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Regulatory Affairs

ENTRESTO®
(sacubitril/valsartan)

50 mg, 100 mg, 200 mg Film-coated tablets

International Package Leaflet

Effective date:	13-Jul-2023
Safety Label Change Tracking Number:	N/A
Document status:	Final

ENTRESTO®

Entresto® 50 mg film-coated tablets (sacubitril/valsartan).

Entresto® 100 mg film-coated tablets (sacubitril/valsartan).

Entresto® 200 mg film-coated tablets (sacubitril/ valsartan).

1. DESCRIPTION AND COMPOSITION

Pharmaceutical form

Film-coated tablets.

50 mg: Violet white ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “LZ” on the other side.

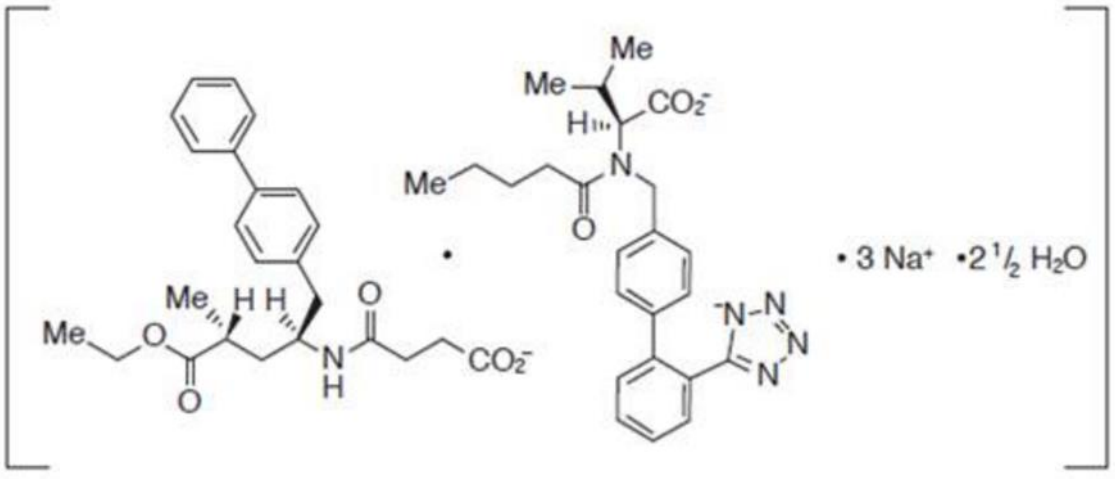
100 mg: Pale yellow ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L1” on the other side.

200 mg: Light pink ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L11” on the other side.

Active substances

sacubitril/valsartan

Entresto® contains a crystalline salt complex of the anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5 respectively. The empirical formula of the complex (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:



Following oral administration, the complex dissociates into sacubitril (which is further metabolized to sacubitrilat) and valsartan.

Entresto film coated tablets contains 50 mg (sacubitril/valsartan).*

Entresto film coated tablets contains 100 mg (sacubitril/valsartan).*

Entresto film coated tablets contains 200 mg (sacubitril/valsartan).*

* Certain dosage strengths may not be available in all countries.

Excipients

microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc and colloidal silicon dioxide

Excipients of film coating:

hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, iron oxide red (E 172)

For 50 and 200 mg: iron oxide black (E 172). For 100mg: iron oxide yellow (E 172).

2. INDICATIONS

Heart failure- Adult

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.

Clinical judgment should be used in deciding whom to treat as LVEF is a variable measure.

Entresto is administered in place of an ACE inhibitor or ARB.

Heart Failure – Pediatric

Entresto is indicated in children and adolescents aged one year or older for treatment of chronic heart failure with left ventricular systolic dysfunction. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes.

Hypertension

Entresto is indicated for the treatment of essential hypertension in adult patients.

Because of the risk of excessive decrease in blood pressure etc., in principle, Entresto should not be used as a first-line drug for the treatment of hypertension.

3. DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General considerations

Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, Entresto must not be started until 36 hours after discontinuing ACE inhibitor therapy (see section CONTRAINDICATIONS).
Entresto should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Entresto (see section WARNINGS AND PRECAUTIONS and section INTERACTIONS).
If patients experience tolerability issues (symptomatic hypotension, hyperkalemia, renal dysfunction), consideration should be given to adjustment of concomitant medications, or to temporary down–titration of Entresto.

Heart Failure - Adult

The target dose of Entresto is 200 mg twice daily.
The recommended starting dose of Entresto is 100 mg twice daily. A starting dose of 50 mg twice daily is recommended for patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and should be considered for patients previously taking low doses of these agents (see section CLINICAL STUDIES).

The dose of Entresto should be doubled every 2-4 weeks to the target dose of 200 mg twice daily, as tolerated by the patient.

Heart Failure - Pediatric

Table 4-1 shows the recommended dose for pediatric patients. The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient.

Entresto film-coated tablets are not suitable for children weighing less than 40 kg.

Table 4-1 Recommended dose titration

Patient weight	Titration step dose (twice daily)			
	Half the starting dose*	Starting dose	Second dose	Target dose
Pediatric patients less than 40 kg	0.8 mg/kg#	1.6 mg/kg#	2.3 mg/kg#	3.1 mg/kg#
Pediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg#	50 mg	100 mg	150 mg
Pediatric patients at least 50 kg	50 mg	100 mg	150 mg	200 mg

* Half the starting dose is recommended in patients who have not been taking an ACE inhibitor or an ARB or have been taking low doses of these medicinal products, patients who have severe renal impairment (Estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73 m^2) and patients who have moderate hepatic impairment (see special populations).

0.8 mg/kg, 1.6 mg/kg, 2.3 mg/kg and 3.1 mg/kg refer to the combined amount of sacubitril and valsartan and are to be given using film-coated granules.

In patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, half of the starting dose is recommended. After initiation, the dose should be increased following the recommended dose titration in Table 4-1 and adjusted every 3-4 weeks.

Essential hypertension

The recommended starting dose of Entresto is 200 mg once daily. In patients whose blood pressure could not be adequately controlled with Entresto 200 mg once daily, the dose can be increased to 400 mg once daily. In hypertensive patients with heart failure, the heart failure dosing is recommended. Entresto may be used alone or in combination with other antihypertensive agents except angiotensin-converting enzyme (ACE) inhibitors (see section CONTRAINDICATIONS) and angiotensin II receptor blockers (ARBs) (see section WARNINGS AND PRECAUTIONS)

Special populations

Renal impairment

In adult and pediatric patients with heart failure and with severe renal impairment (eGFR <30 mL/min/1.73 m^2), half of the starting dose is recommended. Caution is recommended when using Entresto in these patients due to limited data (see section CLINICAL PHARMACOLOGY). After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks.

