ENTRESTO® 50mg film-coated tablets — Local license number: 026670
ENTRESTO® 100mg film-coated tablets — Local license number: 026672
ENTRESTO® 200mg film-coated tablets — Local license number: 026671

PRESCRIPTION DRUG

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 Heart Failure

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.

Description: ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

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)]*.

The recommended starting dose of ENTRESTO is 100 mg twice-daily.

Double the dose of ENTRESTO after 2 to 4 weeks to the target maintenance dose of 200 mg twice daily, as tolerated by the patient.

2.2 Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents

A starting dose of 50 mg twice-daily is recommended for patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (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 200 mg twice daily, as tolerated by the patient.

2.3 Dose Adjustment for Severe Renal Impairment

A starting dose of 50 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 200 mg twice daily, as tolerated by the patient.

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

2.4 Dose Adjustment for Hepatic Impairment

A starting dose of 50 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 200 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.

3 DOSAGE FORMS AND STRENGTHS

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

ENTRESTO 50 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 100 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 200 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink and debossed with "NVR" on one side and "L11" on the other side.

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)]*
- Hereditary angioedema
- 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 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 *[see Use in Specific Populations (8.1)]*.

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

5.3 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 *[see Adverse Reactions (6.1)]*, 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.

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. 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 *[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 (11.3)]*.

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. 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 *[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 (2.1)]*.

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.

In the PARADIGM-HF trial, subjects were required to complete sequential enalapril and ENTRESTO run-in periods of (median) 15 and 29 days, respectively, prior to entering the randomized double-blind period comparing ENTRESTO 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 ENTRESTO 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 ENTRESTO and 4,229 treated with enalapril. In PARADIGM-HF, patients randomized to ENTRESTO 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 ENTRESTO treated patients and 516 (12.2%) of patients receiving enalapril.

Adverse reactions occurring at an incidence of ≥5% in patients who were treated with ENTRESTO in the double-blind period are shown in Table 1.

Table 1: Adverse Reactions Reported in ≥5% of Patients Treated with ENTRESTO in the Double-Blind Period

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

Orthostasis was reported in 2.1% of patients treated with ENTRESTO 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 ENTRESTO compared to 1.3% of patients treated with enalapril.

Laboratory Abnormalities

Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of >20% were observed in approximately 5% of both ENTRESTO- and enalapril-treated patients in the double-blind period in PARADIGM-HF.

Serum Creatinine

Increases in serum creatinine of >50% were observed in 1.4% of patients in the enalapril run-in period and 2.2% of patients in the ENTRESTO run-in period. During the double-blind period, approximately 16% of both ENTRESTO- and enalapril-treated patients had increases in serum creatinine of >50%.

Serum Potassium

Potassium concentrations >5.5 mEq/L were observed in approximately 4% of patients in both the enalapril and ENTRESTO run-in periods. During the double-blind period, approximately 16% of both ENTRESTO- and enalapril-treated patients had potassium concentrations >5.5 mEq/L.

6.2 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 Entresto 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 1 Adverse Drug Reactions from spontaneous reports and literature cases (frequency not known)

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

7 DRUG INTERACTIONS

7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System

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

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

The concomitant use of ENTRESTO with aliskiren is contraindicated in patients with diabetes *[see Contraindications (4)]*. Avoid use with aliskiren in patients with renal impairment (eGFR <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 ENTRESTO 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 ENTRESTO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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. 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, ENTRESTO 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 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.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, 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, 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 ENTRESTO for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to ENTRESTO, 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.

Data

Animal Data

ENTRESTO treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥ 49 mg sacubitril/51 mg valsartan/kg/day (≤ 0.14 [sacubitrilat, the active metabolite] and 1.5 [valsartan]-fold the maximum recommended human dose [MRHD] of 97/103 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses ≥ 5 mg sacubitril/5 mg valsartan/kg/day (4-fold and 0.06-fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively). ENTRESTO is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at an ENTRESTO dose of ≥ 5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo-fetal effects of ENTRESTO are attributed to the angiotensin receptor antagonist activity.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (4.5-fold the MRHD on the basis of sacubitrilat 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 ENTRESTO during organogenesis, gestation and lactation may affect pup development and survival.

