall survival (HR 0.84; 95% CI [0.78, 0.93], p = 0.0009). This finding was driven entirely by a lower incidence of cardiovascular mortality on Entresto.
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.
- 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.

Warnings and Precautions
- **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 morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue Entresto. 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:** Entresto may cause angioedema. In the double-blind period of PARADIGM-HF, 0.5% of patients treated with Entresto and 0.2% of patients treated with enalapril had angioedema. 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. Entresto should not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy.

- **Hypotension:** Entresto lowers 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. In the double-blind period of PARADIGM-HF, 18% of patients treated with Entresto and 12% of patients treated with enalapril reported hypotension as an adverse event, with hypotension reported as a serious adverse event in approximately 1.5% of patients in both treatment arms. 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.

- **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. In the double-blind period of PARADIGM-HF, 5% of patients in both the Entresto and enalapril groups reported renal failure as an adverse event. 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. 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.

- **Hyperkalemia:** Through its actions on the RAAS, hyperkalemia may occur with Entresto. In the double-blind period of PARADIGM-HF, 12% of patients treated with Entresto and 14% of patients treated with enalapril reported hyperkalemia as an adverse event. 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.

Please see accompanying full Entresto Prescribing Information.