Safety and efficacy of Entresto in patients with essential hypertension and with severe renal impairment (eGFR <30 mL/min/1.73 m^2) have not been established (see section Clinical pharmacology).

No dose adjustment is required in patients with mild (eGFR 60-90 mL/min/1.73 m^2) to moderate (eGFR 30-60 mL/min/1.73 m^2) renal impairment.

Hepatic impairment

In adult and pediatric patients with heart failure and with moderate hepatic impairment (Child-Pugh B classification), half of the starting dose is recommended. After initiation, the dose should be increased following the recommended dose titration every 2-4 weeks.
A starting dose of 100 mg once daily is recommended for essential hypertensive patients with moderate hepatic impairment (Child-Pugh B classification).

No dose adjustment is required when administering Entresto to patients with mild hepatic impairment (Child-Pugh A classification).

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification). Therefore use of Entresto in these patients is not recommended (see section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years of age)

The safety and efficacy of Entresto in pediatric heart failure patients aged below 1 year has not been established. Current available data are described in section 11 (CLINICAL STUDIES) but no recommendation on dosing can be made.
The safety and efficacy of Entresto in pediatric hypertension patients aged below 18 years has not been established.

Geriatric patients (65 years of age and above)

No dosage adjustment is required in patients 65 years of age and above.

Method of administration

For oral use. Entresto may be administered with or without food (see section CLINICAL PHARMACOLOGY).

4. CONTRAINDICATIONS

- Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients.
- Concomitant use with ACE inhibitors (see section WARNINGS AND PRECAUTIONS, DOSAGE REGIMEN AND ADMINISTRATION, and INTERACTIONS). Entresto must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary angioedema
- Concomitant use with aliskiren in patients with Type 2 diabetes (see section

WARNINGS AND PRECAUTIONS and INTERACTIONS).

- Pregnancy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

5. WARNINGS AND PRECAUTIONS

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

- Entresto must not be administered with an ACE inhibitor due to the risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto (see section CONTRAINDICATIONS, DOSAGE REGIMEN AND ADMINISTRATION, and INTERACTIONS).
- Caution is required while co-administering Entresto with direct renin inhibitors such as aliskiren (see section CONTRAINDICATIONS and INTERACTIONS). Entresto must not be administered with aliskiren in patients with Type 2 diabetes (see section CONTRAINDICATIONS).
- Entresto should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Entresto (see section DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

Hypotension

Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical trials. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. If hypotension persists despite such measures, the dosage of Entresto should be reduced or the product should be temporarily discontinued (see section DOSAGE REGIMEN AND ADMINISTRATION). Permanent discontinuation of therapy is usually not required**.** Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with Entresto.

Renal impairment

As for any drug that acts on the renin-angiotensin-aldosterone system, use of Entresto may be associated with decreased renal function. In PARADIGM-HF, the incidence of clinically relevant renal impairment was low and associated treatment discontinuation was observed less frequently in patients receiving Entresto (0.65%) compared to enalapril (1.28%). Down titration of Entresto should be considered in patients who develop a clinically significant decrease in renal function. Caution should be exercised when administering Entresto in patients with severe renal impairment (see sections DOSAGE REGIMEN AND ADMINISTRATION, and CLINICAL PHARMACOLOGY).

Hyperkalemia

As for any drug that acts on the renin-angiotensin-aldosterone system, use of Entresto may be associated with an increased risk of hyperkalemia. In PARADIGM-HF, the incidence of clinically relevant hyperkalemia was low, resulting in treatment discontinuation in 0.26% of Entresto treated patients compared to 0.35% of enalapril treated patients. Medications known to

raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution when co-administered with Entresto. If clinically significant hyperkalemia occurs, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered. Monitoring of serum potassium is recommended especially in patients with risk factors such as severe renal impairment, diabetes mellitus, hypoaldosteronism or receiving a high potassium diet (see section DOSAGE REGIMEN AND ADMINISTRATION).

Angioedema

Angioedema has been reported in patients treated with Entresto. If angioedema occurs, Entresto should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. 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, appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly administered.

Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Entresto must 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 section CONTRAINDICATIONS).

Black patients may have increased susceptibility to develop angioedema.

Patients with renal artery stenosis

Similar to other drugs that affect the renin-angiotensin-aldosterone system, Entresto may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. Caution is required in patients with renal artery stenosis and monitoring of renal function is recommended.

6. ADVERSE DRUG REACTIONS

Heart Failure - Adult

Summary of the safety profile

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

PARADIGM-HF

The safety of Entresto in patients with chronic heart failure with LVEF ≤40% (reduced ejection fraction) was evaluated in the pivotal phase 3 study PARADIGM-HF, which compared patients treated twice daily with Entresto 200 mg (n= 4203) or enalapril 10 mg (n= 4229) . Patients randomized to Entresto received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3271 patients were treated for more than one year.

Discontinuation of therapy due to an AE in the double-blind period of the PARADIGM-HF trial occurred in 450 (10.71%) of Entresto treated patients and 516 (12.20%) of patients receiving enalapril. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalemia and renal impairment.

The overall incidence of adverse drug reactions (ADRs) of Entresto in heart failure patients was comparable to enalapril. The pattern of the ADRs is consistent with the pharmacology of Entresto and the patients underlying conditions.

The overall frequency of adverse reactions was not related to gender, age, or race.

Adverse drug reactions are ranked by System Organ Class and then by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 Adverse Drug Reactions in the PARADIGM-HF, Safety Set

Adverse drug reactions	**Entresto** 200mg twice daily (%)*	**ENALAPRIL** 10 mg twice daily (%)*	**Frequency category**
Metabolism and nutrition disorders			
Hyperkalemia	11.61	14.00	Very common
Hypokalemia	3.31	2.53	Common
Nervous system disorders			
Syncope	2.24	2.70	Common
Dizziness	6.33	4.87	Common
Dizziness postural	0.57	0.28	Uncommon
Headache	2.45	2.51	Common
Ear and labyrinth disorders			
Vertigo	1.45	1.40	Common
Vascular disorders			
Hypotension	17.61	11.97	Very common
Orthostatic hypotension	1.52	0.80	Common
Respiratory, thoracic and mediastinal disorders			
Cough	8.78	12.60	Common
Gastrointestinal disorders			
Diarrhoea	4.62	4.47	Common
Nausea	2.09	2.36	Common
Skin and subcutaneous tissue disorders			
Angioedema	0.45	0.24	Uncommon
Renal and urinary disorders			
Renal impairment	10.14	11.52	Very Common
Renal failure (renal failure, acute renal failure)	4.76	5.30	Common
General disorders and administration site conditions			
Fatigue	2.97	3.05	Common
Asthenia	2.09	1.84	Common

* Safety analysis set

PARAGON-HF

The safety of Entresto in patients with chronic heart failure and LVEF ≥45% (preserved ejection fraction) was evaluated in the pivotal phase 3 study PARAGON-HF, which compared patients treated twice daily with Entresto 200 mg (n=2,419) or valsartan 160 mg (n=2,402). The safety profile of Entresto was consistent with the safety profile in patients with heart failure with reduced ejection fraction.