8.2 Lactation

Risk Summary

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 ENTRESTO.

Data

Following an oral dose (15 mg sacubitril/15 mg valsartan/kg) of [^{14}C] ENTRESTO to lactating rats, transfer of sacubitrilat into milk was observed. After a single oral administration of 3 mg/kg [^{14}C] valsartan to lactating rats, transfer of valsartan into milk was observed.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No relevant pharmacokinetic differences have been observed in elderly (≥65 years) or very elderly (≥75 years) patients compared to the overall population *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dose adjustment is required when administering ENTRESTO 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 24/26 mg twice daily. The use of ENTRESTO in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.7 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 24/26 mg twice daily *[see Dosage and Administration (2.3), Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

9 OVERDOSAGE

Limited data are available with regard to overdosage in human subjects with ENTRESTO. In healthy volunteers, a single dose of ENTRESTO 583 mg sacubitril/617 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated.

Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of ENTRESTO. Symptomatic treatment should be provided.

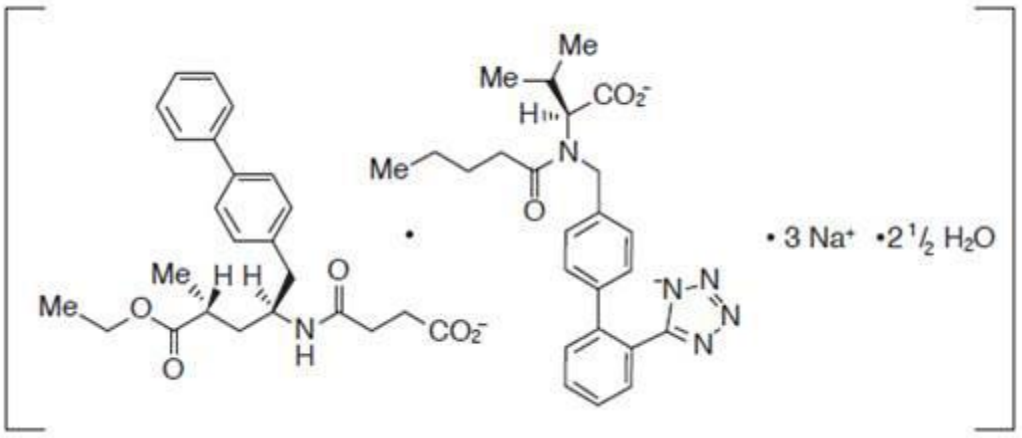
ENTRESTO is unlikely to be removed by hemodialysis because of high protein binding.

10 DESCRIPTION

ENTRESTO (sacubitril and valsartan) is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker.

ENTRESTO contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to sacubitrilat) and valsartan. The complex is chemically described as Octadecasodiumhexakis(4-{[(1S,3R)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate)hexakis(N-pentanoyl-N-{[2´-(1H-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15).

Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3$ 2.5 H_2O. Its molecular mass is 957.99 and its schematic structural formula is:



ENTRESTO is available as film-coated tablets for oral administration, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan. The tablet inactive ingredients are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, and iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172).

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

ENTRESTO contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. ENTRESTO inhibits neprilysin (neutral endopeptidase; NEP) via sacubitrilat, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT_1) 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 sacubitrilat, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT_1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

11.2 Pharmacodynamics

The pharmacodynamic effects of ENTRESTO 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 renin-angiotensin system blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of ENTRESTO 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, ENTRESTO significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. ENTRESTO also blocked the AT_1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, ENTRESTO decreased plasma NT-proBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril.

QT Prolongation: In a thorough QTc clinical study in healthy male subjects, single doses of ENTRESTO 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan had no effect on cardiac repolarization.