PANORAMA-HF

The safety of Entresto in pediatric patients with chronic HF was evaluated in a randomized, active-controlled, 52-week PANORAMA-HF study of 375 pediatric HF patients aged 1 month to <18 years compared to enalapril. The safety profile observed in pediatric patients aged 1 month to <18 years who received treatment with Entresto was similar to that observed in adult patients. Safety data in patients aged 1 month to <1 year were limited.

Essential Hypertension

Summary of the safety profile

The safety of Entresto in patients with essential hypertension was evaluated in clinical trials involving more than 7,000 hypertensive patients (over 3,500 treated with Entresto).
In a pooled group of short-term, double-blind, controlled studies, 3,272 patients were exposed to Entresto with median duration of 8 weeks, dizziness occurred at a higher frequency in patients treated with Entresto than in patients treated with olmesartan (see Table 2).
Adverse drug reactions are ranked by System Organ Class and then by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 2 Adverse Drug Reactions in the pooled hypertension clinical studies

Adverse drug reactions	Entresto	Olmesartan monotherapy	Frequency category
	N= 3272 n (%)	N=1352 n (%)	
Nervous system disorders			
Dizziness	49 (1.5)	12 (0.9)	Common

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 3 Adverse Drug Reactions from spontaneous reports and literature cases (frequency not known)

Immune system disorders

Hypersensitivity (including rash, pruritus, and anaphylaxis)

7. INTERACTIONS

Anticipated interactions resulting in a contraindication

ACE inhibitors: The concomitant use of Entresto with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE inhibitor therapy may increase the risk of angioedema. Entresto must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of Entresto (see section CONTRAINDICATIONS, and DOSAGE REGIMEN AND ADMINISTRATION).

Aliskiren: The concomitant use of Entresto with aliskiren is contraindicated in patients with Type 2 diabetes (see section CONTRAINDICATIONS).

Anticipated interactions resulting in concomitant use not being recommended

Entresto should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Entresto (see section WARNINGS AND PRECAUTIONS).

Concomitant use with aliskiren should be avoided in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2) (see section WARNINGS AND PRECAUTIONS).

Observed interactions to be considered

Statins: *In vitro* data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. Entresto may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of Entresto increased the Cmax of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold.
Caution should be exercised upon co-administration of Entresto with statins. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered.

Sildenafil: Addition of a single dose of sildenafil to Entresto at steady state in patients with hypertension was associated with greater BP reduction compared to administration of Entresto alone. Therefore, caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with Entresto.

Anticipated interactions to be considered

Potassium: Concomitant use of potassium-sparing diuretics (e.g, triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if Entresto is co-administered with these agents (see section WARNINGS AND PRECAUTIONS).

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 Inhibitors): In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of Entresto and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on

Entresto who are taking NSAIDs concomitantly.

Lithium: The potential for a drug interaction between Entresto and lithium has not been investigated. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use with Entresto. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Transporters: The active metabolite of sacubitril (sacubitrilat), and valsartan are OATP1B1, OATP1B3 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) or MRP2 (e.g. ritonavir) may increase the systemic exposure to sacubitrilat or valsartan, respectively. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

No significant interactions

No clinically meaningful drug-drug interaction was observed upon co-administration of Entresto and furosemide, digoxin, warfarin, hydrochlorothiazide, amlodipine, metformin, omeprazole, carvedilol, intravenous nitroglycerin or a combination of levonorgestrel/ethinyl estradiol. No interaction is expected with atenolol, indomethacin, glyburide, or cimetidine.

CYP 450 Interactions: In vitro metabolism studies indicate that the potential for CYP 450 - based drug interactions is low since there is limited metabolism of Entresto via the CYP450 enzymes. Entresto does not induce or inhibit CYP450 enzymes.

8. PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

As for other drugs that also act directly on the RAAS, Entresto must not be used during pregnancy (see section CONTRAINDICATIONS). Entresto exerts its effects via angiotensin II antagonism. As a result, a risk to the fetus cannot be excluded. There have been reports of injury to the developing fetus (e.g. spontaneous abortion, oligohydramnios and newborn renal dysfunction), when pregnant women have taken valsartan. Patients should be advised to discontinue Entresto as soon as pregnancies occur and to inform their physicians.

Animal Data

Entresto treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥100 mg/kg/day [≤0.72 fold the maximum recommended human dose (MRHD) on the basis of AUC] and rabbits at doses ≥ 10 mg/kg/day [2 fold and 0.03 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 ≥ 10 mg/kg/day. The adverse embryo-fetal effects of Entresto are attributed to the angiotensin receptor antagonist activity.

Pre- and postnatal development studies in rats conducted with sacubitril at doses up to 750

mg/kg/day [2.2 fold the MRHD on the basis of 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.

Lactation

Risk Summary

It is not known whether the components of Entresto are transferred into human milk. The components of Entresto, sacubitril and valsartan were transferred into the milk of lactating rats. Because of the potential risk for adverse drug reactions in breastfed newborns/infants, Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast-feeding or to discontinue Entresto while breast-feeding, taking into account the importance of Entresto to the mother.

Females and males of reproductive potential

Females patients of child-bearing potential should be advised about the consequences of exposure to Entresto during pregnancy and to use contraception during treatment with Entresto and for 1 week after their last dose.

Infertility

There are no available data on the effect of Entresto on human fertility. Entresto did not show any effects on fertility or early embryonic development in rats up to a dose of 150 mg/kg/day (≤1.0 fold and ≤0.18 fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively).

9. OVERDOSAGE

Limited data are available with regards to overdosage in human subjects with Entresto. In healthy adult volunteers, a single dose of Entresto 1200 mg, and 900 mg multiple doses (14 days) have been studied and were well tolerated.

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

Entresto is unlikely to be removed by hemodialysis due to high protein binding.

10. CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Entresto exhibits the novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via sacubitrilat, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits and renal effects of Entresto in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitrilat and the simultaneous inhibition of the deleterious effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), thereby promoting vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal

blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects. Sustained activation of the renin- angiotensin-aldosterone system results in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

Pharmacodynamics (PD)

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 RAAS 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 compared to baseline. Entresto also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, Entresto decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. In PARAGON-HF, Entresto decreased NT-proBNP, troponin and soluble ST2 (sST2) and increased urine cGMP compared to valsartan. In PANORAMA-HF, a reduction in NT proBNP was observed at weeks 4 and 12 for Entresto (40.2% and 49.8%) and enalapril (18.0% and 44.9%) compared to baseline. The NT proBNP levels continued to decrease over the duration of the study with a reduction of 65.1% for Entresto and 61.6% for enalapril at week 52 compared to baseline. While BNP is a neprilysin substrate, NT-proBNP is not. Therefore, NT-proBNP (but not BNP) is a suitable biomarker for monitoring of heart failure patients treated with ENTRESTO.

In a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1200 mg Entresto had no effect on cardiac repolarization.

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-beta (A-beta) from the brain and cerebrospinal fluid (CSF). Administration of Entresto 400 mg 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 and 1-42. The clinical relevance of this finding is unknown (see section NON-CLINICAL SAFETY DATA).

Pharmacokinetics (PK)

Adult

Absorption

Following oral administration, Entresto dissociates into sacubitril, which is further metabolized to sacubitrilat, and valsartan, which reach peak plasma concentrations in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be ≥ 60% and 23%, respectively. The valsartan in Entresto is more bioavailable than the valsartan in other marketed tablet formulations.

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, while sacubitrilat accumulates by 1.6-fold. Following once daily dosing of

Entresto, steady state levels of sacubitril, sacubitrilat and valsartan are achieved in 5 days with no accumulation in sacubitril and valsartan and 1.2-fold accumulation in sacubitrilat. Entresto administration with food has no clinically significant impact on the systemic exposures of sacubitril, sacubitrilat and 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

Entresto is highly bound to plasma proteins (94% - 97%). Based on the comparison of plasma and CSF exposures, sacubitrilat does cross the blood brain barrier to a limited extent (0.28%). Entresto has an apparent volume of distribution ranging from 75 L to 103 L.

Biotransformation/metabolism

Sacubitril is readily converted to sacubitrilat by esterases; sacubitrilat is not further metabolized to a significant extent. Valsartan is minimally metabolized, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (<10%). Since CYP450 enzyme mediated metabolism of sacubitril and valsartan is minimal, co-administration with drugs that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

Elimination

Following oral administration, 52 – 68% of sacubitril (primarily as sacubitrilat) and ~13% of valsartan and its metabolites are excreted in urine; 37-48% 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 (T1/2) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Linearity/non-linearity

The pharmacokinetics of sacubitril, sacubitrilat, and valsartan are linear in the dose range tested (50 - 400 mg of Entresto).

Special populations

Pediatric patients (aged below 18 years)

Entresto has not been studied in pediatric heart failure patients below one month of age.

The pharmacokinetics of Entresto were evaluated in pediatric heart failure patients aged 1 month to <18 years and indicated that the pharmacokinetic profile of Entresto in pediatric and adult patients is similar (see section Clinical studies).

Entresto has not been studied in pediatric hypertension patients below 18 years of age.

Geriatric patients (65 years of age and above)

The exposures of sacubitrilat and valsartan are increased in elderly subjects by 42% and 30%, respectively, compared to younger subjects. However, this is not associated with clinically relevant effects and therefore no dosage adjustment is necessary.

Gender

The pharmacokinetics of Entresto (sacubitril, sacubitrilat and valsartan) are similar between male and female subjects.

Race/Ethnicity

The pharmacokinetics of Entresto (sacubitril, sacubitrilat and valsartan) are comparable across different race and ethnic groups (Caucasians, Blacks, Asians, Japanese and others).

Renal impairment

A correlation was observed between renal function and systemic exposure to sacubitrilat, but not to valsartan. In adult patients with mild (60 mL/min/1.73 m^2< eGFR<90 mL/min/1.73 m^2) to moderate (30 mL/min/1.73 m^2 ≤ eGFR< 60 mL/min/1.73 m^2) renal impairment the AUC for sacubitrilat was up to 2-fold higher. No dosage adjustment is required in patients with mild or moderate renal impairment. A 2.7-fold higher AUC for sacubitrilat was observed in adult patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Half of the starting dose is recommended in adult and pediatric heart failure patients with severe renal impairment. Caution is recommended when administering Entresto to these patients due to limited data. Safety and efficacy of Entresto in patients with essential hypertension and with severe renal impairment have not been established.
No studies have been performed in patients undergoing dialysis. However, sacubitrilat and valsartan are highly bound to plasma protein and, therefore, unlikely to be effectively removed by dialysis.

Hepatic impairment

In adult patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, sacubitrilat increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects. No dosage adjustments is recommended when administering Entresto to patients with mild hepatic impairment (Child-Pugh A classification) including patients with biliary obstructive disorders. In patients with moderate hepatic impairment (Child-Pugh B classification), half of the starting dose is recommended in adult and pediatric patients with heart failure and 100 mg once daily in hypertensive patients [147]. Entresto has not been studied in patients with severe hepatic impairment. Therefore, its use is not recommended in patients with severe hepatic impairment.

11. CLINICAL STUDIES

Heart Failure - Adult

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind study of 8,442 patients comparing Entresto to enalapril, both given to adult patients with chronic heart failure, NYHA class II/ IV, and systolic dysfunction (left ventricular ejection fraction ≤ 40%), in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF).

Prior to study participation, patients were well treated with standard of care therapy which included ACE inhibitors/ARBs (>99%), beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (83%). The median follow- up duration was 27 months and patients were

treated for up to 4.3 years.

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and entered a sequential single-blind run-in period during which patients received treatment with enalapril 10 mg twice daily, followed by treatment with Entresto 100 mg twice daily, increasing to 200 mg twice daily. Patients were then randomized to the double-blind period of the study to receive either Entresto 200 mg or enalapril 10 mg twice daily [Entresto (n= 4,209); enalapril (n= 4,233)].

The mean age of the population studied was 64 years of age and 19% were 75 years or older. At randomization, 70% of patients were NYHA Class II and 25% were Class III/IV.

In the Entresto group, 76% of patients remained on the target dose of 200 mg twice daily at the end of the study (mean daily dose of 375 mg). In the enalapril group, 75% of patients remained on the target dose of 10 mg twice daily at the end of the study (mean daily dose of 18.9 mg).

Entresto demonstrated clinically relevant and statistically significant superiority to enalapril, reducing the risk of cardiovascular death or heart failure hospitalizations by 20% (hazard ratio (HR): 0.80, 95% CI [0.73; 0.87], 1-sided p =0.0000002) versus enalapril. This effect was observed early and was sustained throughout the duration of the trial. The absolute risk reduction was 4.69%. A statistically significant reduction for CV death and first HF hospitalization was observed (CV death, RRR 20%, HR 0.80; 95% CI [0.71, 0.89], 1-sided p= 0.00004; and hospitalization for heart failure RRR 21%; HR 0.79; 95% CI 0.71, 0.89], 1-sided p= 0.00004); see Table 2 and Figure 1. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in Entresto treated patients compared to enalapril treated patients (HR 0.80, p= 0.0082). Pump failure accounted for 26% of cardiovascular deaths and was reduced by 21% in Entresto treated patients compared to enalapril treated patients (HR 0.79, p = 0.0338).