Amyloid-β: Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of ENTRESTO 194 mg sacubitril/206 mg valsartan 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 $A\beta_{1-40}$ or CSF $A\beta_{1-42}$. The clinical relevance of this finding is unknown *[see Nonclinical Toxicology (12)]*.

Blood Pressure: Addition of a 50 mg single dose of sildenafil to ENTRESTO at steady state (194 mg sacubitril/206 mg valsartan mg once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (~5/4 mmHg, systolic/diastolic BP) compared to administration of ENTRESTO alone.

Co-administration of ENTRESTO did not significantly alter the BP effect of intravenous nitroglycerin.

11.3 Pharmacokinetics

Absorption

Following oral administration, ENTRESTO dissociates into sacubitril and valsartan. Sacubitril is further metabolized to sacubitrilat. The peak plasma concentrations of sacubitril, sacubitrilat, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be ≥ 60%. The valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.

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

Distribution

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

Metabolism

Sacubitril is readily converted to sacubitrilat by esterases; sacubitrilat is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (< 10%).

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 ($T_{1/2}$) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.

Linearity/Nonlinearity

The pharmacokinetics of sacubitril, sacubitrilat, and valsartan were linear over an ENTRESTO dose range of 24 mg sacubitril/26 mg valsartan to 194 mg sacubitril/206 mg valsartan.

Drug Interactions:

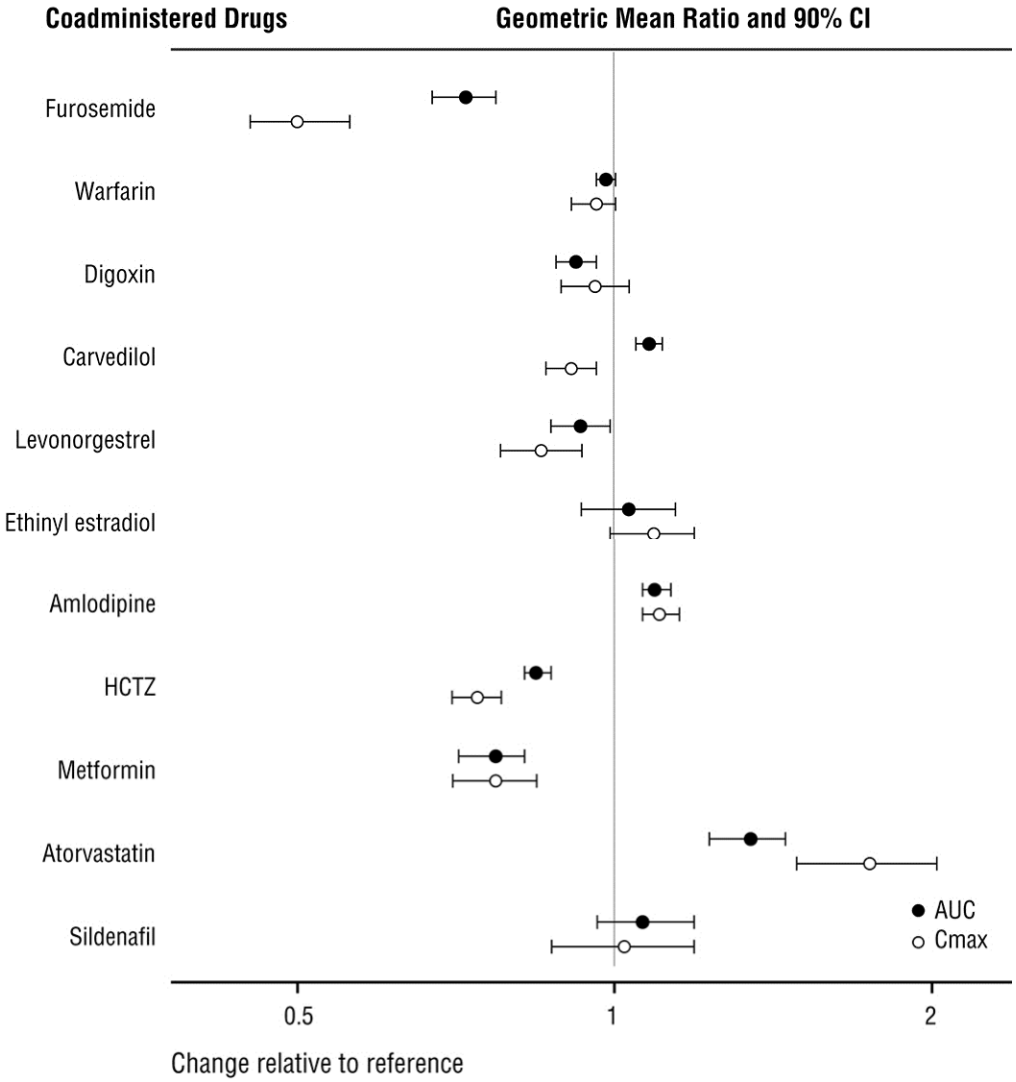
Effect of co-administered drugs on ENTRESTO:

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 ENTRESTO. 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, sacubitrilat or valsartan.

Effect of ENTRESTO on co-administered drugs:

In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. The effects of ENTRESTO on the pharmacokinetics of coadministered drugs are summarized in Figure 1. Co-administration of Entresto increased the C_{max} of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Caution should be exercised when co-administering Entresto with statins. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were coadministered.

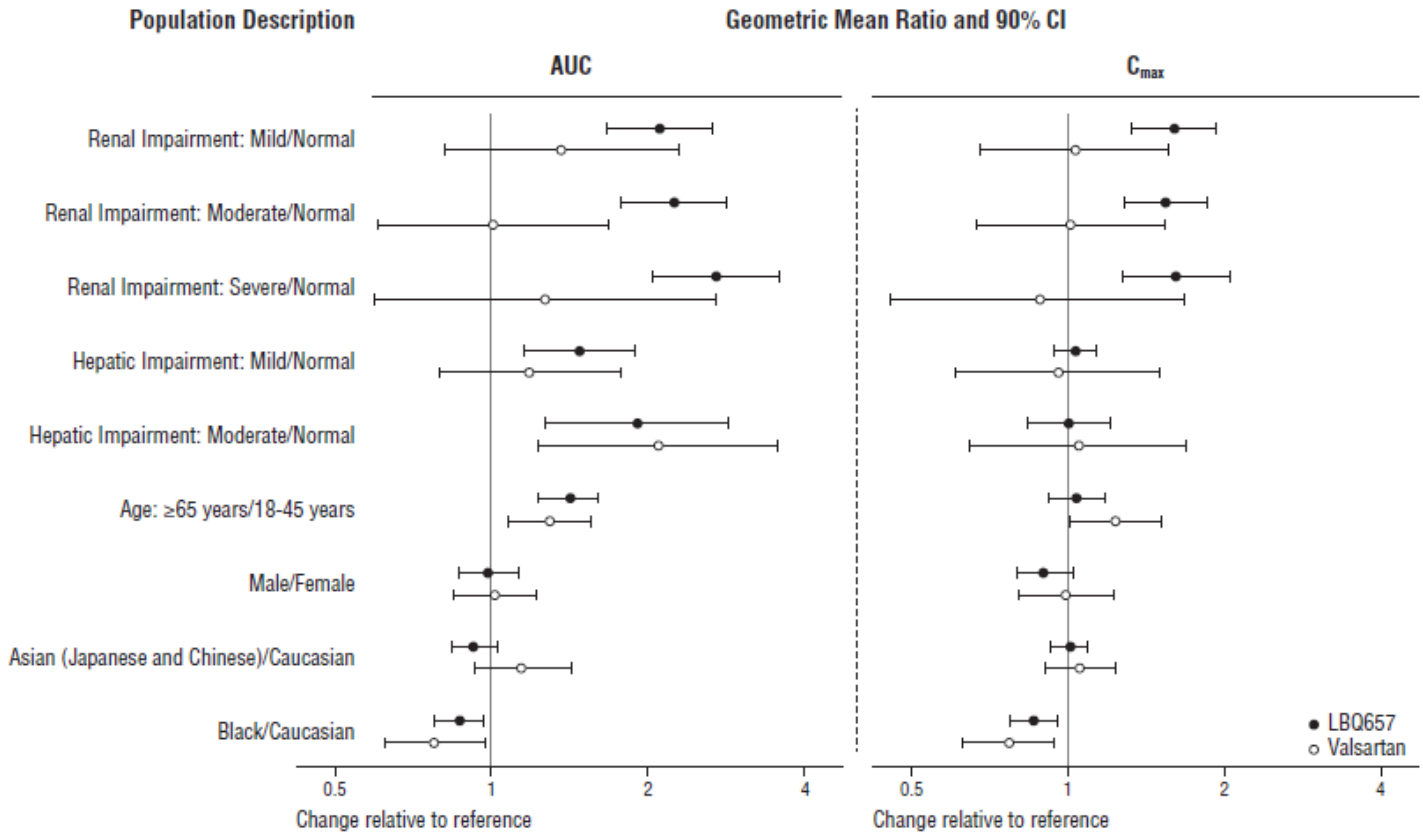
Figure 1: Effect of ENTRESTO on Pharmacokinetics of Coadministered Drugs