This risk reduction was consistently observed across subgroups including: age, gender, race, geography, NYHA class, ejection fraction, renal function, history of diabetes or hypertension, prior heart failure therapy, and atrial fibrillation.

Entresto also significantly reduced all-cause mortality by 16% compared with enalapril (RRR 16%, HR 0.84; 95% CI [0.76 to 0.93], 1-sided p=0.0005) (Table 3). The absolute risk reduction was 2.84%.

Table 4 Treatment effect for the primary composite endpoint, its components and all-cause mortality – PARADIGM-HF

	Entresto **N = 4187[#] n (%)**	**Enalapril N = 4212[#] n (%)**	**Hazard Ratio (95% CI)**	**Relative Risk Reduction**	**p-value *****
Primary Composite Endpoint of CV Death and Heart Failure Hospitalizations*	914 (21.83)	1117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual Components of the primary composite endpoint					
CV Death **	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	0.00004
First Heart Failure Hospitalization	537 (12.83)	658 (15.62)	0.79 (0.71, 0.89)	21%	0.00004
Secondary Endpoint					

All-cause mortality	711 (16.98)	835 (19.82)	0.84 (0.76, 0.93)	16%	0.0005

*The primary endpoint was defined as the time to first event.

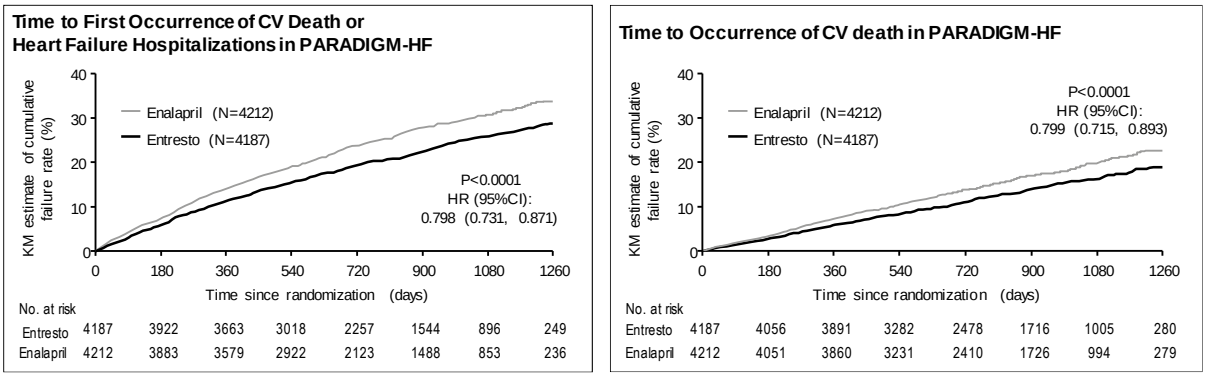
** CV death includes all patients who died up to the cut-off date irrespective of previous hospitalization.

*** One-sided p-value.

♯ Full analysis set

The Kaplan-Meier presented in the figure below (left) shows time to first occurrence of the primary composite endpoint of CV death or heart failure hospitalization. Entresto treatment effect was evident early and sustained for the duration of the study. The Kaplan- Meier figure presented below (right) shows the time to CV death endpoint.

Figure 1 Kaplan-Meier curves for the primary composite endpoint and the CV death component – PARADIGM-HF



Overall, there were fewer all cause hospital admissions in patients treated with Entresto compared to enalapril, including a 12% relative risk reduction for the first hospitalization (HR 0.88 [95% CI: 0.82, 0.94], P<0.001), and a 16% relative rate reduction for total number of hospitalizations (RR 0.84 [95% CI: 0.78, 0.91], P<0.001).

Entresto demonstrated a significantly better clinical summary score for the domains related to HF symptoms and physical limitations as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), a self- administered questionnaire. More patients had improved NYHA functional class from baseline to Month 8 on Entresto (16%) compared to enalapril (14%), and fewer patients had worsened NYHA functional class (10% vs 13%, respectively).

PARAGON-HF

PARAGON-HF, was a multicenter, randomized, double-blind trial comparing Entresto and valsartan in 4,796 adult patients with symptomatic heart failure with preserved ejection fraction (left ventricular ejection fraction ≥45%), and structural heart disease [either left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)]. Patients with a systolic blood pressure of < 110 mmHg and patients with any prior echocardiographic LVEF < 40% at screening were excluded.

The primary endpoint of PARAGON-HF was the composite of total (first and recurrent) heart failure (HF) hospitalizations and cardiovascular (CV) death.

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received valsartan 80 mg twice-daily, followed by Entresto 100 mg twice-daily. Patients on prior low doses of an ACEi or ARB began the run-in

period receiving valsartan 40 mg twice-daily for 1-2 weeks. Patients who successfully completed the sequential run-in periods were randomized to receive either Entresto 200 mg (N=2,419) twice-daily or valsartan 160 mg (N=2,403) twice-daily. The median follow-up duration was 35 months and patients were treated for up to 4.7 years.

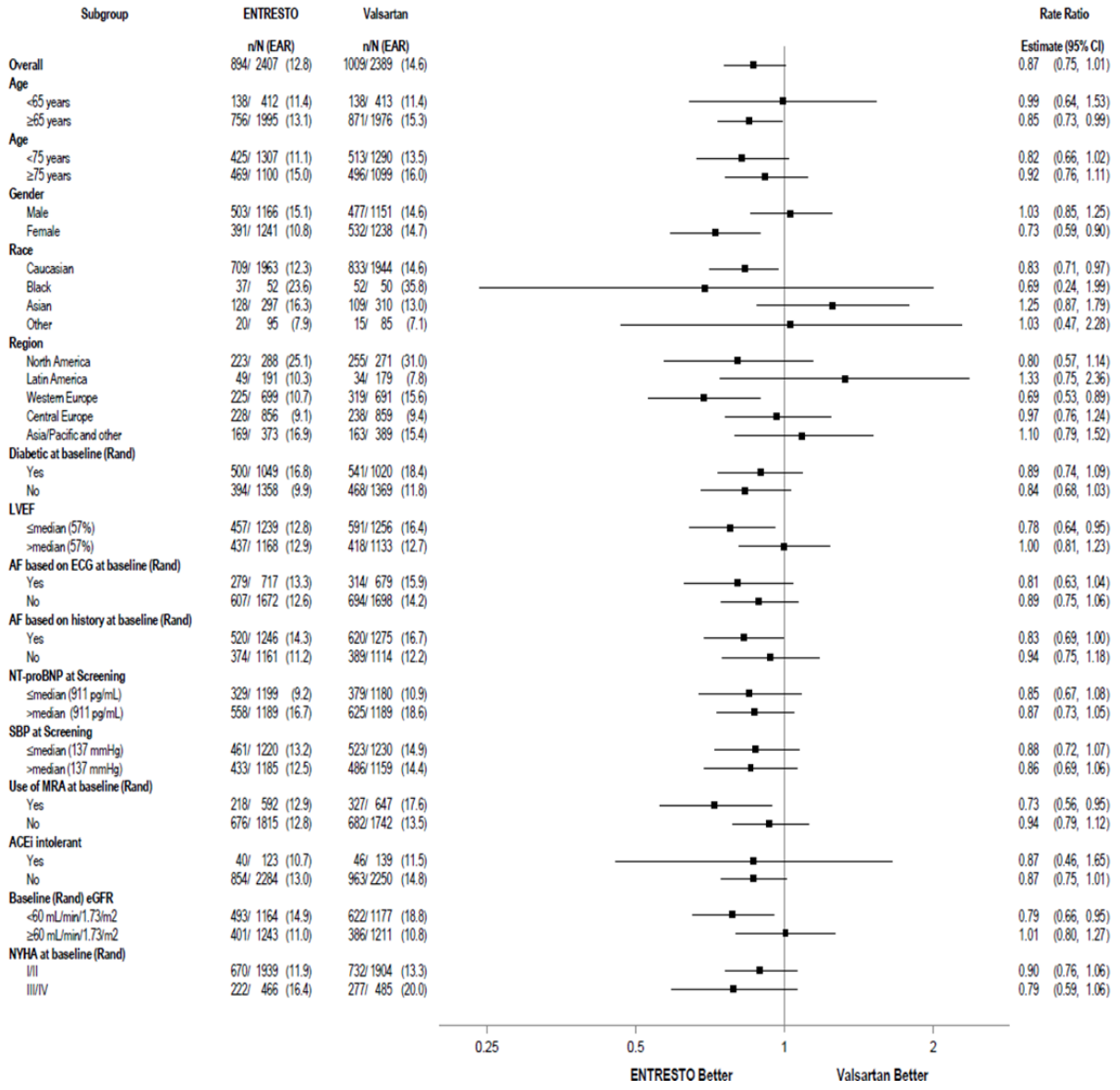
The mean age of the population studied was 73 years and 52% were female. At randomization, 77% of patients were NYHA Class II, 19% were NYHA Class III, and 0.4% were NYHA Class IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic etiology in 36% of patients. Furthermore, 96% had a history of hypertension, 23% had a history of myocardial infarction, 46% had an eGFR < 60 mL/min/1.73 m^2, and 43% had diabetes mellitus. Most patients were taking beta-blockers (80%) and diuretics (95%).

In PARAGON-HF, Entresto reduced the rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death, based on an analysis using a proportional rates model, by 13% compared to valsartan (rate ratio [RR]; 0.87; 95% CI [0.75, 1.01], p = 0.059). The treatment effect was primarily driven by the reduction in total HF hospitalizations in patients randomized to Entresto of 15% (RR 0.85; 95% CI [0.72, 1.00]).

Entresto reduced by 14% the rate of the composite endpoint of total worsening heart failure (HF hospitalizations and urgent HF visits) and CV death (RR 0.86; 95% CI [0.75, 0.99]).

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes (Figure 2).

Figure 2 Primary Composite Endpoint of Total HF Hospitalizations and CV Death – Subgroup Analysis - PARAGON-HF



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.

In an analysis of the relationship between LVEF and outcome in PARADIGM-HF and PARAGON-HF, patients with LVEF below normal (up to approximately 60%) treated with Entresto experienced greater risk reduction (Table 4 and Figure 3, and Figure 4). LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment; prescribers should use clinical judgment in deciding whom to treat. In both studies the treatment effect with Entresto was demonstrated early and sustained throughout the duration of the trials (Figure 1 and 4).

Table 5 Treatment Effect for Composite Endpoints (Primary and Expanded) and Components for LVEF ≤ 60% - PARAGON-HF

	Entresto N = 1,688		Valsartan N = 1,683		Effect Size (95% CI)
Efficacy Endpoints	**n**	**Event Rate[a]**	**n**	**Event Rate[a]**	
Composite endpoint of total (first and recurrent) HF hospitalizations and CV death	619	12.7	761	15.9	RR = 0.79 (0.67, 0.94)
Composite endpoint of total worsening HF[b] and CV death	653	13.3	798	16.7	RR = 0.80 (0.67, 0.94)
Individual components of the composite endpoints					
Total HF Hospitalizations	469	9.6	594	12.4	RR = 0.76 (0.62, 0.92)
CV Death	150	3.1	167	3.5	HR = 0.88 (0.71, 1.10)
Total worsening HF[b]	503	10.3	631	13.2	RR = 0.75 (0.62, 0.91)
Secondary Endpoints	**n/N**	**Change From Baseline (SE)**	**n/N**	**Change From Baseline (SE)**	**Treatment difference (95% CI)**
KCCQ Clinical Summary Score (CSS) change at 8 months	1578/1677	-1.67 (0.42)	1571/1671	-2.71 (0.42)	LSM = 1.03 (-0.13, 2.20)
	n/N	**Event Rate**	**n/N**	**Event Rate**	**Treatment difference (95% CI)**
NYHA class favorable change at 8 months	1481/1625	N/A	1452/1618	N/A	OR = 1.42 (1.08, 1.88)[c]
Renal composite endpoint[d]	22/1688	0.45	47/1683	0.99	HR = 0.45 (0.27, 0.75)
All-cause death	256/1688	5.23	267/1683	5.57	HR = 0.94 (0.79, 1.11)

Abbreviations: RR = rate ratio, HR = hazard ratio, OR = odds ratio, SE = standard error

[a] Event rate per 100 patient-years

[b] The composite of worsening HF included total (first and recurrent) urgent HF visits and HF hospitalizations. An urgent HF visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring intravenous treatment.

[c] The odds ratio for the NYHA class change represents the model-based common odds ratio of improvement and non-worsening, with OR >1 reflecting favorable changes in the Entresto group.

[d] Defined as renal death, reaching end stage renal disease, or ≥50% decline in estimated glomerular filtration rate (eGFR) relative to baseline.