Specific Populations

Effect of specific populations on the pharmacokinetics of sacubitrilat and valsartan are shown in Figure 2.

Figure 2: Pharmacokinetics of ENTRESTO in Specific Populations



Note: Child-Pugh Classification was used for hepatic impairment.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for ENTRESTO. The sacubitrilat C_{max} at the high dose (HD) of 1200 mg/kg/day in male and female mice was, respectively, 14 and 16 times that in humans at the MRHD. The sacubitrilat C_{max} in male and female rats at the HD of 400 mg/kg/day was, respectively, 1.7 and 3.5 times that at the MRHD. 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 MRHD on a mg/m^2 basis.

Mutagenicity and clastogenicity studies conducted with ENTRESTO, sacubitril, and valsartan did not reveal any effects at either the gene or chromosome level.

Impairment of Fertility

ENTRESTO did not show any effects on fertility in rats up to a dose of 73 mg sacubitril/77 mg valsartan/kg/day (≤1.0-fold and ≤ 0.18-fold the MRHD on the basis of the AUCs of valsartan and sacubitrilat, respectively).

12.2 Animal Toxicology and/or Pharmacology

The effects of ENTRESTO on amyloid-β concentrations in CSF and brain tissue were assessed in young (2 to 4 years old) cynomolgus monkeys treated with ENTRESTO (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks. In this study, ENTRESTO affected CSF Aβ clearance, increasing CSF Aβ 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in Aβ levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with ENTRESTO at 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no amyloid-β accumulation in the brain.

13 CLINICAL STUDIES

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.

PARADIGM-HF

PARADIGM-HF was 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/1.73m^2, 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; see Table 2 and Figure 3. 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 [0.76, 0.93], p = 0.0009) (Table 2). This finding was driven entirely by a lower incidence of cardiovascular mortality on ENTRESTO.

Table 3: Treatment Effect for the Primary Composite Endpoint, its Components, and All-cause Mortality

	ENTRESTO N=4,187 n (%)	**Enalapril N=4,212 n (%)**	**Hazard Ratio (95% CI)**	***p*-value**
Primary composite endpoint of cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	<0.0001
Cardiovascular death as first event	377 (9.0)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events: *				
Cardiovascular death**	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76, 0.93)	0.0009

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity

**Includes subjects who had heart failure hospitalization prior to death

The Kaplan-Meier curves presented below (Figure 3) show time to first occurrence of the primary composite endpoint (3A), and time to occurrence of cardiovascular death at any time (3B) and first heart failure hospitalization (3C).

Figure 3: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure A

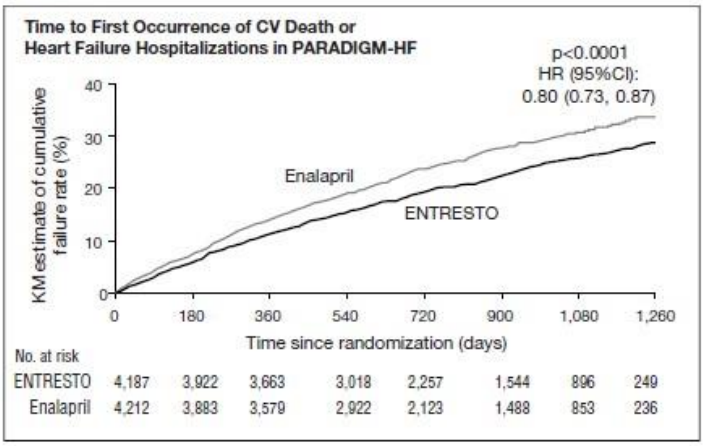


Figure B

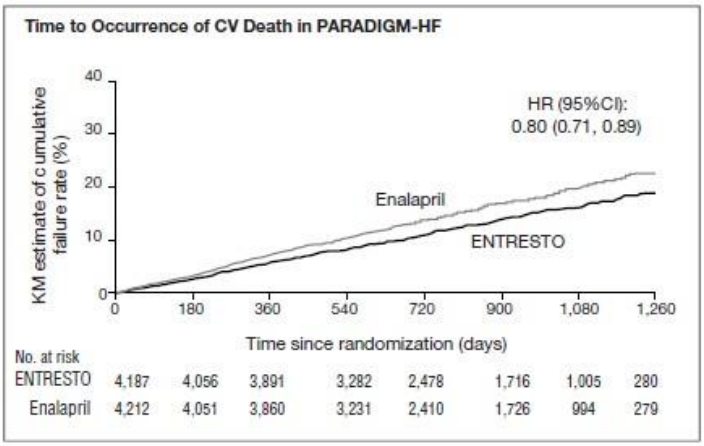
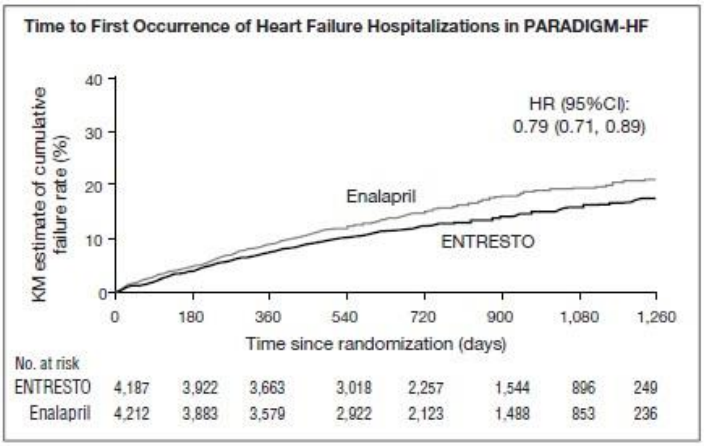