Figure 3 Mean Number of Events Over Time for the Primary Composite Endpoint of Total HF Hospitalizations and CV Death in patients with LVEF ≤ 60% - PARAGON-HF

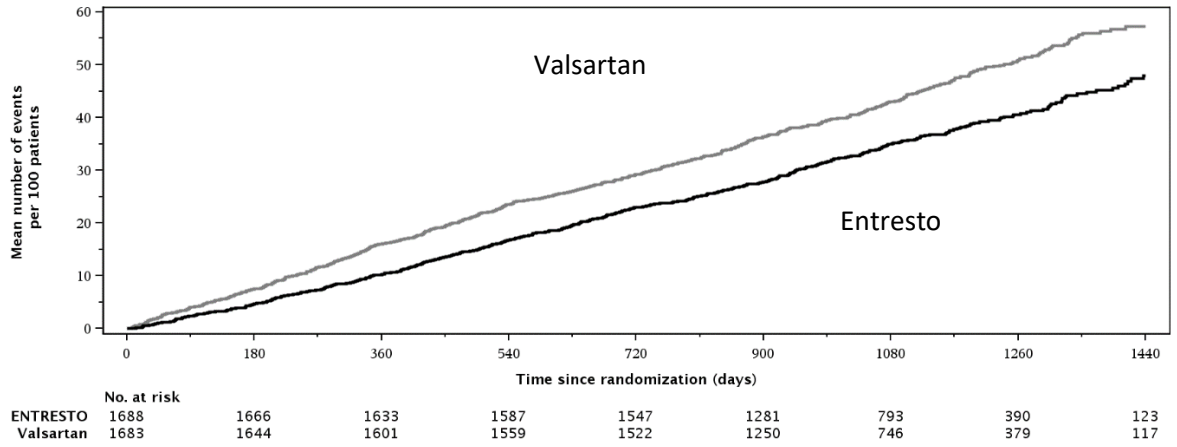
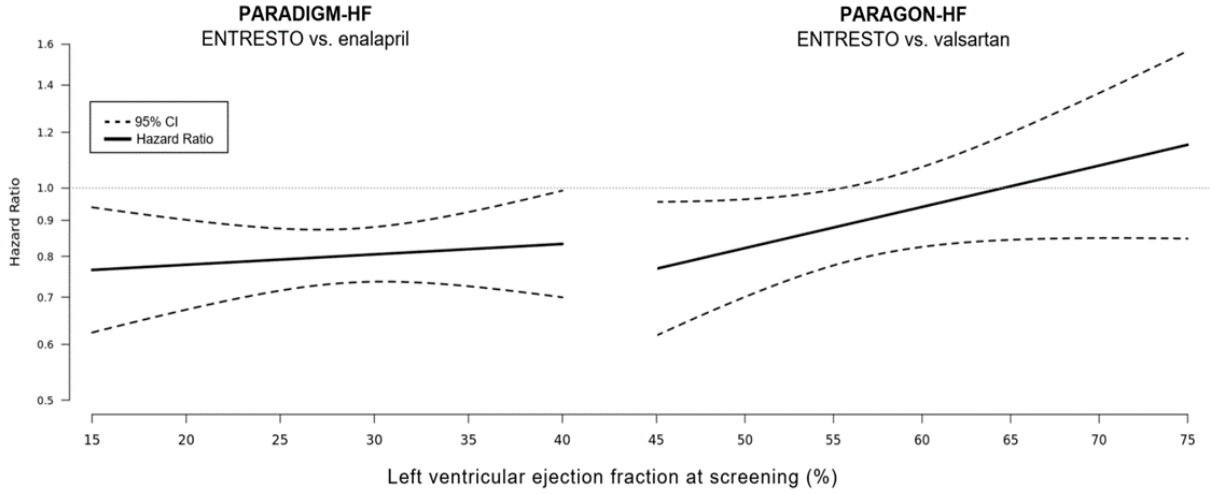


Figure 4 Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by LVEF in PARADIGM-HF and PARAGON-HF



TITRATION

TITRATION was a 12-week safety and tolerability study in 538 patients with chronic heart failure (NYHA class II/IV) and systolic dysfunction (left ventricular ejection fraction ≤ 35%) naive to ACE inhibitor or ARB therapy or on varying doses of ACE inhibitors or ARBs prior to study entry. Patients initiated Entresto 50 mg twice daily, were uptitrated to 100 mg twice daily and then to the target dose of 200 mg twice daily with either a 3-week or 6-week regimen.

Overall, 76% of patients achieved and maintained the target dose of Entresto 200 mg twice daily without any dose interruption or down-titration over 12-weeks. More patients who were naïve to previous ACE inhibitor or ARB therapy or on low dose therapy (equivalent to <10 mg of enalapril/ day) were able to achieve and maintain Entresto 200 mg when uptitrated over 6 weeks versus 3 weeks.

PARAMOUNT

PARAMOUNT, a randomized, double-blind trial in patients with left ventricular ejection fraction ≥ 45% comparing 200 mg of Entresto (n=149) to 160 mg of valsartan (n=152) twice daily, demonstrated statistically greater reduction (p= 0.0050) in NT pro-BNP from baseline to Week 12. The reduction from baseline in NT-proBNP was similar at Weeks 12 and 36 in patients treated with Entresto, while NT-proBNP decreased from Week 12 to 36 in patients treated with valsartan. Significant reductions in left atrial size, both left atrial volume index (p=0.0069) and left atrial dimension (p=0.0337) were observed at Week 36. A statistically significant improvement in NYHA class was noted at Week 36 (p=0.0488).

Heart Failure – Pediatric

PANORAMA-HF was a multinational, randomized, double-blind study comparing Entresto and enalapril in 375 pediatric patients aged 1 month to <18 years with heart failure due to systemic left ventricular systolic dysfunction (LVEF ≤45% or fractional shortening ≤22.5%). Patients with systemic right ventricle, single ventricle, restrictive cardiomyopathy or hypertrophic cardiomyopathy were excluded from the study.

The primary objective was to determine whether Entresto was superior to enalapril in the treatment of HF in pediatric patients with HF over a 52-week treatment duration based on a global rank primary endpoint.

The global rank primary endpoint was derived by ranking patients (worst-to-best outcome) based on clinical events such as death, initiation of mechanical life support, listing for urgent heart transplant, worsening HF, measures of functional capacity (NYHA/ROSS scores), and patient-reported HF symptoms (Patient Global Impression Scale [PGIS]).

At randomization, 9 patients were aged 1 month to <1 year, 61 patients were aged 1 year to <2 years, 85 patients were aged 2 to <6 years and 220 patients were aged 6 to <18 years. At baseline, 15.7% of patients were NYHA/ROSS class I, 69.3% were class II, 14.4% were class III and 0.5% were class IV. The mean LVEF was 32%. The most common underlying causes of heart failure were cardiomyopathy related (63.5%). Prior to study participation, patients were treated most commonly with ACE inhibitors/ARBs (93%), beta-blockers (70%), aldosterone antagonists (70%), and diuretics (84%).

The target maintenance dose of Entresto was 2.3 mg/kg twice daily in pediatric patients aged 1 month to <1 year and 3.1 mg/kg twice daily in patients aged 1 to <18 years with a maximum dose of 200 mg twice daily. The target maintenance dose of enalapril was 0.15 mg/kg twice daily in pediatric patients aged 1 month to <1 year and 0.2 mg/kg twice daily in patients aged 1 to <18 years with a maximum dose of 10 mg twice daily.

The Mann-Whitney Odds of the global rank primary endpoint was 0.907 (p=0.424), numerically in favor of Entresto (see Table 6). Entresto and enalapril showed comparable clinically relevant improvements in the secondary endpoints of NYHA/ROSS functional class and PGIS score change compared to baseline. At Week 52, the NYHA/ROSS functional class changes from baseline were: improved in 37.7% and 34.0%; unchanged in 50.6% and 56.6%; worsened in 11.7% and 9.4% of patients for Entresto and enalapril respectively. Similarly, the PGIS score changes from baseline were improved in 35.5% and 34.8%; unchanged in 48.0% and 47.5%; worsened in 16.5% and 17.7% of patients for Entresto and enalapril respectively. NT-proBNP was substantially reduced from baseline in both treatment groups. The magnitude of NT-proBNP reduction with Entresto was similar to that observed in adult heart failure patients treated with Entresto in PARADIGM-HF. Because Entresto improved outcomes and reduced NT-proBNP in PARADIGM-HF, the

reductions in NT-proBNP coupled with the symptomatic and functional improvements from baseline seen in PANORAMA-HF were considered a reasonable basis to infer clinical benefits in pediatric heart failure patients. The results were consistent across the age groups 1 year and older. There were too few patients below 1 year to evaluate the efficacy of Entresto in this age group.

Table 6 Treatment effect for the primary global rank endpoint in PANORAMA-HF

	Entresto N=187	**Enalapril N=188**	**Treatment effect**
Global rank primary endpoint	Probability of favorable outcome (%)*	Probability of favorable outcome (%)*	Odds** (95% CI)
	52.4	47.6	0.907 (0.72, 1.14) p-value 0.424

*The probability of favorable outcome or Mann-Whitney probability (MWP) for the given treatment was estimated based on percentage of wins in pairwise comparisons of global rank score between sacubitril/valsartan-treated patients versus enalapril-treated patients (each higher score counts as one win and each equal score counts as half a win).

**Mann-Whitney Odds was calculated as the estimated MWP for enalapril divided by the estimated MWP for Entresto, with odds <1 in favor of Entresto and >1 in favor of enalapril.

Essential Hypertension

The antihypertensive effect of Entresto was evaluated in two randomized, double-blind, active-controlled, 8-week studies evaluating the efficacy and safety of Entresto in comparison to olmesartan (CLCZ696A2315 and CLCZ696A1306) in more than 2,500 adult patients of which more than 1,700 patients received Entresto. Both studies demonstrated non-inferiority as well as superiority of the mean sitting systolic blood pressure (msSBP) lowering effect of both Entresto 200 mg once daily (2.3 and 5.0 mmHg in each study, respectively) and Entresto 400 mg once daily (3.5 and 7.0 mmHg) compared to olmesartan 20 mg once daily. Consistent results were observed in mean diastolic BP.
Additionally, persistency of blood pressure lowering effect was demonstrated in a 52-week, safety, tolerability and efficacy, open-label, extension study (CLCZ696A2219E1) in which 341 patients were receiving Entresto as a monotherapy or in combination with amlodipine and hydrochlorothiazide.

12. NON-CLINICAL SAFETY DATA

Non-clinical safety studies conducted with Entresto included assessment of safety pharmacology, repeated dose toxicity genotoxicity carcinogenicity and reproductive and development toxicity Entresto had no adverse effects on vital organ systems. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of AT_1 receptor blockade.

Carcinogenicity, mutagenesis and genetic toxicity

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for Entresto. The doses of sacubitril studied (high dose of 1200 and 400 mg/kg/day in mice and rats, respectively) were about 29 and 19 times, respectively, the maximum recommended human dose (MRHD) on a mg/m^2 basis. 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 maximum recommended human dose 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.

Fertility, reproduction and development

See section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Other preclinical findings

The effects of Entresto on amyloid-beta concentrations in cerebrospinal fluid (CSF) and brain tissue were assessed in young (2-4 years old) cynomolgus monkeys treated with Entresto (50 mg/kg/day) for 2 weeks. In this study, Entresto had a pharmacodynamic effect on CSF A beta clearance in cynomolgus monkeys, increasing CSF Aβ 1-40, 1-42, and 1-38 levels; there was no corresponding increase in A beta levels in the brain. Increases in CSF A beta 1-40 and 1-42 were not observed in a 2 week healthy volunteer study in humans (see section CLINICAL PHARMACOLOGY). Additionally, in a toxicology study in cynomolgus monkeys treated with Entresto at 300 mg/kg/day for 39-weeks, there was no amyloid- beta accumulation in the brain.

Juvenile animal data

Sacubitril

Sacubitril given orally to juvenile rats from postnatal day (PND) 7 to PND 35 or PND 70 (an age approximately equivalent to neonatal through pre-pubertal development or adulthood in humans) at doses ≥400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, based on Entresto pediatric clinical dose of 3.1 mg/kg twice daily) resulted in decreases in body weight, bone length, and bone mass. The decrease in body weight was transient from PND 10 to PND 20 and the effects for most bone parameters were reversible after treatment stopped. Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657 at the 3.1 mg/kg twice daily dose of Entresto. The mechanism for these findings in juvenile rats, and consequently, the relevance to human pediatric population is unknown. Clinical data in pediatric patients (PANORAMA-HF study) did not show evidence that Entresto has an impact on body weight, height, head circumference and fracture rate. Bone density was not measured in the study.

Valsartan

Valsartan given orally to juvenile rats from PND 7 to PND 70 (an age approximately equivalent to neonatal through adulthood in humans) produced persistent, irreversible kidney damage at all dose levels. Exposure at the lowest tested dose of 1 mg/kg/day was approximately 0.2-fold the exposure at 3.1 mg/kg twice daily dose of Entresto based on AUC. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children less than 1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year**.**

13. INCOMPATIBILITIES

Not applicable.

14. STORAGE

Entresto should not be used after the date marked “EXP” on the pack.
Storage requirements: Do not store above 30°C, protect from moisture. Store in the original package.
Entresto must be kept out of the reach and sight of children.

15. INSTRUCTIONS FOR USE AND HANDLING

Not applicable.

16. PRESENTATION

ENTRESTO 50 mg: One paper box contains two Alu-Alu blister packs (PA/AL/PVC) of 14 tablets each.
ENTRESTO 100 mg: One paper box contains two Alu-Alu blister packs (PA/AL/PVC) of 14 tablets each.
ENTRESTO 200 mg: One paper box contains eight Alu-Alu blister packs (PA/AL/PVC) of 7 tablets each

Manufacturer:

- Novartis Farma S.p.A., Torre Annunziata (NA), Italy
- Novartis Saglik, Gida Ve Tarim Urunleri San Ve Tic. A.S., Istanbul, Turkiye

International Package Leaflet

Information issued: Jul 2023

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