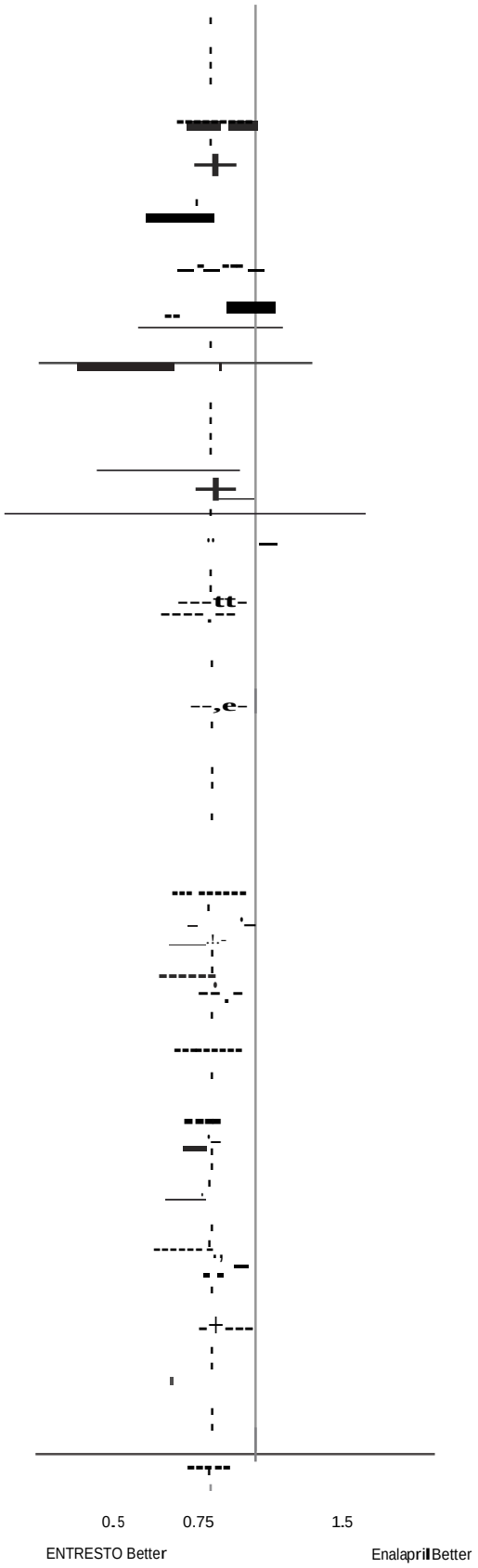
Figure C



A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. The results of the primary composite endpoint were consistent across the subgroups examined (Figure 4).

Figure 4: Primary Composite Endpoint (CV Death or HF Hospitalization)- Subgroup Analysis

Subgroup	Percentage of total population (%)	ENTRESTO n/N (%)	Enalapril n/N (%)
Overall	100	914/4,187 (21.8)	1,117/4,212 (26.5)
Age (years)			
<57	24.3	222/1,043 (21.3)	248/ 994 (24.9)
57- <64	22.7	182/ 917 (19.8)	263/ 992 (26.5)
64- <72	25.8	229/1,084 (21.1)	273/1,081 (25.3)
72	27.2	281/1,143 (24.6)	333/1,145 (29.1)
Gender			
Male	78.2	756/3,308 (22.9)	902/3,259 (27.7)
Female	21.8	158/ 879 (18.0)	215/ 953 (22.6)
Weight (kg)			
<67.5	25.0	221/1,037 (21.3)	269/1,061 (25.4)
67.5- <79	24.8	241/1,041 (23.2)	287/1,038 (27.6)
79- <91.7	25.2	231/1,048 (22.0)	283/1,069 (26.5)
91.7	25.1	221/1,060 (20.8)	278/1,044 (26.6)
Race			
Caucasian	66.0	598/2,763 (21.6)	717/2,781 (25.8)
Black	5.1	58/ 213 (27.2)	72/ 215 (33.5)
Asian	18.0	179/ 759 (23.6)	204/ 750 (27.2)
Native American	2.0	15/ 84 (17.9)	22/ 88 (25.0)
Other	8.9	64/ 368 (17.4)	102/ 378 (27.0)
Region			
US	5.2	58/ 225 (25.8)	77/ 209 (36.8)
Outside-US	94.8	856/3,962 (21.6)	1,040/4,003 (26.0)
NYHA Class			
NYHA class II	70.5	578/2,998 (19.3)	742/2,921 (25.4)
NYHA class III	24.0	292/ 969 (30.1)	329/1,049 (31.4)
NYHA class IV	0.7	10/ 33 (30.3)	11/ 27 (40.7)
Estimated GFR (mlJmin/1.73m')			
<54	24.7	280/1,021 (27.4)	344/1,054 (32.6)
54- <66	24.0	218/1,018 (21.4)	279/1,000 (27.9)
66- <79	24.9	205/1,037 (19.8)	238/1,054 (22.6)
79	26.4	211/1,111 (19.0)	256/1'104 (23.2)
Diabetes			
No	65.4	519/2,736 (19.0)	661/2,756 (24.0)
Yes	34.6	395/1,451 (27.2)	456/1,456 (31.3)
Systolic blood pressure (mmHg)			
<110	20.8	208/ 834 (24.9)	249/ 913 (27.3)
110 - <120	23.0	223/ 990 (22.5)	249/ 941 (26.5)
120- <130	24.5	202/1,041 (19.4)	264/1,018 (25.9)
130	31.7	281/1,322 (21.3)	355/1,340 (26.5)
Ejection fraction (%)			
<25	19.4	215/ 784 (27.4)	271/ 849 (31.9)
25- <30	20.8	191/ 861 (22.2)	255/ 885 (28.8)
30- <34	28.5	243/1,229 (19.8)	281/1'162 (24.2)
34	31.3	265/1,313 (20.2)	310/1,315 (23.6)
Atrial fibrillation			
No	63.2	552/2,670 (20.7)	637/2,638 (24.1)
Yes	36.8	362/1,517 (23.9)	480/1,574 (30.5)
NT-proBNP			
≤Median	49.9	299/2,079 (14.4)	403/2,116 (19.0)
>Median	49.9	614/2,103 (29.2)	711/2,087 (34.1)
Hypertension			
No	29.3	245/1,218 (20.1)	303/1,241 (24.4)
Yes	70.7	669/2,969 (22.5)	814/2,971 (27.4)
Prior use of ACE inhibitor			
No	22.2	221/ 921 (24.0)	246/ 946 (26.0)
Yes	77.8	693/3,266 (21.2)	871/3,266 (26.7)
Prior use of ARB			
No	77.5	691/3,258 (21.2)	866/3,249 (26.7)
Yes	22.5	223/ 929 (24.0)	251/ 963 (26.1)
Prior use of aldosterone antagonist			
No	44.4	399/1,916 (20.8)	494/1,812 (27.3)
Yes	55.6	515/2,271 (22.7)	623/2,400 (26.0)
Prior hosptalization for heart failure			
No	37.2	262/1,580 (16.6)	348/1,545 (22.5)
Yes	62.8	652/2,607 (25.0)	769/2,667 (28.8)
Time since diagnosis of heart failure			
≤1 year	30.0	202/1,275 (15.8)	240/1,248 (19.2)
>1-5 years	38.5	392/1,621 (24.2)	447/1,611 (27.7)
>5 years	31.5	320/1,291 (24.8)	430/1,353 (31.8)
Cause of heart failure			
Non-ischemic	40.0	339/1,681 (20.2)	420/1,682 (25.0)
Ischemic	60.0	575/2,506 (22.9)	697/2,530 (27.5)
Any ICD (including CRT-D)			
No	85.2	761/3,564 (21.4)	942/3,592 (26.2)
Yes	14.8	153/ 623 (24.6)	175/ 620 (28.2)



Note: The figure above presents effects in various subgroups, *all* of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

14 STORAGE AND HANDLING

ENTRESTO (sacubitril/valsartan) is available as unscored, ovaloid, biconvex, film-coated tablets, with dosage strength of 50 mg, 100mg or 200mg. All strengths are packaged in bottles and unit dose blister packages.

Store below 30℃. Protect from moisture. Store in the original package. Keep out of reach of children.

Manufacturing Site

Manufacturing site: Novartis Farma S.P.A.
Address: Via Provinciale Schito 131, 80058 Torre, Annunziata, Italy
Pharmaceutical company: Novartis (Taiwan) Co., Ltd.
Address: 11/F, No. 99 Sec. 2 Jen-Ai Road, Taipei

US-PI: 7 Jul 2015
IPL: 10 Jul 2017
TWI-241017